Advanced Orofacial Rhabdomyosarcoma: A Retrospective Study of 31 Cases

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Int Arch Otorhinolaryngol 2016;20:207–211.

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Abstract

Introduction Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma encountered in childhood and adolescence. Early diagnosis of pediatric cases is critical to improving outcomes, especially when socioeconomic status and geographical access to specialist services can reduce opportunities for early cancer detection and treatment.

Objective The objective of this study is to determine factors that can delay referral and treatment in specialist pediatric oncology center upon our population specificities.

Methods This retrospective study involved 31 children between 2003 and 2013. Children affected by histologically confirmed RMS occurring as a primary lesion in the orofacial area were included.

Results The median age was 8 $\pm$ 4.22 years (range: 3 months – 15 years). The male to female ratio was 1.8:1. Most of the patients had advanced stage disease at presentation (81.7% group had 3–4 pretreatment staging) with parameningeal involvement in 80.6% of the cases. The 2-year event-free survival rate was 17.7 $\pm$ 7.8% for all the patients. Delay of admission to our unit and abandonment of treatment seem to be important factors for the dismal prognosis.

Conclusion Patient's location, socioeconomic status and health care coverage have had an impact on longer delays in seeking care and on follow-up. More studies are needed for implementation of a better management practices and a better supportive care upon specificities of our population.

Keywords

- rhabdomyosarcoma
- orofacial
- children

Introduction

Rhabdomyosarcoma (RMS) is the most common histologic type of soft tissue sarcoma in children, accounting for 6% of all malignancies in patients under 15 years of age.[1,2] Males have a slight predilection, with a male-to-female ratio of 1.3–1.[3] The most common sites of this tumor in children are head and neck (35%), followed by the genitourinary tract (23%), and extremities (17%).[4] Head and neck locations are anatomically divided into two categories: parameningeal (including RMS of the nose, nasopharynx, paranasal sinuses, middle ear, mastoid, infratemporal fossa, and pterygopalatine fossa) and non-parameningeal (including RMS of the scalp, orbit, parotid gland, oral cavity, oropharynx, and larynx). Oral lesions are uncommon and account for 10–12% of all head and neck RMS cases.[4,5]

Based on the morphologic features and molecular analysis, the current World Health Organization classification categorizes RMS into three main subtypes: embryonal (encompassing the botryoid, spindle cell, and anaplastic variants), alveolar (including the solid variant), and pleomorphic.[6] There are certain distinctive clusters of features regarding age at diagnosis, site of primary location, and histology. Embryonal subtypes are often localized with a favorable prognosis; in contrast, alveolar subtypes present with distant metastasis and less favorable prognosis.

received
June 16, 2015
accepted
September 28, 2015
published online
February 19, 2016

DOI http://dx.doi.org/10.1055/s-0035-1570117.
ISSN 1809-9777.

Despite improved outcomes of children with RMS in developed countries, survival rates of patients in limited-resource countries continue to remain poor.[7] Poverty, illiteracy, advanced stage at presentation, lack of access to health care, and poor treatment infrastructure pose a major challenge in management of cancer in these countries. This paper aims to explore the epidemiological and pathological characteristics among children with orofacial RMS visiting one of the most important pediatric oncology centers of Morocco. The results can help in developing management strategies to improve the outcomes of our patients.

Material and Methods

We performed this retrospective study at a pediatric hematology and oncology unit from January 2003 to December 2013. Our unit is one of the five Moroccan units dedicated to pediatric oncology, where ~350 newly-diagnosed children with cancer receive treatment annually. Despite improvements in recent years, prevention and treatment of childhood cancer continue to face challenges such as absence of standards for the diagnosis and treatment management, inadequate health coverage with high cost of management, lack of information and communication with patients, and unavailability of palliative care and psychosocial support. Hence, more epidemiological studies in these fields are needed in our country for good monitoring and better planning of health services.

For this study, children affected by histologically confirmed RMS occurring as a primary lesion in the oral and orofacial area were included. Exclusion criteria included incomplete clinical data, orbital tumors, reports with doubtful or controversial diagnosis, and cases of non-Moroccan nationals. We retrospectively reviewed medical records, pathology reports, imaging, surgical treatment, chemotherapy, and radiotherapy protocols. Patients were assigned according to the surgical-histopathologic grouping system used in the inter-group rhabdomyosarcoma studies[8] (►**Table 1**), and to the clinical TNM pretreatment staging system based on site, size, clinical regional nodal status, and distant spread, using preoperative imaging and physical findings[9] (►**Table 2**).

Treatment included chemotherapy, surgery, and radiation therapy. Chemotherapy was used for primary cytoreduction and eradication of gross and micrometastases; local therapy (radiotherapy and/or surgery) was performed in residual

Table 1 Surgical-histopathologic grouping system used in the inter-group rhabdomyosarcoma studies[8]

Group I:
Localized disease, completely resected
A- Confined to organ or muscle of origin
B- Infiltration outside organ or muscle of origin
Group II:
Compromised or regional resection, including:
A- Grossly resected tumors with microscopic residual tumor
B- Regional disease, completely resected, with nodes involved, and/or tumor extension into an adjacent organ
C- Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual tumor
Group III:
Incomplete resection or biopsy with gross residual disease remaining
Group IV:
Distant metastases present at onset

Table 2 Soft Tissue Sarcoma Committee of the Children's Oncology Group: Pretreatment Staging System[9]

Stage	Sites of Primary Tumor	T Stage	Tumor Size	Regional Lymph Nodes	Distant Metastasis
1	orbit, head and neck (non- parameningeal), genitourinary organ (not bladder or prostate), biliary tract	T1 or T2	any size	N0 or N1 or NX	M0
2	bladder, prostate, arm or leg, parameningeal region, other (thorax, abdomen, peritoneum)	T1 or T2	a, $\leq$ 5 cm	N0 or NX	M0
3	bladder, prostate, arm or leg, parameningeal region, other (thorax, abdomen, retroperitoneum)	T1 or T2	a, $\leq$ 5 cm	N1	M0
			b, $>$ 5 cm	N0 or N1 or NX	
4	any site	T1 or T2	any size	N0 or N1 or NX	M1

Abbreviations: M0, absence of metastatic spread; M1, presence of metastatic spread beyond the primary site and regional lymph nodes; N0, absence of nodal spread; N1, presence of regional nodal spread beyond the primary site; T1, tumor confined to anatomic site of origin (noninvasive); T2a, tumor extension and/or fixation to surrounding tissue (invasive), tumor $\leq$ 5 cm in maximum diameter; T2b, tumor extension and/or fixation to surrounding tissue (invasive), tumor >5 cm in maximum diameter; X, unknown N status.

tumor cases. Chemotherapy regimens were as follow: vincristine, actinomycin D, cyclophosphamide (VAC); ifosfamide, vincristine, actinomycin D (IVA); vincristine, actinomycin D, doxorubicin (VAD); carboplatin, epirubicin, and vincristine (CEV); vincristine, ifosfamide, etoposide (VIE).

Summary statistics were used to describe the studied population. The estimated survival probabilities were calculated using the Kaplan-Meier method. We valuated event-free survival (EFS) from the date of diagnosis to the date of disease progression, recurrence, or death due to any cause.

Results

Out of 181 patients diagnosed with RMS in our institution between 2004 and 2013, 31 (17.2%) had orofacial location. The median age of patients was 8 ± 4.22 years (range: 3 months – 15 years). There were 20 boys (64.5%) and 11 girls (35.5%); with a male to female ratio of 1.8:1 (►**Table 3**).

When residence location was classified using rural-urban areas, 41.9% of the patients lived in rural areas. The mean distance between the patients' residence and our center of treatment. More than 70% of the patients did not have health care insurance and less than 55% had a low socioeconomic status.

Clinical manifestations of the malignancy varied largely depending on the areas involved in the tumor. The main drivers for patients to seek treatment were accelerated growth of masses resulting in facial disfigurement and development of pain. Median duration of symptoms before referral to our unit was three months (range: 20 days – 9 months). Bony sites (96.7%) were more involved than soft tissues sites (3.3%). Bony sites included the maxillary sinus, ethmoid sinus, body of the mandible, maxillary alveolar process, hard palate, temporomandibular joint, and pterygopalatine fossa. The only case with soft tissue involvement was in the parotid area.

Twenty-four (77.4%) of the 31 patients presented with primary tumors greater than 5 cm in diameter and more than 80% had a parameningeal involvement. According to the Pretreatment Staging System,[9] 19.3% of the patients were stage 2, 58.1% were stage 3, and 22.6% were stage 4 (►**Table 4**).

Regardless of the tumor localization and stage, multidrug chemotherapy regimens were used in all our patients as first line of therapy. Patients with tumors in stage III were treated by chemotherapy in 45.8% of cases or by chemotherapy + radiotherapy in 45.8%, less than 9% received chemotherapy + surgery ± radiotherapy. Patients with stage 4 were treated with chemotherapy exclusively (85.7%), while only 14.3% underwent chemotherapy and surgery (►**Table 5**).

The mean follow-up of all the patients was 11 ± 12.7 months, ranging from 7 days to 5 years. During the first year, deaths occurred in 35.5% of the cases, abandonment of treatment was found in 16.1%. Patients with stage 4 showed a

Table 3 Distribution of patients by selected sociodemographic characteristics ($n = 31$)

Characteristics	Frequency n (%)
Gender	
Male	20 (64.5)
Female	11 (35.5)
Age at diagnosis	
< 1	2 (6.4)
1–4	6 (19.3)
5–9	14 (45.2)
10–15	9 (29.1)
Origin	
Urban	18 (58.1)
Rural	13 (41.9)
Socioeconomic level	
Low	17 (54.8)
Medium	5 (16.1)
High	9 (29.1)
Health insurance	
Yes	9 (29.1)
No	22 (70.9)
Distance between the patient's origin and center of treatment (Km):	
≤ 20	2 (6.4)
21–100	4 (12.9)
101–300	10 (32.3)
> 300	15 (48.4)

Table 4 Tumor characteristics

Characteristics	n (%)
Duration of Symptoms (months)	
≤ 1	1 (3.2)
1–3	16 (51.6)
> 3	14 (45.2)
Tumor location	
Bony sites	30 (96.7)
Soft tissues sites	1 (3.3)
Tumor size (cm)	
> 5	24 (77.4)
≤ 5	7 (22.6)
Parameningeal involvement	
Yes	25 (80.6)
No	6 (19.4)
IRS grouping	
III	24 (77.4)
IV	7 (22.6)
Stage	
2	6 (19.3)
3	18 (58.1)
4	7 (22.6)
Histology	
Embryonal	29 (93.5)
Alveolar	2 (6.5)
Distant metastases	
Yes	7 (22.6)
No	24 (77.4)

Table 5 Distribution of patients with orofacial RMS by type of treatment and stage at diagnosis

Treatment	Stage at diagnosis		
	2	3	4
Chemotherapy	4 (66.7%)	7 (38.8%)	6 (85.7%)
Chemotherapy + Radiotherapy	2 (33.3%)	9 (50.0%)	–
Chemotherapy + Surgery	–	1 (5.6%)	1 (14.3%)
Chemotherapy + Radiotherapy + Surgery	–	1 (5.6%)	–
Total	6 (100%)	18 (100%)	7 (100%)

dismal outcome, with death occurring in 85.7% and abandonment of treatment in 14.3%. Median survival for these patients was less than 5 months. The 2-year event-free survival rate (EFS) was 17.7 ± 7.8% for all the patients (►**Fig. 1**). According to stage, EFS was 41.7 ± 22.2% for stage 2, 21.6 ± 10.9% for stage 3, and 0% for stage 4 ($p = 0.05$) (►**Fig. 2**).

Discussion

Despite the predilection of RMS for the head and neck region, orofacial presentations are rare.[4] In our population, oral and maxillofacial lesions accounted for 17.2% of all cases of RMS. The mean age of 8 years derived from this study is younger than the mean age of 10 from Al-Khateeb et al[5], but is older than the mean age of 4 years reported by Sbeity et al.[10] Males were more affected than females, with a male to female ratio of 1.8:1. Embryonal subtype was largely predominant in our cases (93.5%), supporting previous observations in the oral and perioral region.[5,11,12]

Currently, the majority of our patients present with advanced disease. More than half (58.1%) of the cases presented in stage 3, while 19.3% had stage 2, and 22.6% had stage 4. Tumors more frequently affected the parameningeal sites (80.6%) and had over 5 cm in size for 77.4% of the cases. Furthermore, our patients showed a low survival rate with an EFS of 17.7 ± 7.8% for all the patients after two years.

The advanced nature of these diseases in our patients relates to late presentation. We found significant delays in diagnosis and delays in admission to our center of treatment. Time interval from onset of symptoms to referral to hospital ranged from 20 days to 9 months. This time appears excessive in comparison to previous studies where duration of lesions varied between 2 weeks and 4 months.[10,12] In all delay studies conducted so far, socioeconomic and environmental factors seem to affect access to specialist services and impact the time taken to complete diagnostic investigations. Among our patients, 70.9% of them have access to a Medical Assistance Scheme (RAMED), which covers costs of care in health centers, dispensaries, diagnostic centers, and public hospitals, but does not shoulder the cost of primary diagnosis examinations (i.e., laboratory exams, radiological explorations, molecular biology), which are typically only available in

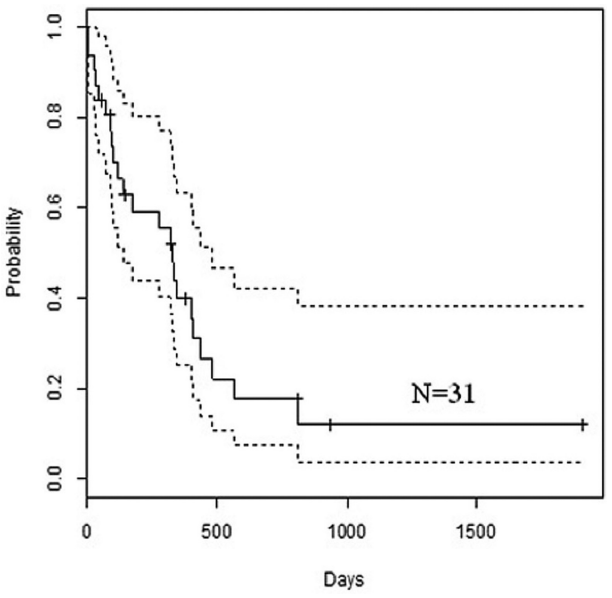

Fig. 1 Event-free survival for patients with orofacial rhabdomyosarcoma.

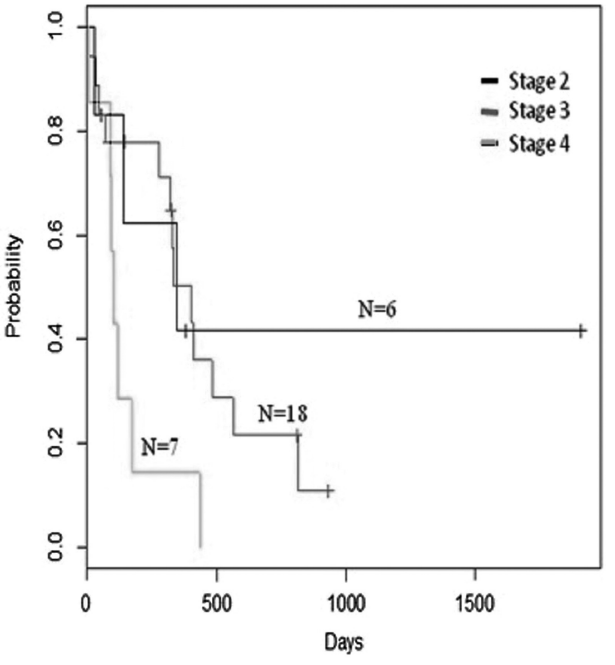

Fig. 2 Event-free survival for patients with orofacial rhabdomyosarcoma by stage at presentation.

private clinics. Populations living far from our hospital face even more obstacles, since traveling to the center of treatment represents a financial cost, in addition to the physical difficulties.

Missed follow-up is another important cause for the dismal prognosis of patients with malignancies in our country. The percentage of patients abandoning treatment in our series was 19.4%. Reasons for abandonment are complex, but often include parental perception of the disease, socio-economic constraints of the families, and access to facilities with appropriate health services. Problems related to transportation and distances and the amount of time required to travel to the treatment center could be other reasons to miss hospital appointments. Regarding our patients, (54.8%) had lower income, (41.9%) are localized in rural areas, and 80.6% are living more than 100 km from our center of treatment.

On the other hand, lack of uniformity in the treatment protocols was another cause of dismal outcome in our advanced cases.[13] Unavailability of some chemotherapy drugs (e.g., ifosphamide), lack of locoregional control when needed, and abandonment of treatment were determinant in treatment failure and relapse. Low income and geographic residency were contributory. Based on these findings, at least three critical lines of actions are needed to improve the prognosis of RMS in Morocco: accessibility to health services for indigent patients with complex needs; reduction of delays between the onset of the first symptoms and the beginning of anticancer treatment, availability of cancer drugs, and use of modern treatment even in resource-limited settings.

Conclusion

This study showed that children with maxillofacial RMS in our institution present late and advanced diseases with a dismal outcome. To enhance the likelihood of disease control, more studies are needed to analyze in detail the distribution delays among patients, practitioners, and the health care system regarding the social and the economic specificities in our population. Improvement of health facilities and use of a multidisciplinary approach are also required.

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