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Local therapy for rhabdomyosarcoma of the hands and feet: Is amputation necessary? A report from the Children's Oncology Group

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Abstract

Purpose—To evaluate the outcome of children with rhabdomyosarcoma (RMS) of the hand or foot treated with surgery and/or local radiotherapy (RT).

Methods—Forty-eight patients with non-metastatic RMS of the hand or foot were enrolled on Intergroup Rhabdomyosarcoma Study Group III, IV-Pilot, and IV. Patients received multi-agent chemotherapy with surgery and/or RT. Twenty-four patients (50%) underwent surgery without local RT, of whom 4 had complete resection and 20 had an amputation. The remaining 24 patients (50%) underwent local RT, of whom 2 required RT for microscopic residual disease following prior amputation. Median follow-up for surviving patients is 9.7 years.

Results—Actuarial 10-year local control is 100%; 10-year event-free (EFS) and overall survival (OS) are 62% and 63%, respectively. Poor prognostic factors for recurrence include gross residual (Group III) disease and nodal involvement ($p=0.01$ and 0.05 , respectively). More patients in the RT group had alveolar histology, Group III disease, and nodal involvement, as compared to the surgery group. There is no difference in 10-year EFS (57% vs. 66%) or OS (63% vs. 63%) between patients who underwent surgery or local RT. Among relapsing patients, there are no long-term survivors. No secondary malignancies have been observed.

Conclusions—Despite having high-risk features, patients treated with local RT achieved excellent local control. Complete surgical resection without amputation is difficult to achieve in the hand or foot. Therefore, we recommend either definitive RT or surgical resection which

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maintains form and function as primary local therapy rather than amputation in patients with hand or foot rhabdomyosarcoma.

Keywords

Rhabdomyosarcoma; local control; radiotherapy; amputation

Introduction

Rhabdomyosarcoma (RMS) accounts for approximately half of pediatric soft tissue tumors in the US with 20% of these cases occurring in the extremity^{1,2}. Survival rates have improved markedly over the last several decades, particularly due to the multidisciplinary studies conducted by the Intergroup Rhabdomyosarcoma Study Group (IRSG) and the Soft Tissue Sarcoma (STS) committee of the Children's Oncology Group (COG) in the US and by others in Europe^{3–9}. The purpose of these studies is to improve survival rates of children with RMS while decreasing treatment-related morbidity and mortality. Through the IRSG studies, poor prognostic factors have been identified that enable risk stratification and risk-based therapy with an emphasis on decreasing toxicity^{10–12}.

Despite advances in therapy, outcome for children with extremity RMS remains inferior to that of more favorable sites^{13–15}. In IRS III, the 5-year survival rate for patients with extremity tumors was 74% as compared to 95% for favorable orbital sites⁵. Preserving functional outcome without compromising cure is of particular importance in RMS of the hands and feet. Although current recommendations for local therapy include complete resection only if function can be preserved, some children still undergo amputation for distal extremity tumors¹⁶. There are sparse data comparing the different local treatment modalities and their efficacy at achieving local control for extremity sites. If primary RT results in equivalent local control and survival to surgery, it should be recommended as an alternative to a functionally debilitating amputation. In this study, we evaluate local therapy and outcome in patients with non-metastatic RMS of the hand or foot on IRS III, IV-Pilot (IVP), and IV.

Methods and Materials

Patients

Eligible patients with non-metastatic RMS of the hand or foot treated on IRS III, IV-P, and IV were analyzed. The eligibility requirements for these studies have been published previously^{5,6,17,18}. All patients were previously untreated, under 21 years, and had histologically-confirmed RMS including the undifferentiated sarcoma subtype. Informed consent was obtained according to National Cancer Institute guidelines. 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 according to Clinical Stage using the IRS pretreatment TNM classification (Table 1) as well as Group after initial surgery according to the IRSG surgical-pathologic system (Table 2)¹⁹. All patients in this study 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. Central review of pathology was conducted by the IRSG pathology subcommittee members.

Treatment

Patients were treated according to previously published IRSG protocols^{5,6,17,18}. Time from surgery to starting therapy is detailed in prior reports. All patients received multi-agent chemotherapy based on IRSG trial, pretreatment Stage, and post-surgical Group^{5,6,17}. In IRS-IV, outcome did not differ based on the various chemotherapy regimens tested and therefore, patients were not stratified according to the chemotherapy regimen on this study^{5,6}. Patients with Stage 2, Group I tumors with embryonal histology received no RT. All other patients with Group I tumors, unless an amputation was performed, and all patients with Group II tumors received 41.4 Gy of conventionally-fractionated RT (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)¹⁸. Since HFRT was not found to change outcome, patients were not stratified according to radiation fractionation¹⁸.

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.

End Points and Statistical Methods

Local control was calculated from start of treatment to time of first failure, defined as disease progression or recurrence at or adjacent to the primary site. Regional failure is defined as disease progression or recurrence within a regional lymph node site as defined by IRSG protocols (epitrochlear, axillary, or infraclavicular regions for the hand and popliteal, inguinal, or femoral for the foot). Event-free survival was calculated from the start of treatment to the time of first event, defined as progression, recurrence, or death from any cause. Overall survival was calculated from the start of treatment to death from any cause. Survival for patients never experiencing an event was censored at time of last patient contact.

Records of all patients were reviewed for toxicity, including secondary malignancy and functional outcome. Follow-up information was obtained from detailed patient flow sheets on IRS III and IVP and post-treatment follow-up forms on IRS IV. Follow-up intervals for functional information were calculated from start of treatment to date of last physician evaluation. Functional outcome was not a primary endpoint of IRSG studies.

Estimates of survival were calculated by the Kaplan-Meier method and comparisons were made using the log-rank test^{20,21}. Cox hazard model univariate analyses were performed for the following factors: age, gender, primary site, histology, tumor size, Stage, Group, nodal involvement, and IRSG study. Multi-variate analysis was not performed due to small number of events.

Results

Patient and Clinical Characteristics

Forty-eight patients with non-metastatic RMS of the hand or foot were enrolled onto IRS III (1984–1991), IVP (1987–1991), and IV (1991–1997). IRS III and IVP were closed on September 1, 2005 and IRS IV was closed on September 1, 2006 with no further follow-up data collected after these dates. The median follow-up was 9.7 years (range, 2.1–19.5 years) among survivors. Patient and tumor characteristics are detailed in Table 3. The median age at study entry was 10 (range 0.1–19) years. Local control was evenly divided between those having surgery only (n=24) and those receiving RT (n=24). Patients treated with RT had either gross total resection at diagnosis (n=13) or biopsy/partial resection at diagnosis

(n=11). By protocol design, the majority of patients who underwent RT had alveolar histology (88%) and Group III tumors (46%) as compared to those who underwent surgery (46% and 13%, respectively).

Local therapy details, including amputation procedures, are detailed in Table 4. Twenty-four patients (50%) underwent local RT (including two who had prior amputation with microscopic residual disease) and thus are considered “RT” for analysis of local treatment modality. The remaining 24 patients are considered “surgery” for local treatment modality. Negative margins at the primary site were achieved for all 24 patients in the surgery group following amputation (20 patients) or complete resection without amputation (4 patients). In total, 22 patients (46%) underwent amputation of the primary site, 19 at initial presentation and 3 at second-look surgery performed 8–21 weeks following start of treatment. Complete surgical resection without amputation was achieved in only 6 patients (13%) in this cohort. Surgery was more often performed on tumors of the feet as compared to tumors of the hands (71% vs. 29%, $p = 0.01$).

Regional lymph node biopsy or dissection was performed in 35 patients (73%); of these, 16 (46%) had lymph node involvement. Although the frequency of lymph node biopsy or dissection was similar between the surgery and the RT groups (79% vs 67%, $p = 0.25$), lymph nodal involvement was more common in patients in the RT group than the surgery group (46% vs 21%, $p = 0.04$).

Treatment Outcome

Median follow-up for surviving patients is 9.7 years. The estimated 10-year EFS and OS rates for all patients are 62% and 63%, respectively (Figure 1). Seventeen patients (35%) recurred: 5 with regional failure only, 8 with distant failure only, 3 with both regional and distant failure, and one with an unknown site of failure. There are no local recurrences. The majority (88%) of failures occurred within 3 years of the start of treatment, with only two late failures at 3.7 years and 9.7 years.

Prognostic Factors for Recurrence and Survival

Patient and disease characteristics predictive of worse EFS and OS in univariate analysis include Group III disease and nodal involvement (Table 5). IRSG study, age, gender, site (hand vs. foot), histology, size, and local treatment modality (surgery vs. RT) are not predictive of EFS or OS. There is no statistically significant difference in EFS and OS between the surgery only and local RT groups. Figure 2 shows a Kaplan-Meier curve of EFS for patients with and without nodal involvement. No second cancers or deaths from causes other than RMS are seen in the patients whose disease did not recur. There are no long term survivors among those whose disease recurred.

Functional outcome

Of the surviving 31 patients, follow up information regarding growth and/or functional outcome is available in 27; of these, 8 underwent amputation, 13 received RT, 2 underwent both amputation and radiation, and 4 underwent complete surgical resection without RT or amputation. According to physicians' evaluations, there is no evidence of significant functional impairment in any of the surviving patients. For the patients who underwent RT, the median follow-up time for evaluation of growth and/or functional outcome is 4.8 (range: 2.3–10.0) years.

In two patients who underwent radiation therapy to the foot, the affected limb is shorter by 1.3 cm and 1.5 cm at 3.9 and 8.3 years follow-up, respectively. In 3 patients who underwent radiation therapy to the hand, slight hypoplasia of the treated tissues was observed. Two

children who underwent RT to tumors of the hand are reported to be active in skiing and karate at 2.8 and 5.4 years follow-up, respectively.

Discussion

Significant progress has been made in the treatment of pediatric RMS, evidenced by the improving survival rates with each subsequent IRSG study^{3–5}. Despite this increase, children with unfavorable prognostic factors continue to fare poorly; the objective of ongoing COG studies is to tailor treatment based upon risk group. The extremity is an unfavorable site often associated with additional poor prognostic factors, such as alveolar histology and regional nodal involvement^{13,22}. In this study, we focused on RMS of the hands and feet because of the unique challenges of treating such a functionally critical site.

Local Control

No local failures have occurred in this cohort with a median follow-up of 9.7 years, regardless of local treatment modality. Despite the RT cohort having more high risk features, including gross residual tumor and lymph node involvement, the local control was 100% for both groups. In addition, there is no statistically significant difference in EFS and OS observed between patients who were treated with RT versus those treated with complete surgical resection, although the number of patients in each subset was small as was the power to detect differences. Current treatment recommendations for patients with extremity sarcomas are for initial complete resection to achieve negative margins if feasible without compromising function, i.e. Group I patients. In cases where aggressive resection is undertaken, careful preoperative planning must be performed. However, complete surgical resection without at least partial amputation was achieved in only 4 patients (8%) in the surgical group and 6 patients overall (13%), highlighting the difficulty of achieving a complete resection in the hand or foot. Due to the anatomic constraints of these sites, wide surgical margins are typically not possible and in most cases, at least a ray amputation is required to achieve a gross total resection.

Alternatively, definitive or adjuvant RT can be a very effective treatment modality without resulting in significant morbidity. Proper positioning and immobilization is required for simulation when irradiating an extremity site and involved nodal regions. Bolus may be required to provide adequate dose to the skin and surgical scar. Radiation dose should be minimized to weight-bearing sites (e.g. ball of the foot), palms and soles, nail beds, and wrist and ankle joints whenever possible. Sparing a strip of normal skin and underlying subcutaneous tissue will avoid circumferential irradiation and decrease the risk of lymphedema. Three-dimensional conformal RT planning techniques should be used to ensure optimal dose homogeneity and coverage. Thus, aggressive surgical procedures such as amputation are no longer justified in the initial treatment strategy in RMS of the hands or feet.

In this series, patients with foot tumors were more likely to undergo surgery than RT, whereas the opposite was true for patients with hand tumors. This is likely due to the surgeon's reluctance to perform an aggressive resection or amputation of a functional hand. Based on these results, we recommend that in lieu of amputation, the treating team instead consider surgical resection if form and function can be preserved with adjuvant RT for microscopic residual disease, or definitive local RT if surgical resection with optimal functional preservation is not possible. Local control is excellent following RT to the hand or foot, sparing a child from a possible functionally and cosmetically debilitating surgery.

Other RMS sites where initial surgical resection is rarely recommended include the orbit, parameningeal sites, and bladder/prostate. In these sites, multi-agent chemotherapy and RT

offer an excellent chance of local control with equivalent survival when compared to aggressive initial resection. The role of debulking surgery remains unclear in many sites, such as the retroperitoneum^{23,24}. Current COG studies are evaluating the role of tumor resection following neoadjuvant chemotherapy. Results from these studies should help clarify the role and timing of surgery in this disease.

Prognostic Factors

Unlike prior RMS reports, age, alveolar histology, size, and stage do not emerge as prognostic factors in our study, which may be due to the small patient numbers. The only two factors that are associated with poor EFS and OS are Group III disease and regional nodal involvement, which have also been reported as poor prognostic factors in previous IRSG studies. Patients in the RT group were more likely to have nodal involvement, Group II/III disease, and alveolar histology based on protocol design. Despite these differences, EFS and OS did not differ between these groups. Local control also was excellent and therefore, radiotherapy could be considered in all patients as a local treatment modality.

In this study, as in IRS IV, Group III patients fared worse than Group I or II patients, and Group I and II patients had similar EFS and OS. Although it is commonly believed that Group I patients have a superior prognosis, IRS IV demonstrated that Group II patients actually fare better than Group I patients. This may be explained by the routine RT that Group II patients receive for microscopic residual disease following resection⁶.

Previous studies in patients with RMS of the extremity have shown that survival is significantly better for patients without regional nodal spread as compared to those whose lymph node status was not evaluated¹³. This is likely due to the inadequacy of clinical assessment of lymph node status. For example, 17% of patients with clinically negative nodes in IRS-IV were found to have microscopic disease¹⁵. Nodal involvement determines both Stage and Group and thus treatment regimen and prognosis. In our study, 46% of patients had pathologic evidence of nodal involvement. This high incidence of nodal involvement confirms the need for nodal sampling at diagnosis to ensure accurate staging and treatment, as is the requirement on current COG studies. We recommend regional nodal assessment with sentinel node biopsy in children with RMS of the extremity^{25–27}. In addition, the initial work-up should include MRI imaging of the entire extremity and regional nodal basin for evaluation of the extent of disease and FDG-PET scans when possible.

In this study, a significant number of patients (n=8) suffered a regional nodal recurrence, 50% of which occurred in an in-transit nodal region. We are currently investigating the incidence of in-transit nodal recurrences to determine the optimal management for patients at risk for this pattern of spread. Based on the in-transit nodal recurrences seen in this cohort, it is clear that these nodal sites need to be adequately evaluated at diagnosis and subsequently treated should they be involved.

Functional Outcome

Assessment of functional outcome was not a primary study objective in the IRSG III, IVP, and IV protocols, thus complications such as altered growth or development may have been under-reported. Prior IRSG studies did not include a standardized method for reporting functional outcome; in this study, information was obtained from reports recorded on flow-sheets. In addition, the length of follow-up is shorter for functional data than for event-free and overall survival as follow-up forms after an extended period of time only captured survival status. Follow-up information was available in 87% of surviving patients in this study over a median of 4.8 years for the RT group and no significant functional deficits were

noted despite slight limb length discrepancy or soft tissue hypoplasia reported in 5 of the 15 patients who underwent local RT. For future study design, it is important for functional outcome to be determined using objective measures, such as used in the National Cancer Institute (NCI) pediatric sarcoma studies, and documented over long periods of follow-up^{28,29}. To optimize functional outcome following treatment, each child should be evaluated by orthopedic and physical therapy specialists, who can design and implement appropriate rehabilitation regimens.

With improved RT techniques and attention towards minimizing dose to sensitive structures, several studies have reported good local control with minimal toxicity and excellent functional outcome following conservative surgery and RT to the hand and foot in both pediatric and adult sarcoma^{30–32}. The NCI investigators reviewed records of 28 children treated with extremity preservation for hand/foot sarcomas³³. Local control for RMS was 100% and all but one survivor were capable of hand/foot function for routine activities without orthotic requirements. As a result, they recommend deferring amputation for management of local recurrences, as a functional hand or foot provides better quality of life than a prosthesis³³. In a review of 41 adult patients, Jyorthirmaya reported major dysfunction in only 3 patients, partly due to surgery, with no grade 3 toxicity (RTOG criteria) in subcutaneous tissue, bone or joints³⁴. Similarly, a more recent study from the University of Florida reported excellent local control (91%) and maintenance of function in all 21 sarcoma patients following limb-conserving treatment³⁵. Ray resection of the hand, whether border or central, can lead to substantial decrease in grip strength and dexterity³⁶. Ray resection in the foot is better tolerated, which is reflected by the willingness of surgeons to perform a limited amputation for local control in the foot³⁷.

Local control following radiation therapy and/or surgery is 100% in our patients with RMS of the hands and feet. Excellent long-term functional outcome has been reported in patients who undergo definitive or post-operative RT in the hand or foot.^{30–32} As a result, we recommend initial local therapy of either definitive RT or surgical resection preserving form and function. If a complete resection risks functional impairment or an amputation, RT should be selected as a more appropriate local therapy. All patients with extremity RMS should undergo imaging of the entire extremity and regional nodal sites with adequate lymph node staging with pathologic confirmation. A multi-modality evaluation prior to treatment is necessary for all children diagnosed with RMS of the hands and feet.

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Figure 1.
EFS and OS for all 48 patients.

Figure 2.
EFS for patients with and without lymph node involvement ($p=0.05$).

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 or N ₁	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 (%)	Local RT (24 total)	Surgery only (24 total)	p-value
IRS Study				
III (1984–1991)	24 (50)	14 (58)	10 (42)	p = 0.02
IVP (1987–1991)	6 (13)	5 (21)	1 (4)	
IV (1991–1997)	18 (38)	5 (21)	13 (54)	
Sex				
Male	23 (48)	9 (38)	14 (58)	p = 0.10
Female	25 (52)	15 (63)	10 (42)	
Age				
≤ 10 yo	25 (52)	10 (42)	15 (63)	p = 0.10
> 10 yo	23 (48)	14 (58)	9 (38)	
Group				
I	20 (42)	2 (8)	18 (75)	p < 0.01 **
II	14 (29)	11 (46)	3 (13)	
III	14 (29)	11 (46)	3 (13)*	
Stage				
2	25 (52)	11 (46)	14 (58)	p = 0.32
3	23 (48)	13 (54)	10 (42)	
Location				
Hand	22 (46)	15 (63)	7 (29)	p = 0.01
Foot	26 (54)	9 (38)	17 (71)	
Histology				
Embryonal	11 (23)	1 (4)	10 (42)	p < 0.01
UDS	5 (10)	2 (8)	3 (13)	
Alveolar	32 (67)	21 (88)	11 (46)	
Size				
≤ 5 cm	36 (75)	19 (79)	17 (71)	p = 0.48
> 5 cm	12 (25)	5 (21)	7 (29)	
Node biopsy/dissection				
Yes	35 (73)	16 (67)	19 (79)	p = 0.25
No	13 (27)	8 (33)	5 (21)	
Nodal involvement				
Yes	16 (33)	11 (46)	5 (21)	p = 0.04 **
No	32 (67)	13 (54)	19 (79)	

* All 3 Group III patients underwent amputation at second-look surgery 8–21 weeks following start of treatment.

** These differences occurred by protocol design.

Table 4

Details of local treatment

Surgery only (24 patients)	Radiation Therapy (24 patients)
9 Complete amputations	11 Definitive RT (Group III)
1 Forequarter amputation of upper extremity	6 tumors of the hand
3 Syme's amputations of the foot	5 tumors of the foot
5 Below-knee amputations	13 Adjuvant RT (Group I or II)
11 Incomplete amputations	11 Microscopic margins (Group II) **
5 Ray amputations of 2–4 digits	2 Complete resections (Group I)
4 hand (digits 2–3, 2–5, 4–5, and 4–5)	
1 foot (digits 4–5)	
5 Ray amputations of 1 digit	
4 border digits of the foot *	
1 border digit of the hand	
1 Pharyngectomy of the hallux	
4 Complete resections without amputation (Group I)	

* Border digits are digits 2 and 5. Central digits are digits 3 and 4.

** Two patients underwent amputations (ray amputation of 3 digits of the hand and 4 digits of the hand) with positive margins (Group II), thus requiring adjuvant RT.

Table 5

Prognostic factors for EFS and OS

	10-year EFS (%)	p-value	10-year OS (%)	p-value
IRS Study				
III (1984–1991)	66	p = 0.39	72	p = 0.42
IVP (1987–1991)	50		50	
IV (1991–1997)	59		55	
Sex				
Male	73	p = 0.32	69	p = 0.30
Female	52		58	
Age				
≤ 10 yo	72	p = 0.28	69	p = 0.24
> 10 yo	50		58	
Group				
I	70	p = 0.01	79	p = 0.02
II	78		76	
III	36		31	
Stage				
2	79	p = 0.05	77	p = 0.07
3	46		51	
Location				
Hand	72	p = 0.31	70	p = 0.30
Foot	53		57	
Histology				
Embryonal	56	p = 0.83	69	p = 0.85
UDS	80		80	
Alveolar	62		60	
Size				
≤ 5 cm	68	p = 0.25	66	p = 0.39
> 5 cm	47		56	
Nodal involvement				
Yes	44	p = 0.05	42	p = 0.05
No	71		75	
Local therapy				
Local RT	57	p = 0.58	63	p = 0.99
Surgery alone	66		63	