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Late events occurring five years or more after successful therapy for childhood rhabdomyosarcoma: a report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group

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Abstract

The aim of our study was to describe late failures in children who initially survived event-free five years from a diagnosis of rhabdomyosarcoma. Charts of children enrolled in the Intergroup Rhabdomyosarcoma Study Group (IRSG) trials III, IV pilot and IV (1984–1997) who survived five years event-free and subsequently experienced an adverse event (disease recurrence, second malignant neoplasm or death from other causes) were reviewed. Of the 2534 enrolled patients, 1160 were event-free at five years and 48 subsequently experienced a late event. The estimated 10-year event rate for the 1160 patients who were alive and event-free at five years was 9% (95% Confidence Interval (CI) 5%, 13%). Patients with both advanced disease (Group III/IV) and large primary tumours at diagnosis (>5 cm) were at the highest risk for late events (19%; 95% CI 8%, 30%). Late events after successful treatment for rhabdomyosarcoma occur in 9%. Those with advanced disease and large primary tumours have the highest risk of late events.

Keywords: Rhabdomyosarcoma; Relapse; Second malignant neoplasm; Failure

1. Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in children and adolescents [1]. With combined modality therapy, approximately 70% of patients are expected to survive five years after their initial diagnosis [2]. As the number of survivors has increased, attention has shifted to the long-term outcomes and consequences of therapy. Although the causes of death among long-term survivors from a variety of cancers have been well described and include recurrent malignancy, second malignant neoplasms (SMNs), and late organ dysfunction [3–7], the frequency and aetiology of late events after successful therapy for paediatric RMS have not been examined comprehensively. Understanding late events is important for counselling and the long-term follow-up of RMS survivors, as well as being useful in evaluating and refining current risk-directed therapies for paediatric RMS [8].

The objectives of this study were to evaluate the prevalence and types of late events in children with RMS treated with contemporary therapies and to examine factors associated with an increased risk of complications.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the records of all children who were treated in three consecutive Intergroup

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Rhabdomyosarcoma Study Group (IRSG) trials: IRSG-III (1984–1991), IRSG-IV pilot (1987–1991) and IRSG-IV (1991–1997) and identified all patients known to be alive and event-free at five years from study entry. We subsequently reviewed the late events in these patients. A late event was defined as disease recurrence (at any location), development of a SMN, or death from any cause as a first event. Disease recurrence was classified as local, regional, or distant.

The documentation of adverse events relied upon reporting from participating institutions. The IRSG protocols called for institutions to report follow-up of surviving patients annually starting in the fifth year following study entry. After the 10th year of follow-up, it was typical for institutions to see patients only every other year. Approximately quarterly, the IRSG Statistical Center informed member institutions of patients whose follow-up was considered delinquent. If institutions indicated that patients had been lost to follow-up, no additional effort to follow these patients was made. No effort was made to use the National Death Index or other death registries to identify deaths among patients who were reported lost to follow-up.

We analysed the relationship between clinical and treatment variables and the occurrence of a late event. The clinical variables examined were age, gender, primary tumour site, tumour size, invasiveness, IRSG Group [9], IRSG Stage [9], and tumour histology. Treatment variables examined were chemotherapeutic regimen and radiation therapy assigned.

2.2. Statistical considerations

To determine event rates, we measured event probability from five years after the original diagnosis to the date of the first event. The Kaplan–Meier method was used to estimate probabilities of an event, and we calculated standard errors according to Greenwood's formula [10]. Cumulative incidence curves were used to estimate the rate of occurrence of particular failure subtypes. Patient subsets were compared using the log-rank test. We used the Cox proportional hazards model to determine predictors of late events. Statistical significance was defined as $p < 0.05$.

All statistical analyses were performed using the SAS statistical program (SAS-PC, Version 8.0; SAS Institute Inc., Cary, NC). Data used in this analysis was current as of January 2001.

3. Results

A total of 2534 eligible patients were entered onto IRSG studies III, IV pilot, and IV between 1984 and 1997. Of these, 1160 were known to be alive and disease-free at five years after study entry. Of the 1374 patients excluded from this analysis, 833 (61%) experienced an event prior to five years, 300 (22%) were enrolled onto the IRSG-IV and censored with up to date data and 241 (17%) were lost to follow-up before five years without apparent failure. Sixty-six percent of the patients not known to have failed during the follow-up beyond five years had been seen within two years of the time the database was frozen for analysis (1/2001), and an additional 19% had dates last seen within four years of that date. Thus, at the time the database was frozen, 85% of patients had been seen within the previous four years. The median follow-up after the five year mark was 3.9 years (range: 0.002–10.9 years). A late event was identified in 48 patients at a median of 2.1 years after the five year mark (range: 0.01–8.9 years). Twenty-two events were recurrent RMS, 17 were SMNs, and nine were deaths due to other causes.

The estimated five year and 10 year event rates for the 1160 patients alive and failure-free at five years were 5% (95% Confidence Interval (CI) 4%, 7%) and 9% (95% CI 5%, 13%), respectively (Fig. 1). The number of subjects followed to five and 10 years were 433 and nine, respectively. The estimated cumulative incidence of the specific subtypes of failures at five and 10 years were 2.4% and 2.7% for recurrence, 1.9% and 2.4% for SMN, and 0.8% and 3.5% for death as a first event. Patients with disease recurrence or a diagnosis of a SMN had a median survival of two years from the event (range: 0.01–7.84 years).

3.1. Demographic and clinical features of the patients with late events

The median age at initial RMS diagnosis for the 48 patients who had late events was 5.5 years (range: 1.3–24.0 years) and 19 (40%) were female.

Table 1 describes the clinical characteristics and treatments received by the 48 patients. Among the 22 patients whose disease recurred, 17 (77%) relapses were local (14 isolated, three combined local and distant), three (14%) were distant only, one (5%) was combined regional and distant, and one (5%) was unknown. Of the same 22 patients, 18 (82%) had Group III or IV disease at diagnosis, 14 (64%) had primary tumours >5 cm, and 17 (77%) were assigned to receive radiotherapy as part of their initial treatment.

Of the 17 patients whose disease recurred late at the initial primary site, all were assigned to receive radiotherapy, but only 12 were known to receive local radiotherapy according to specified protocol guidelines. Two patients did not receive radiotherapy because of young age, two received radiotherapy at lower doses than the protocol specified (30.9 and 35.7 Gy), and the radiotherapy dose was unavailable for one individual who received radiotherapy off-protocol because of a poor response to initial chemotherapy.

Among 17 patients with SMNs, 14 had solid and three had haematological malignancies. The most

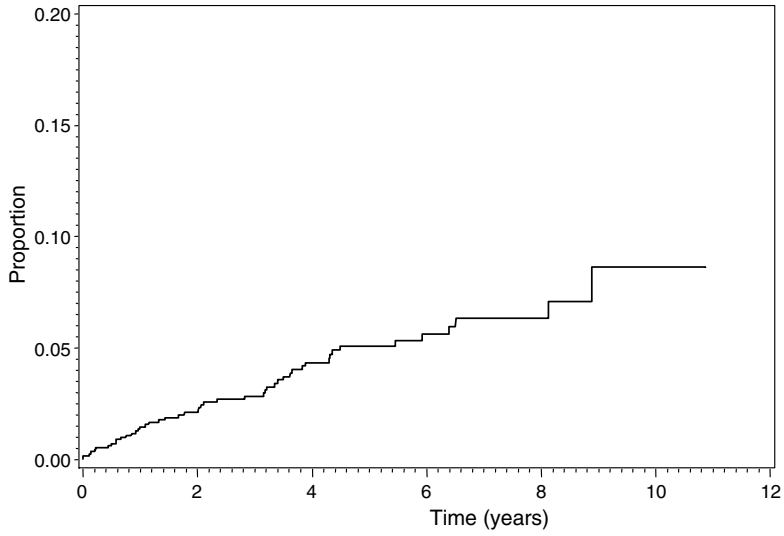

Fig. 1. Probability of experiencing a late event for the 1160 children surviving event-free five years from entry onto study. Time zero on figure is from five years following diagnosis.

common solid SMN was osteogenic sarcoma, occurring in six patients. The remaining cases of solid tumours included two cases of lymphoma (cutaneous and lymphoblastic) and single cases of malignant fibrous histiocytoma, supratentorial primitive neuroectodermal tumour, epidermoid carcinoma, squamous cell carcinoma, cystosarcoma phylloides and unspecified sarcoma. Nine of 14 solid malignancies were known to have occurred within the original radiation field. The three haematological SMNs consisted of two cases of acute myelogeneous leukaemia (AML) and one case of myelodysplastic syndrome (MDS). An abnormal clone from one child with AML had an 11q23 abnormality and a clone from the child with MDS had deletions of chromosomes 5 and 7. Of 17 patients who developed a SMN, 16 (94%) had advanced-stage disease (Group III or IV) at RMS diagnosis, 11 (65%) had primary tumours larger than 5 cm in diameter, and 16 (94%) were assigned radiotherapy in doses ranging from 36 to 61.6 Gy.

Among the nine deaths reported as a first event, five might be related to complications from the previous therapy. Two deaths from cardiomyopathy occurred at 8.9 and 11.5 years from the RMS diagnosis; these patients received doxorubicin at cumulative doses of 480 and 360 mg/m^2, respectively, and the former patient received 45 Gy to the left chest and abdomen to treat RMS arising from the diaphragm. One patient who developed biliary obstruction after surgery and radiotherapy to a hepatic primary tumour died of liver failure at 13.9 years from RMS diagnosis. One death from renal failure at 8.6 years from diagnosis was attributed to previous ifosfamide therapy. One death at 8.3 years was attributed to multiple cerebral arteriovenous malformations in a child who had received cranial irradiation for paranasal RMS. Three deaths were accidental and one individual died of sepsis in apparent complete remission. Among these nine patients, eight (89%) were Group III or IV at diagnosis, eight (data unavailable for one patient) had primary tumours >5 cm in diameter, and eight (89%) were assigned radiotherapy.

3.2. Factors predictive of late event

Table 2 illustrates that five factors were predictive of a late event on univariate analysis: IRSG Group, tumour size, IRSG Stage, primary site and tumour invasiveness. Specifically, the probability of a late event at 10 years after five failure-free years for the 385 patients with Group I or II disease was 2% compared with 12% for the 775 patients with Group III or IV disease ($P = 0.007$). Similarly, the 548 patients with primary tumours >5 cm at diagnosis had a higher estimated event rate of 15% compared with 3% for the 505 patients with primary tumours $\leqslant 5$ cm ($P = 0.002$). On multivariate analysis, only IRSG Group and tumour size were independent predictors of late events.

When Group and size were considered together, the patient subset with both Group III/IV disease and primary tumour >5 cm (comprising 40% of all patients who were failure-free at five years) was found to be at high-risk of experiencing a late event, compared with the remaining low-risk subset (either Group I/II tumours or $\leqslant 5$ cm). The probability of an event at 10 years for high-risk patients was 19% (95% CI 8%, 30%) compared with 3% for low-risk patients ($P < 0.001$, Fig. 2). The estimated failure-free survival for these patient subsets measured from on-study at 5 and 15 years was 55% and 45% for high-risk patients compared with 77% and 75% for the low-risk patients. When high- and low-risk patients were compared, the recurrence risk following

Table 1
Characteristics and treatment assigned to those experiencing a late event after five years event-free[a] ($N = 48$)

Protocol and regimen	Number with recurrence as first late event ($N = 22$)	Number with SMN as first late event ($N = 17$)	Number with death as first late event ($N = 9$)	Number without failure ($N = 1112$)
Clinical variables				
IRSG Clinical Group				
I	2	1	0	206
II	2	0	1	172
III	16	13	6	622
IV	2	3	2	112
IRSG Stage				
1	4	4	0	377
2–4	18	12	8	675
T Stage				
T-1	7	5	2	482
T-2	14	12	7	504
Clinical nodal involvement				
Negative	6	8	1	803
Positive	16	9	8	164
Size				
$\leqslant 5$ cm	8	5	0	493
>5 cm	14	11	8	514
Initial primary site				
Head and neck – non-parameningeal	1	4	0	90
Head and neck – parameningeal	9	3	2	248
Orbit	3	1	0	111
Extremity	3	2	1	162
Bladder/prostate	1	2	2	136
Other	5	5	4	365
Histology				
Embryonal	12	14	7	812
Alveolar/undifferentiated	10	3	2	272
Age (years)				
<1	0	0	0	65
1–9	12	14	7	777
$\geqslant 10$	10	3	2	270
Gender				
Male	12	9	8	673
Female	10	8	1	439
Treatment variables				
IRSG-III (Total)	10	10	7	588
Reg 31 (VA)	1	0	0	
Reg 32 (VA + RT)	2	3	0	
Reg 33 (VAAdr + RT)	1	0	0	
Reg 34 (VAC ± Adr – DTIC + RT)	0	2	0	
Reg 35 (VAdrC + CDDP ± VP16 ± RT)	2	2	3	
Reg 36 (VAdrC ± CDDP/ VP16 + RT)	2	1	3	
Reg 37B (VAdrC + CDDP ± VP16 + RT)	0	1	1	
Reg 38 (VAdrAC + CDDP + RT)	2	1	0	
IRSG-IV pilot (Total)	7	6	1	213
Reg 39A (VAC + RT)	1	2	0	
Reg 39B–H (VAI + RT)	3	1	1	

Table 1 (*continued*)

Protocol and regimen	Number with recurrence as first late event ($N = 22$)	Number with SMN as first late event ($N = 17$)	Number with death as first late event ($N = 9$)	Number without failure ($N = 1112$)
Reg 39C (VIE + RT)	1	2	0	
Reg 39F (I Adr-VAC + RT)	2	1	0	
IRSG-IV (Total)	5	1	1	311
Reg 42 (VAI + RT)	1	0	0	
Reg 43/47 (VIE + RT)	2	0	0	
Reg 44 (VA ± RT)	0	0	0	
Reg 45 (VAC ± RT)	2	1	0	
Reg 48 (VM-VAC + RT)	0	0	1	
Radiotherapy	17/22 (77%)	16/17 (94%)	8/9 (89%)	837/1082 (77%)

Abbreviations: Reg, regimen; V, vincristine; A, actinomycin D; RT, radiotherapy; Adr, doxorubicin; C, cyclophosphamide; DTIC, dacarbazine; CDDP, cisplatin; VP16, etoposide; I, ifosfamide; E, etoposide; M, melphalan; SMN, second malignant neoplasm; IRSG, Intergroup Rhabdomyosarcoma Study Group; H, hyperfractionated radiotherapy.

[a] Columns do not always add up to total because of missing data.

five-years failure-free was similar (5% versus 2%, $P = 0.15$). However, the high-risk subset had significantly higher risk of SMNs (5% versus 1%, $P = 0.009$) and death as the first event (9% versus <1%, $P = 0.005$) compared with the low-risk subset.

4. Discussion

Our study demonstrates that children with RMS who are treated with contemporary protocols and remain event-free for five years after initial diagnosis have a modest risk (9% at 10 years) of late events after the five year time point. The most common late event observed in our series was disease recurrence, which occurred in approximately half of our patients, followed by SMNs and death from other causes as a first event. Although several case reports and small series have documented late recurrence and toxicities of therapy in long-term survivors of soft tissue sarcoma [11–24], this is the first report to examine comprehensively late events in a cohort of children with RMS treated similarly on multi-institutional cooperative group trials.

In this study, rather than examining risk factors for recurrence, SMNs and late deaths separately, we combined them into a single outcome termed an 'adverse event'. The 'adverse-event' free survival is an outcome that is clinically meaningful to families and health-care workers and, ultimately, refers to the proportion of children that will remain well in long-term follow-up.

In this report, we found that the distribution of late events was similar to that observed in other series of paediatric tumours. For example, in one report of 119 late events in children with Hodgkin's disease, 76 (64%) were due to disease relapse or tumour progression, 21 (18%) were SMNs and 22 (18%) were non-neoplastic deaths [25]. In a report from the Childhood Cancer Survivor Study, causes of mortality were examined in subjects diagnosed with cancer before 21 years who had survived five years from diagnosis [3]. This report included 171 deaths among 1641 patients with soft tissue sarcoma, resulting in a standardised mortality ratio of 8.6 (95% CI 7.4%, 10.0%). Overall recurrence of the original cancer was the leading cause of mortality, accounting for 67% of deaths, followed by treatment-related causes including SMNs. That report differs from ours because ours is restricted to patients with RMS or undifferentiated sarcoma who remained event-free for the first five years, while the Childhood Cancer Survivor Study included all soft tissue sarcomas and may have included some who relapsed or developed a SMN within the first five years, but whose deaths occurred after the five year mark. Therefore, the results of these two studies are generalisable to different populations.

Our report emphasises those children with RMS who are treated with contemporary trials and who survive failure-free for at least five years from diagnosis are likely cured of their disease and have a low-risk of death or SMNs over the following 10 years. For those with either resected disease or small tumours who then receive chemotherapy with or without radiotherapy, the likelihood of a late event is only 3%. Therefore, for this subset of children, the risk of late failure is small and we might limit further therapy modifications to decreasing the total therapy duration, cumulative doses of alkylating agents or radiotherapy doses.

Conversely, patients with both large tumours and Group III or IV disease are at a higher risk of late events (19%). Their risk of late recurrence is not statistically significantly different from that of low-risk patients (5% versus 2%) and the observed difference in risk results from more SMNs and late deaths as a first event. This increase in SMNs and late deaths as a first event in the high-risk group may be related to receipt of more aggressive therapy, both drugs and larger doses of radiotherapy, which are required to treat the more advanced disease [26]. However, since it is recurrence that is the most common cause of late events, this suggests that

Table 2
Univariate analysis of factors associated with late failure[a]

Characteristic	Total number of patients	Cumulative failure rate at 10 years (%)	*P* value
IRS Clinical Group			0.05
I	210	2	
II	175	2	
III	654	12	
IV	121	10	
IRS Stage			0.007
1	385	4	
2	205	3	
3	402	15	
4	106	11	
T Stage (TMN)			0.04
T-1	496	7	
T-2	533	11	
Clinical nodal involvement			0.18
Negative	833	9	
Positive	174	8	
Size			0.002
$\leqslant 5$ cm	505	3	
>5 cm	548	15	
Initial primary site			0.035
Head and neck – non-paramengineal	94	7	
Head and neck – parameningeal	263	10	
Orbit	115	5	
Extremity	169	4	
Pelvic	196	0	
Bladder/prostate	141	8	
Other	182	17	
Histology			0.40
Embryonal	825	9	
Alveolar/undifferentiated	255	3	
Age (years)			0.11
<1	65	0	
1–9	811	9	
$\geqslant 10$	174	7	
Gender			0.98
Male	702	8	
Female	458	7	

[a] Columns do not always add up to total because of missing data.

new treatment strategies are needed to prevent these late, primarily local recurrences while avoiding to more SMNs and late organ dysfunction. Thus, further research should also examine predictors of local late recurrence and develop strategies to optimise local control. We had group and size information on 2291 of the 2534 eligible patients. A total of 1032 were both Group III/IV and size >5 cm (45%). This subset made up 40% of the patients who survived to five years failure-free and had known "size" (416/1053). It is proportionally lower than might be expected because fewer of these patients are expected to be failure-free at five years (because they are risk factors for early failure as well).

Follow-up data for patients treated on these studies was actively sought from the participating institutions, and most of the patients included in this report had nearly complete follow-up to the time the database was frozen for analysis. Nevertheless, approximately 15% of patients had follow-up that was more than four years out of date. However, we anticipated that those lost to follow-up would have an adverse event experience similar to the observed patients. In addition, the follow-up period for patients enrolled in IRSG-IV is relatively short and, hence, further late events might be expected with additional follow-up.

These results suggest that researchers should consider altering treatment guidelines in future protocols to

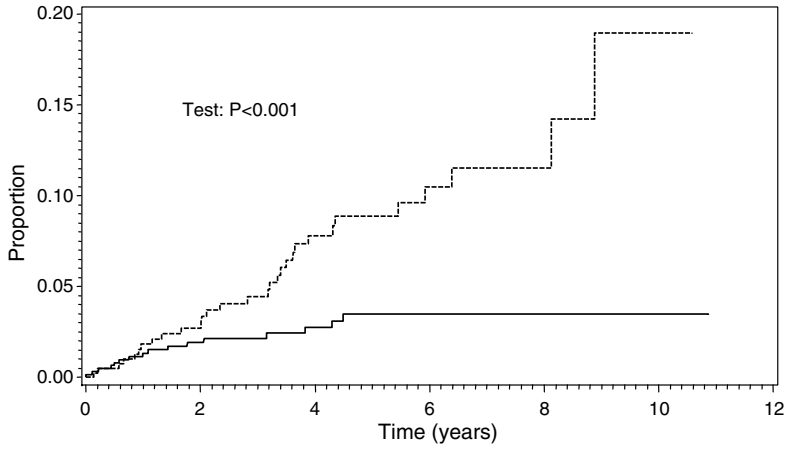

Fig. 2. Probability of experiencing a late event for those with both advanced (stage III or IV disease at diagnosis) and large (>5 cm) primary tumours (dotted line) is higher compared with the remainder of the group (solid line). Time zero on figure is from five years following diagnosis.

diminish the risks of organ toxicity and SMNs. Some modifications have already been incorporated into current therapeutic protocols such as avoidance of doxorubicin and epipodophyllotoxins to decrease the risk of cardiomyopathy [27] and secondary AML [28], respectively. An area that warrants further consideration is whether conformal radiotherapy will decrease late events by decreasing the radiation field size and whether this modification can be made without compromising long-term disease control.

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