RESEARCH PAPER

Pediatric Rhabdomyosarcoma in India: A Single-center Experience

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Objective: Analyze the profile and outcome of children with rhabdomyosarcoma from a pediatric-oncology unit.

Design: Retrospective analysis of case records over 23 years (1990-2012).

Setting: Government-run, tertiary-care, university hospital in Northern India.

Participants: 159 children (<12-years) with a diagnosis of rhabdomyosarcoma were enrolled. The median age was 4 years; 13% were infants.

Main outcome measure: Five-year event free survival.

Results: The median symptom interval was 2-months. Head and neck region was the most frequent site (44%), followed by tumors in the extremity (15.7%). The majority (67%) of the tumors were located at 'unfavorable' sites; 68% were >5 cm in size. The most frequent (58%) pathological subtype was embryonal. Treatment was based on the 'Intergroup Rhabdomyosarcoma Study (IRS) Group' risk-stratification. 33% were 'low-risk' children, 11% were 'high-risk'. Treatment-refusal (18%) and abandonment (33%) were major impediments. The median ± SE five-year event free survival of those taking treatment was 43.6 ± 6%.

Conclusions: Large sized tumors, tumors at unfavorable locations, and treatment refusal/abandonment contributed to inferior outcome in children with rhabdomyosarcoma.

Keywords: *Outcome, Sarcoma, Survival, Treatment refusal.*

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children, with an annual incidence of 4.3/million below the age of 20 years [1]. Multimodality treatment has resulted in a 5-year survival of approximately 67% [2]. The current focus is on reduction of treatment-related toxicity, improving cure-rates for relapsed disease by inclusion of novel agents, and identification of newer prognostic factors for risk-adapted therapy [3].

There is limited data on the outcome of this disease from developing countries, including India [4-6]. The multidisciplinary approach mandated for managing RMS is often a hindrance for orchestrated treatment, as well as data collection in pediatric oncology units in developing countries. Selected studies from India have reported sub-optimal survival (13-25%) [4,5]. The factors contributing to poor survival include, treatment abandonment, infection related mortality, lack of surgical expertise for local disease-control, and failure to deliver chemotherapy in a timely manner due to poor compliance [4-6]. The aim was to analyze the profile and outcome of children with RMS from a pediatric oncology unit. The purpose was to characterize the disease profile in our population and to identify hindrances for improving survival.

Methods

The study was performed in a government-run, tertiary-care, university hospital in Northern India. A retrospective analysis of case-records of children (age <12 years at diagnosis) with RMS presenting to the pediatric-oncology clinic over a 23-year (1990-2012) period was performed after Institutional Ethical Clearance. The patients were classified by the 'Intergroup Rhabdomyosarcoma Study (IRS) Group' staging and grouping system as low, intermediate or high-risk [7]. The IRS 'group' was determined after the initial surgical procedure, prior to systemic therapy and was based on the extent of residual tumor after surgery with consideration of regional lymph node involvement. The IRS 'stage' was based on tumor size, invasiveness, nodal status, and the site of primary tumor. The group and stage were both taken into consideration for the final risk stratification. The favorable sites included orbit, superficial head and neck, biliary tree, vagina, and para-testis; the remaining sites are considered unfavorable [7,8]. The tumor size was based on the largest dimension of the primary tumor reported in the pretreatment imaging. Nodal involvement

was based on physical examination, imaging studies and/or node sampling at surgery. Pathology was classified as 'embryonal,' 'alveolar,' 'pleomorphic' or 'not otherwise specified (NOS).' Molecular tests were not available. Staging investigations included a computed tomography (CT) of the chest and a bone scan. Cerebrospinal fluid (CSF) was examined for para-meningeal tumors. A bone marrow examination was performed for noticeable hematological abnormality, or in the presence of other sites of metastasis. Congenital RMS was defined as presentation within the first month of life with history of onset of symptoms since birth [9].

Treatment included neo-adjuvant chemotherapy, followed by surgical excision (wherever feasible), radiotherapy (for residual disease, if any, and, for inoperable tumors), and adjuvant chemotherapy, based on the Children's Oncology Group (COG) protocols [7]. Low-risk patients received vincristine and actinomycin-D for 22 weeks, while intermediate and high-risk groups were treated with vincristine, actinomycin-D, and cyclophosphamide for the duration of 43-weeks. The specific high-risk protocol was not administered due to apprehension regarding toxicity. The response was evaluated by radiological imaging (CT/Magnetic Resonance Imaging) following week 9-12 of chemotherapy. Survival estimates were calculated using the Kaplan-Meier method. Analysis was performed with SPSS v20.0 (IBM).

RESULTS

The data of 159 patients was collected. The median age at presentation was 4 years (Interquartile range, IQR 2;7). There were 20 (13%) infants; 5 (3%) had congenital rhabdomyosarcoma. Nine (6%) children were >10 years at presentation. The male:female ratio was 2.7:1. The median symptom interval was 2 months (IQR 1;5). Head and neck region was the most frequent site (44%), followed by tumors in the extremity (15.7%) (***Table* I**). Majority (67%) of the tumors were located at unfavorable sites. Size was documented in 101 patients; 69 (68%) were >5 cm. Nodal status was documented in 76 and was positive in 36 (47%). Thirteen (8%) had evidence of metastasis at diagnosis. The most frequent (58%) pathological subtype was embryonal. Information required for risk-stratification was available for 126; low-risk: 42 (33%), intermediate-risk: 70 (56%) and high-risk: 14 (11%) [7]. Of the 129 patients in whom treatment was initiated, surgery was performed in 63 (49%), while 54 (42%) received radiotherapy; 31 (24%) received both.

Caregivers of 28 (18%) patients refused treatment at the outset. In addition, 52 (33%) abandoned treatment at various phases of therapy. The remaining had a mean (SD) follow-up duration of 4.4 (2.6) years (range: 0.5-10), including two patients with ongoing treatment.

Among the 77 patients who completed treatment, there were 36 survivors, 7 with progressive disease, 5 deaths due to febrile neutropenia, and 29 relapses at a median duration of 11 months (IQR 7;15) following diagnosis. The latter received palliative care. Median ± SE five-year event-free survival (EFS) after excluding patients with treatment refusal/abandonment was 43.6 ± 6%. When abandonment/refusal were included as events, the 5-year EFS dropped to 21.3 ± 3.4% (***Fig.* 1**). The last two years (2011-12) demonstrated a similar rate of refusal/abandonment (54% for 2011-12 *versus* 50% for 1990-2010). The survival was site-dependent; favorable sites, including orbit (EFS 57.1 ± 1.8%) demonstrated superior survival as compared to the following primary sites: parameningeal (35.2 ± 1.5%) extremities (36 ± 1.6%) and bladder-prostate (22.2 ± 1.2 %) (P=0.03).

DISCUSSION

The study reports 159 children with RMS over a 23-year (1990-2012) period. Several tumors were >5 cm in size at presentation. The majority were located at unfavorable sites. Treatment refusal and abandonment were major concerns. Overall, a 5-year EFS of 43.6 ± 6% was documented. Orbit as the primary site demonstrated superior survival as compared to parameningeal, extremities and bladder-prostrate primaries.

TABLE I DETAILS OF PATIENTS (N=159) WITH RHABDOMYOSARCOMA

Characteristic	*No. (%)*
Site	
Para-meningeal	33 (20.8)
Extremity	25 (15.7)
Orbit	20 (12.6)
Head and neck: Others	17 (10.8)
Bladder	16 (10)
Pelvic/Abdomino-pelvic	15 (9.4)
Genitourinary(non-bladder/prostate)	13 (8.2)
Trunk	11 (6.9)
Retroperitoneal	3 (1.8)
Biliary	2 (1.3)
Others	5 (3.1)
Histological subtypes	
Embryonal	92 (57.9)
Botryoid variant	6 (3.8)
Alveolar	8 (5)
Pleomorphic	6 (3.8)
Not otherwise specified	47 (29.6)

WHAT IS ALREADY KNOWN?

- Five-year survival for pediatric rhabdomyosarcoma is sub-optimal in Indian centers.

WHAT THIS STUDY ADDS?

- 5-year Event-free Survival of 43.6 ± 6% was observed in Indian patients who received complete treatment.
- Large sized tumors (68%), tumors at unfavorable location (67%), treatment-refusal (18%) and abandonment (33%) were identified as reasons for the sub-optimal outcome.

The limitations of the study include the extended duration of enrollment, precluding uniformity in diagnostic and therapeutic modalities. In addition, high-risk protocol was not administered for likelihood of increasing treatment related mortality. Treatment refusal and abandonment were major predicaments.

The clinical and investigational profile of our patients was comparable to that reported from the West. Prevalence in infants (13%) was similar to previous reports (5-10%) [9]. The median age was consistent with prior SEER (Surveillance, Epidemiology and End-results Program) data, as well as previous reports from India [4-6, 10]. A size exceeding 5 cm has been demonstrated to be predictive of mortality [11]. This could plausibly imply a delayed referral. However, the impact of a delayed diagnosis on the outcome in RMS is ambiguous, plausibly due to the intrinsic biology of the tumor [12]. It is hypothesized that early presentation might signify a more aggressive biology. The proportion of tumors at unfavorable sites (67%) in this study was akin to that reported in a multi-institutional study (55%) [13]. The pathology was embryonal in 58% [14]. Pleomorphic RMS, rarely reported in children (1%), was described in 4% [13]. RMS-NOS was reported in 30%; previous reports noted a lower frequency (13%). This could plausibly be attributed to the pathologists' inability at accurate characterization [13].

Earlier studies from India have reported inferior remission (25%) and cure-rates (13%) [4,5]. Survival in other developing countries, including Nigeria were sub-optimal (28%) [15]. More recent studies have reported encouraging results. Salman, *et al.* [16] from Lebanon reported a 5-year disease-free survival of 64%. A multi-centric study from China reported 10-year EFS of 53.4 ± 5.1% [17]. In 2012, Dua, *et al.* [6] from India reported an improved 5-year EFS of 57.1 ± 13.2% in a limited numbers of patients. The survival is superior in the more developed Asian countries, including Korea (5-year EFS: 59%) and Singapore (5-year EFS: 75%) [18,19]. Non-adherence to treatment has been previously reported from

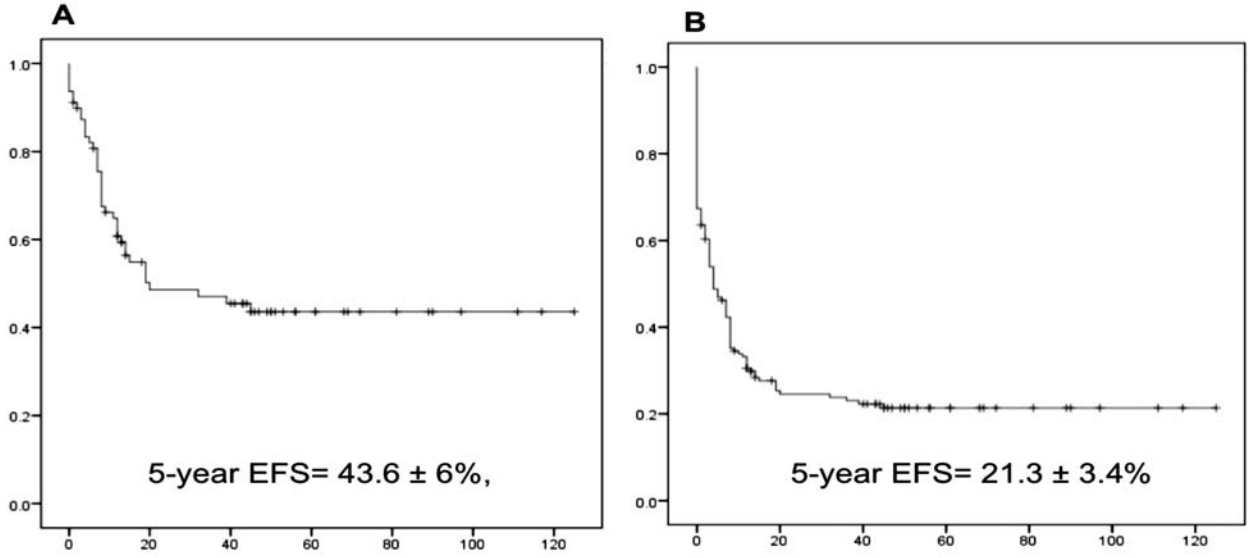

FIG. 1 *Five-year event-free survival in childhood rhabdomyosarcoma: (a) Excluding treatment refusal/abandonment; (b) Including treatment refusal/abandonment as events*.

the two studies from India (30% and 60%) [4,5], and has been a major cause of inferior outcome in the developing world [20,21]. A complex interplay of biological, socio-economic and treatment-related factors underlie the challenge [21].

In conclusion, in comparison to the West, children with RMS from India had an inferior survival despite similar disease characteristics. Treatment refusal/ abandonment were recognized as major impediments to improving outcome. The measures incorporated in the unit in the recent years to reduce abandonment include, repetitive counseling sessions with the extended family as stakeholders, active collection of government funds with the help of social workers provided by non-government organizations, support for nutrition, as well as tracking of defaulters. Incorporation of measures to improve survival need to be studied by future researchers.

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