RESEARCH COMMUNICATION

Rhabdomyosarcoma in Karachi 1998-2002

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Abstract

The epidemiological features of rhabdomyosarcoma (RMS), an uncommon malignancy composed of cells with histopathologic features of striated muscle, were studied in Pakistan. Incident RMS cases recorded at the Karachi Cancer Registry during 1998 to 2004 were reviewed and to ensure maximum completness of data, only those registered between 1998 and 2002 were considered for the present study. Two hundred and seventeen cases were reported to the Karachi Cancer Registry during this five-year period. One hundred and forty eight of the patients (60.4% males; 39.6% females) were residents of Karachi. The crude and standardized annual incidence rates/100,000 were 0.3 for males and 0.2 for females. The incidence was 0.5 in children below 15 years of age. The primary RMS sites in males were head and neck (28.1%), extremities (25.8%), genitourinary (GU) tract (17.9%), trunk (9.0%), orbit (7.9%), and retroperitoneum (3.4%). RMS occurred at other sites in 7.9% of the patients. Corresponding frequencies in females were head and neck (35.6%), extremities (16.9%), GU tract (16.9%), trunk (8.5%), orbit (8.5%) and other sites in 13.6%. Approximately 60% of the cases were childhood RMS and three fourths were below 21 years. The mean age of RMS cases all sites, males, was 18.5 years (95% CI 15.6; 21.4); for childhood RMS, 7.5 years (95% CI 6.0; 9.2); and for adult RMS 34.2 years (95% CI 28.3;40.2). In females, the corresponding figures were 18.2 (95% CI 13.7; 22.7); 6.6 (95% CI 5.0; 8.1) and 33.9 (95% CI 27.5; 40.5), respectively. One hundred cases were retraceable, and the mean survival time, RMS all sites and ages in both genders, was 1.5 years (95% CI 1.1; 1.9). The 5-year survival was 10%, and 3-year survival was 30% whereas 16.7% of the patients died within a year of diagnosis. The indicators of poor prognosis, a late presentation, rapid evolution, advanced disease, tumor burden (tumor size > 5.cms) and regional lymph node involvement, are characteristic of RMS in Karachi.

Recent advances in RMS multimodality treatment protocols have improved RMS prognosis in patients with limited disease. Pakistan should focus on early diagnosis and prompt treatment of malignancies. This requires health education for the general population to create awareness and training of health professionals at all levels to promote early diagnosis. An RMS group is required , which would monitor the treatment, recurrence, patient education and provide psychosocial support. Cytogenetic studies are advised for a better understanding of biologic differences in RMS cases in this population.

Key Words: Rhabdomyosarcoma - Karachi - Pakistan

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Introduction

The objective was to study the epidemiological features of rhabdomyosarcoma (RMS) in Karachi, a city located on the coast of Arabian Sea, latitude: 24 -56'-00" and longitude: 67 -01'-00". RMS, an uncommon malignancy is composed of cells with histopathologic features of striated muscle in various stages of embryogenesis. Classified as a small, round, blue cell tumor of childhood, RMS is derived from primitive undifferentiated mesenchymal cells. It can be divided into 4 major histologic categories: Embryonal (ERMS, 55%), botryoid and spindle cell variants of ERMS (5%), alveolar (ARMS, 20%), and pleomorphic undifferentiated sarcoma (UDS, 20%). RMS accounts for approximately 3.5% of childhood cancers and 2% of cases among adolescents and young adults. (Ries et al., 1999; Gurney et al., 1995) Tumors can arise anywhere in the body except in the bone. Treatment response and prognosis vary

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widely depending on location and histology (Parham, 2001; Newton et al., 1995).

ERMS the most common subtype is observed in children, and accounts for 40-60% of all RMS cases in this age group. (Parham, 2001; Offret et al., 1976) These tumors are most commonly observed in the genitourinary or the head and neck region. ERMS cells show a loss of specific genome material from the short arm of chromosome 11 (11p15.5), suggesting the presence of a tumor suppressor gene. A molecular feature characteristic of ERMS is its lack of gene amplification and a hyperdiploid cellular DNA content. (Gordan et al., 2001; Merlino and Helman, 1999; Scrable et al., 1989; Koufos et al., 1985) The botryoid variant of ERMS is distinguished by the formation of polypoid grapelike tumor masses, and morphologically malignant cells in an abundant myxoid stroma. It is more commonly observed under mucosal surface of body orifices such as the vagina, bladder, nasopharynx, and biliary tract. The spindle cell variant of ERMS is most frequently observed at the paratesticular site (Leuschner et al., 1993).

ARMS is more frequent in adolescents and involves the extremities, trunk, and perianal/perirectal region. Translocation [t(2;13) or t(1;13)], occurs between the transcriptional activation domain of FKHR gene on chromosome 13 and either the DNA-binding domain of the neuromuscular developmental transcription factors, coded by PAX3 gene on chromosome 2 (55%) or the PAX7 gene on chromosome 1 (20%). (Merlino and Helman, 1999; Barr, 1999) The resulting hybrid molecule is a potent transcription activator, which contributes to the cancerous phenotype by abnormally activating or repressing other genes. (Sorensen et al., 2002) ARMS demonstrates gene amplification, and its DNA content is typically tetraploidy. Pleomorphic RMS, the least common of all subtypes, occurs in patients aged 30-50 years. It is rarely observed in children and morphologically cross striations are virtually nonexistent. Other molecular aberrations involved in RMS pathogenesis are p53 mutations (approximately one half of patients), elevated N-myc (10% of patients with ARMS), point mutations in N-ras and K-ras oncogenes (usually embryonal), and elevated levels of insulinlike growth factor-2, suggesting autocrine and paracrine growth factor pathways (Timothy, 2002).

Most cases of RMS occur sporadically with no recognized risk factors, although a small proportion is associated with genetic conditions. (Gurney et al., 1995) These conditions include Li-Fraumeni cancer susceptibility syndrome with germline p53 mutations (Diller et al 1995; Li and Fraumeni 1969), neurofibromatosis type I (Matsui et al., 1993), Beckwith-Wiedemann syndrome (Samuel et al., 1999; Hartley et al., 1988), Rubinstein-Taybi syndrome and Gorlin basal cell nevus syndrome. A higher incidence of congenital anomalies in the genitourinary tract, central nervous system (Arnold-Chiari malformation), gastrointestinal tract and cardiovascular systems is observed in RMS patients. Environmental risk factors include parental use of marijuana and cocaine, intrauterine x-ray exposure, and exposure to alkylating agents (Timothy, 2002).

Computed axial tomography (CT-scan) and magnetic resonance imaging (MRI) typically show a mass adjacent to or attached to muscles, (Hopper et al., 1992) however, the diagnosis of RMS depends on microscopic confirmation. Ultrastructural studies are largely of academic interests and for confirmation of RMS if facilities are available.

Methodology

Incident RMS cases recorded at the Karachi Cancer Registry for Karachi Division (KD), during 1st January 1998 to 30th June 2004 were reviewed. To ensure maximum completion of data, cases registered between 1st January 1998 to 31st December 2002 were considered for the present study. The data were classified using ICD-O2 (International Classification of Diseases-Oncology, 2nd edition) and computerized using a customized version of Canreg-3, with internal checks on the validity of entered data. (WHO 1990) Manual and computerized validity checks for the cancer data were performed as per recommendations of International Agency for Research on Cancer (IARC) and International Association of Cancer Registries (IACR). (Parkin et al., 1994; Skeet, 1991) This involved factors influencing comparability i.e. classification and coding. To ensure validity only histologically verified cases were included in the study. The residency status of cases was re-ascertained and rechecked. People residing in the specified geographical regions for more than six months were considered residents. Demographical variables recorded were the hospital patient-number, date of incidence, name, age, sex, address, ethnicity, topography, morphology, grading and staging. Tumors were categorized according to the UICC, TNM staging system, to standardize with the staging systems in other parts of the world (Lawrence et al., 1997).

Incidence rates were calculated based on the 1998 census for Karachi Division (population of 9,802,134; males 5,261,712, females 4,540,422) assuming an annual growth rate of 3.5% and Karachi South, the southern-most district of the city (population of 1,724,915; males 929,394 and females 795,521), annual growth rate of 1.94%. (Census 1998) The growth rates were based on the inter-census growth-rate and measures for inflow and outflow of population, calculated by the Federal Bureau of Statistics. Standardized incidence rate was calculated with an external reference population, the 'world' population with a given ' standard' age distribution. (Segi, 1960) The methodology applied was direct standardization, using 5-year age groups. The rates given are the annual incidence per 100,000 population, averaged over the number of years for which data are presented. The data were analyzed using EPI 6 and SPSS 10.0.

Results

Two hundred and seventeen cases of RMS were reported to the Karachi Cancer Registry during a five-year period,

1998-2002. One hundred and forty eight cases (60.4% males; 39.6% females) were residents of Karachi Division, the rest were referrals from different geographical locations of Pakistan. The crude and standardized incidence rates for KD and KS were 0.3/100,000 annually (males) and 0.2/100,000 annually (females). The incidence was 0.5/100,000 annually in children, below 15 years of age.

All cases were clinically diagnosed as RMS, and histologically verified. Immunochemistry studies were positive for desmin, vimentin, and HHf35 actin and negative for epithelial markers, (Cytokeratin CAM 5.2 and MNF) and S100. Leucocyte Common Antigen (LCA), PAN B and T, and retinoblastoma markers were used in a few cases of undifferentiated RMS and were negative. Ultrastructural and cytogenetic studies were not conducted on any histopathological specimen.

The most common primary RMS sites in males were head and neck (28.1%), extremities (25.8%), genitourinary (GU) tract (17.9%), trunk (9.0%), orbit (7.9%), and retroperitoneum (3.4%). RMS occurred at other and not otherwise specified (NOS) sites in 7.9% of the patients. Corresponding frequencies in females were head and neck (35.6%), extremities (16.9%), GU tract (16.9%), trunk (8.5%), and orbit (8.5%). RMS occurred at other and NOS sites in 13.6% of patients. (Table 1) The gender-ratio (M: F) was 1.5 for all sites and ages. The range of the gender ratio was 0.6-3.0 as differences existed according to the site of primary disease and age at diagnosis. (Table 2)

Approximately 60% of the cases were childhood RMS and three fourths of the cases were below 21 years. A fourth of the cases were adult RMS with a range of 21-72 years. RMS all sites at presentation showed 37.1% males and 42.3% females were younger than 10 years. (Tables 3 and 4) The mean age of RMS cases all sites and ages, male gender was 18.5 years (95% CI 15.6; 21.4); for childhood RMS cases it was 7.5 years (95% CI 6.0; 9.2); and adult cases it

Table 1. Frequency of RMS by Site and Gender

Gender	Adults		Childhood		All age groups		All RMS
	Males # (%)	Females # (%)	Males # (%)	Females # (%)	Males # (%)	Females # (%)	# (%)
Head and Neck	8 (22.2)	10 (41.7)	17 (32.1)	11 (31.4)	25 (28.1)	21 (35.6)	46 (31.1)
GU tract	3 (8.3)	5 (20.8)	13 (24.5)	5 (14.3)	16 (17.9)	10 (16.9)	26 (17.6)
Extremity	13 (36.1)	5 (20.8)	10 (18.9)	5 (14.3)	23 (25.8)	10 (16.9)	33 (22.3)
Orbit	3 (8.3)	2 (8.3)	4 (7.5)	3 (8.6)	7 (7.9)	5 (8.5)	12 (8.1)
Trunk	3 (8.3)	1 (4.2)	5 (9.4)	4 (11.4)	8 (9.0)	5 (8.5)	13 (8.8)
Retroperitoneum	3 (8.3)	-	-	-	3 (3.4)	-	3 (2.0)
Unspecified sites	3 (8.3)	1 (4.2)	4 (7.5)	7 (20.0)	7 (7.9)	8 (13.6)	15 (10.1)
Total	36 (99.8)	24 (100)	53 (99.9)	35 (100)	89 (100)	59 (100)	148 (100)

Table 2. Gender (M:F) and Childhood: Adult Ratios

M:F Ratio	Adults	Childhood	All age groups	M:F Ratio Timothy C*	Childhood: Adult	
					Male	Female
All sites	1.5	1.5	1.5	1.2-1.4	1.5	1.5
Head and Neck	0.8	1.6	1.2		2.1	1.1
Genitourinary tract	0.6	2.6	1.6	2.1-3.3	4.3	1.0
Extremity	2.6	2.0	2.3	0.79	0.8	1.0
Orbit	1.5	1.3	1.4	0.88	1.3	1.5
Trunk	3.0	1.3	1.6		1.7	4.0
Other sites	3.0	0.6	0.9		1.3	7.0

Table 3. Frequency of RMS (all sites) by Age Group and Gender

Age Group	Males n=89		Females n=59		Total n=148	
	# (%)	C.freq.	# (%)	C.freq.	Freq.	C.freq.
0-4 years	21 (23.6)	23.6	15 (25.4)	25.4	36 (24.3)	24.3
5-9 years	12 (13.5)	37.1	10 (16.9)	42.3	22 (14.9)	39.2
10-14 years	21 (23.6)	60.7	9 (15.3)	57.6	30 (20.3)	59.5
15-20 years	11(12.4)	73.1	8 (13.6)	71.2	19 (12.8)	72.3
21-35 years	9 (10.0)	83.1	5 (8.5)	79.7	14 (9.5)	81.8
>35 years	15 (16.9)	100.0	12 (20.3)	100.0	27 (18.2)	100.0

C.freq – cumulative frequency

was 34.2 years (95% CI 28.3;40.2). In females, the corresponding figures were 18.2 years (95% CI 13.7; 22.7); 6.6 years (95% CI 5.0; 8.1) and 33.9 years (95% CI 27.5; 40.5) respectively. (Table 5) A variation in the incident age, distribution by age group and mean age was observed when results were stratified by gender and primary site of disease. (Tables 1 to 5)

Fifty-eight cases of head and neck RMS, including 12 cases of ocular RMS (ORMS) were reported; these were predominantly childhood and adolescent malignancies in both genders. ORMS originated in the orbit (75.0%), conjunctiva (16.7%) and eyelid (8.3%). Eleven cases presented with proptosis, associated with conjunctivitis in four cases. One case presented with eyelid swelling. Six cases were observed in the right eye, four were observed in the left eye and in two cases, laterality was not specified. Head and neck RMS (excluding ORMS) involved oral cavity and oropharynx (13.1%), face and neck (56.5%), and parameningeal sites (30.4%) which include the paranasal sinuses, nasal cavity, and middle ear. GU tract RMS was entirely a childhood malignancy in males except for a single case of testicular RMS in an adolescent male. In females, uterine RMS was also observed in the sixth and seventh decades. (Table 4) Tumors classified according TNM staging were a stage III disease at presentation in 70% cases.

Hundred cases were retraceable, the mean survival time for these patients, RMS all sites, and ages in both genders was 1.5 years (95% CI 1.1; 1.9). There was a marginal difference in the adult and childhood survival. The survival for childhood RMS was 1.5 years (95% CI 1.0; 2.1) and adult RMS was 1.4 years (95% CI 1.0; 1.9). The 5-year survival was 10%, and 3-year survival was 30% whereas 16.7% of the patients died within a year of diagnosis.

Discussion

The current series is compatible with published data as regards incidence and distribution of cases by primary tumor site or topography, however there is a higher proportion of adult RMS, and a lower survival. The ASR of RMS in Karachi Division and Karachi South was identical. (0.5/ 100,000 or 5 cases per 1,000,000 annually) in children, below 15 years of age and comparable to the US where the ASR is 6 cases per 1,000,000 annually for the same age group.

Table 4. Frequency of RMS by Site, Age Group and Gender

Females	Head & Neck n=21		Extremities n=10		Trunk n=5		GU tract n=10	
	Freq.	C.freq	Freq.	C.freq	Freq.	C.freq	Freq.	C.freq
0-4 years	33.3	33.3	30.0	30.0	20.0	20.0	11.1	11.1
5-9 years	19.1	52.4	-	30.0	-	20.0	11.1	22.2
9-14 years	-	52.4	20.0	50.0	60.0	80.0	22.2	44.4
15-20 years	19.0	71.4	10.0	60.0	-	80.0	11.1	55.5
21-35 years	9.6	81.0	10.0	70.0	-	80.0	11.1	66.7
>35 years	19.0	100.0	30.0	100.0	20.0	100.0	33.3	100.0
Males	Head & Neck n=25		Extremities n=23		Trunk n=8		Utract n=16	
0-4 years	18.2	18.2	21.7	21.7	25.0	25.0	46.5	46.5
5-9 years	27.3	45.5	4.3	26.0	12.5	37.5	-	46.5
9-14 years	18.2	63.7	17.5	43.5	25.0	62.5	46.5	93.0
15-20 years	4.5	68.2	17.5	61.0	12.5	75.0	7.0	100.0
21-35 years	13.6	81.8	12.9	73.9	12.5	87.5	-	-
>35 years	18.2	100.0	26.1	100.0	12.5	100.0	-	-

C.freq-cumulative frequency

Table 5. Mean Age of RMS by Site, Age and Gender

	Adults		Childhood		All age groups	
Males	Mean Age	95% CI	Mean Age	95% CI	Mean Age	95% CI
All sites	34.2	28.3; 40.2	7.5	6.0; 9.2	18.5	15.6; 21.4
Head and Neck	31.4	18.9; 43.8	6.1	3.2; 8.9	17.3	9.2; 25.5
Genitourinary tract	17.0	-	7.8	2.1; 13.6	8.9	3.4; 14.4
Extremity	40.2	27.2; 53.3	7.7	2.4; 13.1	29.4	18.3; 40.4
Trunk	32.0	8.7; 72.7	7.8	0.9; 14.7	16.9	3.6; 30.1
Females						
All sites	33.9	27.5; 40.5	6.6	5.0; 8.1	18.2	13.7; 22.7
Head and Neck	32.2	18.7; 45.8	6.1	2.9; 9.3	19.1	10.1; 28.3
Genitourinary tract	50.0	-	6.3	1.8; 10.8	12.6	3.0; 28.2
Extremity	39.7	20.7; 58.6	7.5	1.4; 13.5	23.6	10.2; 36.9
Trunk	48.0	-	10.3	2.3; 18.2	17.8	3.8; 39.4

(Timothy C, 2002) There is a dearth of published incidence data for RMS, an uncommon malignancy, therefore incidence rates are not a major parameter of comparison. There are few published articles, mostly multi-centre studies, a few registry reports or single case reports of adult RMS. No significant geographic or race predilection has been identified however, a study in Jordan by Al-Khateeb in 2002 identified maxillofacial RMS in Jordanians as a clinically different disease from other populations.

The Karachi data are reliable as all RMS cases were histologically verified, and confirmed based on immunochemistry; morphological confirmation being essential for specific RMS diagnosis. Rhabdomyoblasts rarely exhibit discernible muscle striations under light microscopy therefore immunochemical stains, like desmin, vimentin, and muscle specific actin are used for RMS confirmation, though these stain smooth muscle as well. Myogenin and (transcription factor) MyoD1 are more specific for skeletal muscle. (Parham, 2001) The residency status of patients was verified and non-residents of Karachi were excluded from analyses. Thus, stringent precautions were taken to prevent miscategorization or misdiagnosis in case selection, albeit at the risk of under-registration.

The distribution of cases by primary tumor site was compatible with other published data, which cite head and neck (28%), extremities (24%), genitourinary (GU) tract (18%), trunk (11%), orbit (7%), and retroperitoneum (6%) as the commonest RMS sites. (Timothy C, 2002; Crist et al., 1995; Maurer et al., 1993) Age-related differences exist for different sites of primary disease; two age peaks tend to be associated with different tumor locations. Young patients (2 to 6 years) tend to have head and neck or GU tract primary tumors, while adolescents (14 to 18 years) tend to have extremity, truncal, or paratesticular primaries. Internationally 73% of the GU tract RMS patients are younger than 5 years when there is bladder or prostate involvement. In patients with GU tract RMS without bladder or prostate involvement, 27% are older than 15 years. Forty two percent of the orbit RMS cases are aged 5-9 years. (Timothy C, 2002) In the current series GU tract RMS was predominantly a childhood malignancy in males, however cases of uterine RMS were observed in the elderly, and a third of the RMS trunk, ORMS and extremity cases were observed in adults.

The major difference in our study and other published series is a higher proportion of adult RMS. There was an equal proportion of childhood (below 15 years of age) and adult (above 15 years of age) cases, the childhood to adult ratio being 1.1 in males and 1.4 in females, one fourth of the cases were above 21 years of age. As opposed to this RMS has widely been reported as the most common soft tissue sarcoma in children, which less commonly affects adults. Approximately 87% of patients are younger than 15 years, and 13% of patients are aged 15-21 years. (Timothy C, 2002). A delayed presentation and diagnosis in Karachi could be a plausible reason for an insignificant number of cases, mis-categorized as adult cases, however serious consideration has to be given to the proportion of adult cases that were diagnosed in the third to eighth decade, as late as 72 years of age, and these cases were not recurrences. RMS is definitely rare in subjects older than 45 (Baldi et al, 2004).

The cases were categorized by TNM (tumor, node, metastasis) system which takes the size and location into consideration. The other available options were 'Initial staging system', adopted by the first 3 intergroup RMS studies, and Risk classification (Maurer et al., 1993; Maurer et al., 1988). The 'Initial staging system' groups patients based on extent of disease and completeness of initial surgical resection. As we did not have reliable information of the surgical process and residual disease this system could not be utilized. The UICC TNM staging does not take the extent of surgery into account, thus it was more feasible for our registry system. The risk classifications, is more appropriate for planning treatment options and efforts should be made to classify and treat patients accordingly (Table 6).

Table 6. Risk Classification

Surgicopathologic (clinical)	Group (I-III are for localized disease)
Group I	Tumor completely removed
Group II	Microscopic residual tumor, involved regional nodes, or both
Group III	Gross residual tumor
Group IV	Distant metastatic disease
RMS staging system	
Stage 1	Orbit, head/neck (not parameningeal), and GU tract (not bladder/prostate)
Stage 2	Other locations, N0, or NX
Stage 3	Other locations, N1 if tumor less than 5 cm, N0 or NX (if tumor >5 cm)
Stage 4	Any site with distant metastases
Low-risk patients are those with the following embryonal histology:	
Stages 1-3 in groups I-II (or III for orbit only)	
Stage 1 in group III	
Intermediate-risk patients are those with the following embryonal histology:	
Stages 2-3 in clinical group III (nonorbit)	
High risk	
Stage 4 in clinical group IV if patient is younger than 14 years	

The survival in Karachi is the lowest reported in literature; however, there are not many published survival studies from developing countries for comparison. In the more developed countries, localized disease amongst children is treatable with more than 70% 5-year survival. (Crist et al., 2001; Crist et al., 1993) Recent reports suggest a 90% 5-year RMS survival with current treatments if associated with favorable prognostic factors viz. undetectable distant metastases at diagnosis; primary sites in the orbit and non-parameningeal, head/neck and genitourinary nonbladder/prostate regions; grossly complete surgical removal of localized tumor at the time of diagnosis; embryonal/ botryoid histology; tumor size < or = 5 cm; and age younger than 10 years at diagnosis. With metastatic disease, the 5-year event-free survival rate is less than 30% (Raney et al 2001).

Published series have reported definitively worse results for adults with RMS compared with children; doubt has been expressed whether RMS is the same disease in adults as it is in children In adults 5-year event-free survival and 5-year overall survival (OS) were 28% and 40%. (Ferrari et al., 2003) It is plausible that the higher proportion of adult cases in Karachi may adversely be affecting the survival, yet the survival in children is no better then the adult cases.

Survival is also dependent on biological defects. Cases associated with the PAX7 occur in younger patients and have longer event-free survival rates than those associated with PAX3 gene rearrangements. (Sorensen, 2002) The high incidence of childhood RMS and associated high adult presentation in Karachi may be manifestations of a different genetic pattern, more compatible with a rapid evolution and poor prognosis. As cytogenetic studies were not conducted, the doubt persists.

The indicators of poor prognosis, a late presentation, rapid evolution, advanced disease, tumor burden (tumor size > 5.cms.) and regional lymph node involvement are characteristic of RMS in Karachi. Precious time loss as patients shop around for better treatment modalities, changing clinicians during treatment and in search of faith healers, alternate and miracle treatments are additional more realistically preventable reasons for poor prognosis and high mortality.

Conclusion

There are no known preventive measures for RMS, which in Karachi is a disease with poor prognosis. Recent advances in RMS multimodality treatment protocols have improved RMS prognosis in patients with limited disease. Pakistan should focus on early diagnosis and prompt treatment of cancers. This requires health education for the general population to create awareness and healthcare planning focused on capacity building for training health professionals at all levels to promote early diagnosis An RMS group is required in the country, which would monitor the treatment, the recurrences, patient education and psychosocial support to cope with adverse treatment effects. Cytogenetic studies are advised for a better understanding of biologic differences in RMS cases in this population.

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