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Regional Nodal Involvement and Patterns of Spread Along In-transit Pathways in Children with Rhabdomyosarcoma of the Extremity: A Report from the Children's Oncology Group

Trang H. La, MD¹, Suzanne L. Wolden, MD², David A. Rodeberg, MD³, Douglas S. Hawkins, MD⁴, Kenneth L. Brown, MD⁵, James R. Anderson, PhD⁶, and Sarah S. Donaldson, MD¹

¹ Department of Radiation Oncology, Stanford University, Stanford, CA

² Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

³ Department of Surgery, University of Pittsburg School of Medicine, Pittsburg, PA

⁴ Division of Hematology/Oncology, University of Washington School of Medicine, Seattle, WA

⁵ Department of Orthopedics, BC Children's Hospital, Vancouver, BC

⁶ Department of Biostatistics, College of Public Health, University of Nebraska Medical Center, Omaha, NE

Abstract

Purpose—To evaluate the incidence and prognostic factors for regional failure, with attention to in-transit pathways of spread, in children with non-metastatic rhabdomyosarcoma (RMS) of the extremity.

Materials/Methods—Intergroup Rhabdomyosarcoma Studies III, IV-Pilot, and IV enrolled 226 children with RMS of the extremity. Failure at in-transit (epitrochlear/brachial and popliteal) and proximal (axillary/infraclavicular and inguinal/femoral) nodes were evaluated. Median follow-up for surviving patients is 10.4 years.

Results—Fifty-five (24%) of 226 children had clinical or pathologic evidence of either in-transit and/or proximal lymph node involvement (LNI) at diagnosis. The actuarial 5-year risk of regional failure is 12%. The prognostic factors for poor regional control are female gender and LNI at diagnosis. In the 116 patients with a distal extremity primary tumor, 5% had in-transit LNI at diagnosis. The estimated 5-year incidences of in-transit and proximal nodal failure are 12% and 8%, respectively. The in-transit failure rate is 0% in patients who received radiation therapy and/or underwent lymph node sampling of the in-transit nodal site, but 15% in those who did not ($p=0.07$), although 5-year EFS did not differ between these two groups (64% vs. 55%, $p=0.47$).

Conclusions—The high incidence of regional involvement necessitates aggressive identification and treatment of regional lymph nodes in RMS of the extremity. In patients with distal extremity tumors, in-transit failures are as common as failures in more proximal regional sites. Patients who

Corresponding author: Sarah S. Donaldson MD, Department of Radiation Oncology, Stanford University Cancer Center, 875 Blake Wilbur Drive MC 5847, Stanford, CA 94305, Phone: (650) 723-6195, Fax: (650) 723-4812, sarah2@stanford.edu.

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undergo complete lymph node staging with appropriate radiotherapy to the in-transit nodal site, if indicated, are at a slightly lower risk of in-transit failure.

Keywords

rhabdomyosarcoma; regional failure; in-transit nodes; radiation therapy; extremity

Introduction

Although important advances have been made in the treatment of rhabdomyosarcoma (RMS) over the last 30 years, the challenge remains to improve outcome for patients with certain high-risk factors. Through the work of the Intergroup Rhabdomyosarcoma Study Group (IRSG), now the Soft Tissue Sarcoma (STS) committee of the Children's Oncology Group (COG), treatment results of patients have improved significantly over the past few decades¹⁻⁵. Several poor prognostic factors have been identified which include age, primary site, histology, group, stage, and nodal involvement⁶.

In this study, we evaluate regional failure in patients with non-metastatic RMS of the extremity, an unfavorable primary site typically associated with the high-risk alveolar histology and regional lymph node involvement (LNI). Several studies have evaluated local control in this cohort of patients, but few data are available regarding factors predictive of regional failure, which is the focus of this study⁷⁻¹¹. We also evaluate in-transit nodal pathways as a site of involvement at the time of initial staging as well as disease failure. Little attention has been given to in-transit nodal pathways as a site of disease involvement in RMS and we are unaware of prior studies addressing the incidence of in-transit involvement at diagnosis or the rate of failure in in-transit nodal pathways in this disease. To determine the optimal diagnostic and treatment approaches for regional nodal areas in patients with RMS of the extremity, we identified factors predictive of regional failure in this high risk cohort.

Materials and Methods

Patients

We analyzed all eligible patients with non-metastatic RMS of the extremity treated on Intergroup Rhabdomyosarcoma Study Group (IRSG) III, IV-P, and IV. The eligibility requirements for these studies have been published^{2, 5, 12}. All patients were previously untreated, less than 21 years of age, and had histologically-confirmed RMS. Patients with undifferentiated sarcoma (n=43) were eligible for IRSG III, IV, and IV-P but excluded from this analysis. Informed consent was obtained according to National Cancer Institute guidelines. Primary sites included the shoulder, upper arm, elbow, forearm, hand, buttock, thigh, calf, and foot. We evaluated patients with distal extremity tumors, defined as tumors at or distal to the knee or elbow, for the analysis of in-transit nodal disease. Distal extremity tumors included tumors of the forearm, hand, calf, and foot. Records were reviewed for patient and tumor characteristics, treatment, local control, event-free, and overall survival.

Staging

Extent of disease at diagnosis was determined by clinical, radiographic, and surgical methods. Patients were classified into Group after initial surgery according to the IRS surgical-pathologic system (Table 1) as well as Clinical Stage using the IRS pretreatment TNM classification (Table 2) by the IRSG surgical committee members¹³.

All patients were stage 2 or 3 by virtue of their unfavorable primary site. Presence of nodal involvement was confirmed by lymph node biopsy or dissection when available or by imaging and clinical examination if histological confirmation was not available. Lymph node sampling was recommended, but not required, on these studies. Central review of pathology was conducted by the IRSG pathology subcommittee members.

Treatment

Patients were treated according to previously published IRSG protocols. Time from initial diagnostic surgery to study enrollment is detailed in prior reports^{2, 5, 12}. All patients received multi-agent chemotherapy based on IRSG study, pretreatment Stage, and post-surgical Group. Patients with Stage 2, Group 1 tumors with embryonal histology received no radiation therapy (RT). On IRS-IV, patients with Group I, Stage 1 or 2 alveolar RMS did not receive radiotherapy. All other patients with Group 1 tumors, unless an amputation was performed, and all patients with Group II tumors received 41.4 Gy of conventionally-fractionated radiation therapy (CFRT). Patients with Group III tumors received 45-50.4 Gy of CFRT on IRS III. IRS IVP served as a pilot study for hyperfractionation and on IRS IV, Group III patients were randomized to 50.4 Gy of CFRT or 59.4 Gy of hyper-fractionated RT (HFRT). RT was delivered using megavoltage photon or electron beams. The volume irradiated was the presurgical, prechemotherapy volume plus a 2 cm margin. Treatment of clinically or pathologically involved lymph nodes to the same total dose as the primary site was required.

Radiation therapy dose and volume compliance to study guidelines was reviewed by members of the IRSG Radiation Therapy Committee.

End Points and Statistical Methods

The records of all patients that were coded as having any failure or death were reviewed to confirm the nature of the event. Special attention was given to the site(s) of initial failure, particularly in patients with regional failures, for the patterns of failure analysis. Failure patterns were classified as local, regional, or distant and were determined by the initial site(s) of failure only. Regional failures were further classified as proximal or in-transit. Proximal regional lymph node sites include the infraclavicular, axillary, and inguinal-femoral sites. In-transit nodal sites include the epitrochlear, brachial, and popliteal nodes. Subsequent sites of failure did not change the initial classification of failure site.

Local failure was defined as disease progression or relapse exclusively in or adjacent to the primary site. Regional failure was defined as any disease progression or relapse in a draining lymph node site: epitrochlear/brachial, infraclavicular, and/or axillary nodes for upper extremity tumors and popliteal and/or inguinal-femoral for lower extremity tumors. Total local failure refers to patients with both local failure only and those with concurrent local and regional or distant failures. Total regional failure refers to patients with both regional failure only and those with concurrent regional and local or distant failures. Similarly, the total distant failure group is inclusive of all patients with distant failure with or without local and/or regional failure. Therefore, these failure types are not mutually exclusive.

All local or regional control curves were calculated from the study enrollment to the time of first failure, which was defined as progression or relapse at the local or regional site, respectively. Event-free survival curves were calculated from the start of treatment to the time of first event, which was defined as progression, relapse, or death as a first event. Overall survival curves were calculated from the start treatment to death from any cause. Patients never experiencing an event were censored at the time of last patient contact.

Estimates of survival were calculated by the Kaplan-Meier method and comparisons were made using the log-rank test¹⁴. Univariate analyses were performed for the following factors: age, gender, primary site, histology, tumor size, stage, group, nodal involvement, and study. For events subject to competing risks, cumulative incidence curves were calculated and the risks of certain event-types compared using a log rank test. Multivariate comparisons of time-to-event distributions were made using the Cox proportional hazards model¹⁵.

Results

Patient and Clinical Characteristics

A total of 226 eligible patients with non-metastatic RMS of the extremity were enrolled onto IRS-III (1984-1991, n=106), IRS-IVP (1987-1991, n=26), or IRS-IV (1991-1997, n=94). IRS III and IVP were classified as follow-up completed on September 1, 2005 and IRS IV was classified as follow-up completed on September 1, 2006, with no further follow-up data collected after these dates. The median follow-up is 10.4 years (range, 1.4-19.9 years) among survivors. Patient and clinical characteristics are listed in Table 3. The median age is 6.5 years. Fifty-six percent of the patients are female and 58% have lower extremity primary tumors. The majority of tumors (65%) are alveolar histology.

Treatment Outcome

The estimated 5-year EFS for all patients is 61% (95% confidence interval {CI}: 54%, 67%). Both disease stage ($p<0.0001$) and IRS Group ($p<0.0001$) are predictive of EFS. After adjusting for the effect of stage and Group on EFS, neither age, gender, histology, T-stage, N-stage, nor site (lower versus upper limbs) of primary tumor are independently predictive of EFS. Four events occurred after five years of follow-up: one death from a secondary osteosarcoma at 5.8 years, one distant failure at 9.3 years leading to death at 11.0 years, one late local failure at 5.6 years leading to death at 7.6 years, and one late secondary acute myeloid leukemia leading to death from an intracranial hemorrhage at 5.9 years.

Prognostic Factors for Local Failure

The cumulative incidence of local failure is estimated to be 13% at 5 years and differed statistically by IRS Group. Five-year estimates of cumulative local failure among Group I, II, and III patients were 2%, 5%, and 28%, respectively ($p<0.01$). After adjusting for the effect of IRS Group, no additional patient characteristics (study, age, gender, histology, stage, T-stage, tumor size, nodal status and site) are statistically predictive of local failure.

Local failure also differed according to whether or not the patient received radiation therapy, although the difference is not statistically significant. Among Group II and III patients, 5-year local failure is 37% in non-irradiated patients (n=8) and 12% in patients who were irradiated (n=74) ($p=0.07$). Group I patients were excluded from the analysis of effect of irradiation because the majority of these patients were not irradiated according to protocol assignment.

Prognostic Factors for Regional Failure

Fifty-five (24%) patients had clinical or pathologic evidence of LNI at diagnosis. One hundred twenty of the 226 total patients underwent lymph node biopsy or dissection, and of these, 45 (38%) had pathologic LNI. The estimated 5-year incidence of any regional failure among these 226 patients is 12%. Poor prognostic factors for regional control are regional LNI at diagnosis and female gender. Of the 26 patients who suffered a regional failure, 10 had regional LNI at diagnosis. In 3 of these 10 patients, radiation therapy was not delivered to the involved nodal site as directed by protocol guidelines due to patient or physician

refusal. Three patients suffered a regional failure in an irradiated site. In 4 patients, the regional failure occurred in the unirradiated site: 2 in the popliteal region after the inguinal/femoral site was involved and irradiated, 1 in the femoral region after the popliteal site was involved and irradiated, and 1 in the brachial region after the axilla was involved and irradiated.

In-Transit Pathways of Spread

A separate analysis was performed among the patients with a distal extremity tumor to assess the incidence of regional failure in an in-transit pathway. There were 116 patients with a distal extremity tumor: 35 forearm, 2 elbow, 21 hand, 36 calf, and 22 foot. Estimated 5-year EFS was 56% (95% CI: 47%, 65%) for this cohort. All but one failure occurred within 5 years of follow-up.

Among these 116 patients, 11 (9%) underwent in-transit lymph node sampling at diagnosis and 5 had pathologic evidence of in-transit involvement as shown in Table 4. As a result, the estimated incidence of in-transit LNI at diagnosis is 4%. In comparison, 76 patients underwent proximal regional lymph node sampling and 28 had pathologic evidence of lymph node involvement. The estimated incidence of proximal regional LNI is 24%.

Thirteen patients suffered an in-transit failure; sites are detailed in Table 5. The estimated 5-year cumulative incidence of in-transit failure was 12% as compared to an estimated 5-year cumulative incidence of proximal nodal failure of 8% among these 116 patients. Three patients suffered an in-transit failure when the proximal nodal site was initially involved and one patient suffered a proximal nodal failure when the in-transit nodal site was initially involved. The risk of in-transit regional failure was not statistically associated with age, gender, race, stage, histology, size, or study. Patients with lower extremity primary tumors were more likely to have an in-transit failure than patients with upper extremity primary tumors (18% vs. 5%, $p=0.04$) (Figure 1). None of the 22 patients who underwent lymph node sampling (in the form of lymph node biopsy or dissection) and/or received RT to the in-transit nodal region experienced an in-transit failure. However, the 5-year cumulative incidence of in-transit failure for the 94 patients who did not undergo lymph node sampling and did not receive RT to the in-transit nodal region is 15% ($p=0.07$) (Figure 2). The estimated 5-year EFS did not differ between these two groups (64% vs. 55%, $p=0.47$).

Discussion

The extremity is the primary disease site in approximately 20% of all pediatric RMS cases¹⁰. Despite improved treatment strategies for patients with RMS, children with extremity RMS continue to have worse outcome as compared to those with RMS in more favorable sites. Two risk factors associated poor outcome in extremity RMS are alveolar histology and regional lymph node involvement. In previously published RMS studies, regional LN involvement is present in approximately 20-40% of patients with extremity tumors^{7, 16}. The high incidence of regional involvement necessitates aggressive identification and treatment of regional lymph nodes. In a recent IRSG study, the 5-year failure-free survival rate was 31% for patients with Group III alveolar or undifferentiated RMS at unfavorable sites with regional lymph node involvement at diagnosis, which was a similar rate to that for patients with metastatic disease⁶. A previous IRSG study also found involved lymph nodes at diagnosis to be predictive of local and distant treatment failure in group III patients¹⁷. In our study, the only factor predictive of local failure was Group III disease ($p<0.01$). Among Group II and III patients, there was a strong trend towards decreased risk of local failure for those who received radiotherapy as compared to those who did not (37% vs 12% at 5 years, $p=0.07$).

The primary objective in this study is to evaluate the incidence and prognostic factors for regional failure, with attention to in-transit pathways of spread, in children with non-metastatic RMS of the extremities. Twenty-four percent of patients in this study had regional nodal involvement at diagnosis, either in the proximal or in-transit nodal site. The estimated 5-year incidence of regional failure is 12%, although it is unclear why females are more likely to suffer a regional failure as compared to males. In this study, patients with any regional LNI involvement at diagnosis are more likely to suffer a regional failure. Three of the patients did not receive irradiation to the nodal site as directed by protocol guidelines, whereas 3 others did and experienced a failure apparently within the irradiation field. There are insufficient numbers of patients who suffered a failure within the in-transit nodal site when the proximal nodal site was initially involved (n=3) or vice versa (n=1) to justify recommending routine irradiation of the entire affected extremity when the proximal nodal site is involved.

Accurate determination of Stage and Group, and thus treatment regimen and prognosis, depends upon regional nodal assessment. Previous studies in patients with RMS of the extremity show that survival is higher in patients without regional nodal spread as compared to those whose lymph node status was not evaluated¹⁰. In IRS-IV, 17% of patients with clinically negative nodes were found to have microscopic disease upon biopsy, thus altering the treatment regimen to include irradiation of the involved nodal site¹⁸. In this study, 24% of patients had clinical or pathologic evidence of nodal involvement. As lymph node sampling was not a requirement on all these studies, this rate may be an underestimation of the actual incidence of pathologic nodal involvement. Among the patients who underwent nodal sampling, 38% had histologically-proven regional nodal involvement. This high incidence confirms the need for adequate nodal sampling in children with extremity RMS to ensure accurate staging and to guide treatment, as is the requirement on current COG studies¹⁹⁻²¹. If there is biopsy-proven regional nodal involvement, radiation therapy to the involved nodal site is recommended.

By studying the incidence of in-transit nodal involvement at diagnosis and the risk factors for in-transit nodal failure, our goal is to improve locoregional tumor control. In-transit nodal involvement has been most extensively studied in melanoma and is defined as cutaneous or subcutaneous metastases within lymphatic channels located between a primary melanoma and its regional lymph nodes²². In-transit involvement has been reported in 5-10% of patients with melanoma of the trunk or head and neck²³. In patients with melanoma of the distal extremity, in-transit nodal involvement in the epitrochlear or popliteal lymph nodes is estimated to be 0-2%. In a study evaluating patients with melanoma lesions at or distal to the knee, the popliteal site was identified by lymphoscintigraphy as the primary draining site in 7% of patients²⁴. Among the 4,262 total patients in that study, only 13 (0.31%) suffered a failure in a popliteal lymph node. In a similar study of patients with melanoma of the upper extremity, 1.1% suffered a failure in an epitrochlear lymph node²⁵. In comparison, in-transit failure is reported to be as high as 20% in patients with melanomas distal to the elbow or knee with positive sentinel lymph nodes at diagnosis^{22, 26}.

In RMS, in-transit nodal involvement has been given little attention and has not been systematically evaluated. In this study, the incidence of in-transit nodal involvement at diagnosis was only 4%, although very few children underwent in-transit lymph node sampling at diagnosis. Among the 116 patients with distal extremity tumors, only 11 underwent in-transit lymph node sampling and 5 were found to have in-transit involvement at diagnosis. In comparison, 66% of these patients had the proximal nodal region sampled. As a result, the in-transit lymph node sites are likely not adequately evaluated and treated.

Although in-transit nodal involvement was not commonly assessed at diagnosis, the in-transit region is as common a site of failure as the proximal nodal region in patients with distal extremity RMS. This could be a result of inadequate evaluation of in-transit nodal involvement at diagnosis and inadequate treatment of these sites, which should include irradiation of any involved nodal site. As a result, particular attention should be given to in-transit nodal sites at diagnosis and staging in order to identify and optimally treat these sites should they be involved. We recommend magnetic resonance imaging (MRI) imaging of the entire affected extremity to encompass the in-transit pathways of spread, not just of the primary site and proximal nodal region, as well as 18-fluorodeoxyglucose positron emission tomography (FDG-PET).

The role of FDG-PET imaging in the staging of RMS continues to be investigated^{27, 28}. Compared to conventional computerized tomography (CT) and MRI, FDG-PET has the advantage of providing both anatomic and functional assessment of involved sites (Figure 3). Although FDG-PET has been found to be equivalent to conventional imaging modalities in detecting primary pediatric sarcomas, FDG-PET was superior in detecting lymph node involvement in these children with a specificity of 95% compared to 25% for ultrasound, CT, and MRI²⁹. FDG-PET is a less invasive initial staging study than lymph node sampling via biopsy or dissection. As a result, the use of FDG-PET as a means of detecting regional nodal involvement or occult metastatic disease in RMS is being investigated. At this time, histologic confirmation of sites demonstrating FDG uptake is recommended and its role with regards to lymph node sampling continues to evolve. Nonetheless, FDG-PET should be considered as a part of the initial work-up of a patient with extremity RMS whenever possible.

Failures in the in-transit nodal sites are considered rare and only a few cases have been documented in a report by Paulino et al and a study by Viswanathan et al^{30, 31}. Although the incidence of in-transit nodal involvement is only 4% in this study, in-transit failures are as common as failures in more proximal regional sites in patients with distal extremity RMS. As a result, we recommend adequate evaluation of the entire extremity to encompass the in-transit pathways of spread in all patients with primary tumors of the distal extremity. In this study, patients who underwent lymph node sampling and/or radiotherapy to the in-transit nodal sites were at a slightly lower risk of in-transit failure. We believe these patients received complete and accurate nodal staging in order to guide treatment, which should include irradiation of any involved regional nodal site. Whether FDG-PET imaging is sufficient to evaluate regional lymph nodes without requiring surgical sampling needs further investigation.

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Figure 1.
In-transit failure based upon site of the primary tumor.

Figure 2.
In-transit failure based upon whether or not patients underwent lymph node sampling and/or nodal irradiation to the in-transit site.

Figures 3a-c.

FDG-PET scan showing FDG uptake in popliteal lymph nodes (a) in addition to uptake within the primary site in the foot (b-c).

Table 1
IRSG Pretreatment Staging Classification

Stage	Sites	Size	Lymph Node	Metastasis
Stage 1	Orbit, head and neck (non-parameningeal), GU (non-bladder or prostate)	All	N ₀ , N ₁ , or N _x	M ₀
Stage 2	Bladder/prostate, extremity, parameningeal, other (trunk, retroperitoneum, etc...)	≤ 5 cm	N ₀ or N _x	M ₀
Stage 3	Bladder/prostate, extremity, parameningeal, other (trunk, retroperitoneum, etc...)	≤ 5 cm > 5 cm	N ₁ N ₀ , N ₁ , or N _x	M ₀ M ₀
Stage 4	All	All	N ₀ , N ₁ , or N _x	M ₁

Table 2
IRSG Postsurgical Grouping Classification

Group I	Localized disease, completely resected, no microscopic residual
a	Confined to site of origin
b	Infiltrating beyond site of origin
Group II	Total gross resection
a	Gross resection with evidence of microscopic local residual
b	Regional disease with involved lymph nodes, completely resected without microscopic residual
c	Microscopic local and/or nodal residual
Group III	Incomplete resection or biopsy with gross residual disease
Group IV	Distant metastases

Table 3
Patient and tumor characteristics

	No. of Patients (%)
IRS Study	
III (1984-1991)	106 (47)
IVP (1987-1991)	26 (12)
IV (1991-1997)	94 (42)
Sex	
Male	100 (44)
Female	126 (56)
Age	
<= 10 yo	143 (63)
> 10 yo	83 (37)
Group	
I	77 (34)
II	63 (28)
III	86 (38)
Stage	
2	80 (35)
3	145 (64)
unknown	1 (0)
Location	
Upper Extremity	95 (42)
Lower Extremity	131 (58)
Histology	
Embryonal	79 (35)
Alveolar	147 (65)
Size	
<= 5 cm	99 (44)
>5 cm	127 (56)
Node sampling (biopsy or dissection)	
Yes	120 (53)
No	106 (47)
Nodal involvement (n=120)	
Yes	45 (38)
No	75 (63)

Table 4**Patterns of In-transit nodal involvement**

Primary Site	Nodal involvement	Group	Stage	Size of tumor	Histology
Hand	Axilla and epitrochlear	3	3	<5cm	Alveolar
Hand	Epitrochlear	2C	3	<5cm	Alveolar
Calf	Popliteal	2B	3	>5cm	Alveolar
Calf	Popliteal	2B	3	>5cm	Alveolar
Calf	Popliteal	2B	3	>5cm	Alveolar

Table 5
Patterns of In-transit failure (n=13)

Upper Extremity (n=95)	
In-transit alone	2
In-transit and Local Failure	1
Lower Extremity (n=131)	
In-transit alone	6
In-transit and Proximal Regional Failure	1
In-transit and Local Failure	2
In-transit and Distant Failure	1