

## **Rhabdomyosarcoma: The Experience of the Pediatric Unit of Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) (from January 1992 to January 2001)**

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### **ABSTRACT**

Our present study is a retrospective analysis of the treatment results of new rhabdomyosarcoma pediatric patients who had attended the pediatric unit clinic of Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) from January 1992 to January 2001).

**Patients and Methods:** Fifty-five new cases of pediatric rhabdomyosarcoma attended the pediatric unit outpatient clinic of (NEMROCK) from the period of January 1992 until January 2001. Patients were divided into 4 stages and classified into low-risk patients and high-risk patients according to the extent of resection. Stage I, II orbital and stage I para-testicular embryonal rhabdomyosarcomas received 32 weeks of vincristine and actinomycin-D (vincristine 1.5mg/m<sup>2</sup> weekly, actinomycin-D 0.015mg/ Kg/day day 1 to day 5). Other pathologies, sites and stages received 52 weeks of chemotherapy. Chemotherapy regimens included VAC (vincristine 1.5mg/m<sup>2</sup> weekly, actinomycin-D 0.015mg/Kg/day day 1 to day 5 and endoxan 2.2gm/m<sup>2</sup> I.V with mesna every 21 days), VAI (vincristine, actinomycin-D and ifosfamide 1.8gm/m<sup>2</sup> I.V day 1 to day 5 with mesna) or VIE (vincristine, ifosfamide and vepesid 100mg/m<sup>2</sup> I.V day 1 to day 5) [11,12]. Stages I and II received conventional fractionation radiotherapy 4140cGy on week 13, stages III and IV received conventional fractionation radiation therapy 5040cGy also, on week 13. The radiation volume included the tumor bed with a 2cm safety margin at least. Relapsing cases received palliative radiation therapy and chemotherapy (cisplatinum I.V 100mg/m<sup>2</sup> divided over 2 days and vepesid 100mg/m<sup>2</sup> I.V day 1 to day 3 to be recycled every 21 days). Patients were followed-up for 5 years, with a median follow-up of 36 months. Overall survival, disease free survival, treatment response, and complications of treatment were assessed and statistically analyzed.

**Results:** Fifty-five new cases of pediatric rhabdomyosarcoma attended the pediatric unit outpatient clinic of (NEMROCK) and were evaluated. Males constituted about

63.6% of the cases (35 cases) and females 36.4% (20 cases). The median age was 6 years and the ages of the patients ranged from 1 to 9 years. Most of the cases were in early stages (40/55 i.e. 72.7%) versus late stages (15/55, i.e. 27.3%). Pathologically, embryonal type was the commonest statistically (48/55, i.e. 87.3%) compared to the alveolar type (7/55, i.e. 12.7%). Concerning site of the primary tumor it was found to be highest in the head and neck (20/55, i.e. 36.4%) followed by abdominal site (23.6%) excluding the genitourinary system which was classified separately because it included pelvis and abdomen (13/55, i.e. 23.6%). The estimated 5-year Failure Free actuarial Survival (FFSR) for the entire study is 68% [n=55; 95% confidence interval (CI), 63% to 73%], and the estimated 5-year overall actuarial survival (OS) rate is 74% (95% CI, 69% to 79%). Twenty cases experienced relapse during the 5 years follow up (i.e. 36.4%). There was no lost follow-up in the selected group of children studied. In addition, only 3 cases showed distant metastasis at the onset of the study. Complete remission (CR) was achieved in 50.9% of the cases.

**Conclusion:** Despite the advances in the therapy of rhabdomyosarcoma. Nearly 30% of the pediatric cases with rhabdomyosarcoma experience progressive or relapsing disease, which has a fatal end. The factors determining the 5-year survival after relapse at the time of initial diagnosis include histological subtype, and disease cluster. These findings will form the basis of a multi-institutional risk adapted relapse protocol for childhood rhabdomyosarcoma patients.

**Key Words:** *Rhabdomyosarcoma - Embryonal - Alveolar.*

### **INTRODUCTION**

The annual incidence of rhabdomyosarcoma (RMS) in children 20 years of age or younger is 4.3 cases per million children, with approximately 350 new cases diagnosed in the United States each year. Among the extra-cranial solid tumors of childhood, RMS is the third most

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common neoplasm after neuroblastoma and Wilm's tumor. Almost two-thirds of cases of RMS are diagnosed in children aged 6 years or younger, with a smaller incidence peak in early-mid adolescence. The tumor is slightly more common in boys and males (11.8 per million) than in girls and females (10.3 per million) [1]. An international study confirmed previous reports of racial and gender differences in the incidence of RMS [2].

Although these tumors may arise virtually anywhere in the body, certain distinctive clusters of features emerge regarding age at diagnosis, site of primary tumor, and histology. For example, head and neck tumors are most common in children younger than 8 years of age. Especially if arising in the orbit, they are usually of the embryonal variety. On the other hand, extremity tumors are seen more commonly in adolescents and are more frequently of the alveolar subtype. A unique form of RMS arising from the bladder or vagina; the botryoid variant (so named because of its resemblance to a protruding cluster of grapes) is seen almost exclusively in infants [2].

The development of increasingly intensive, large-scale, international, collaborative, multimodality therapeutic protocols for treating these tumors, particularly the inter-group Rhabdomyosarcoma Studies (IRS), has led to a steady improvement in the curability of these neoplasms; especially for the group of patients with locally extensive irresectable tumors. Along with the improvements in outcome, there has appeared an increase in both short- and long-term sequelae of therapy [3].

*Aim of the Study:* Is to evaluate the treatment results of pediatric Rhabdomyosarcoma patients treated in our department, and to assess by uni- and multi-variant analyses the most important prognostic factors affecting treatment and prognosis.

## PATIENTS AND METHODS

The present study is a retrospective analysis of the results of treatment of fifty-five new Rhabdomyosarcoma pediatric patients who had attended the outpatient clinic of the pediatric unit of Kasr El-Aini Center of Radiation Oncology and Nuclear Medicine (NEMROCK) from January 1992 until January 2001.

All cases were subjected to various surgical modalities including surgical biopsy, partial excision, and complete excision of the tumor and the diagnosis was confirmed by pathological examination, the patients were divided into favorable histology (FH) which is considered the embryonal subtype and unfavorable histology (UH); considered the alveolar subtype.

All cases were subjected to clinical history taking including family history of the disease and history of consanguinity. Laboratory investigations included complete blood picture (CBC), renal and liver profiles, cerebro-spinal fluid cytology (CSF) in head and neck rhabdomyosarcoma cases. Radiological investigations included chest X-ray (CXR), abdominopelvic sonography, post operative CT scan to exclude recurrence and/or residual disease. Patients were divided into 4 groups according to the clinical staging system employed in the intergroup Rhabdomyosarcoma Studies I through IV (Table 1).

Table (1): Surgical-histopathologic grouping system used in the inter-group rhabdomyosarcoma studies.

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<i>Group I:</i>
Localized disease, completely resected:
A- Confined to organ or muscle of origin.
B- Infiltration outside organ or muscle of origin.
<i>Group II:</i>
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.
<i>Group III:</i>
Incomplete resection or biopsy with gross residual disease remaining.
<i>Group IV:</i>
Distant metastases present at onset.

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Patients were divided into low-risk and high-risk.

*Low-Risk Patients Included the Following Criteria:*

- 1- Favorable histology.
- 2- Stage I and II disease.
- 3- Age ranging from 1-10 years.
- 4- Favorable sites as the orbit, paratesticular area, head and neck excluding infratemporal

and parameningeal regions and the genitourinary tract with exclusion of the urinary bladder and prostate [4-7].

*High Risk-Group Included the Following Criteria:*

- 1- Unfavorable histology.
- 2- Stage III, IV disease.
- 3- Age >10 years.
- 4- Unfavorable sites as para-meningeal, retro-peritoneal sites and extremities especially with alveolar histology [4-7].

Patients with stage I, II orbital and stage I para-testicular area embryonal disease received 32 weeks of vincristine 1.5mg/m<sup>2</sup> weekly, actinomycin-D 0.013mg/Kg day 1 to day 5 every 21 days without radiation therapy [8]. Patients with other sites received 52 weeks of chemotherapy and radiation therapy on week 13 with 4140cGy for stage I and II, and 5040cGy for stage III and IV by conventional fractionation radiation therapy (CFR) and the treatment volumes included the tumor bed and a 2cm safety margin at least [9,10]. Chemotherapy regimens included VAC (vincristine 1.5mg/m<sup>2</sup> weekly, actinomycin-D 0.015mg/Kg/day day 1 to day 5 and cyclophosphamide 2.2gm/m<sup>2</sup> I.V with mesna every 21 days), VAI (vincristine, actinomycin-D and ifosfamide 1.8gm/m<sup>2</sup> I.V day 1 to day 5 with mesna) or VIE (vincristine, ifosfamide and etoposide 100mg/m<sup>2</sup> I.V day 1 to day 5) [11,12].

Relapsing cases received palliative radiation therapy and second line chemotherapy (cisplatinum I.V 100mg/m<sup>2</sup> divided over 2 days, vespid 100mg/m<sup>2</sup> I.V day 1 to day 3 to be recycled every 21 days) for 6 cycles [13].

The patients were followed-up every 3 months for 5 years with a median follow-up period of 36 months by chest X-ray, abdominopelvic sonar, C-T scan, cerebrospinal fluid cytology for head and neck cases and liver and kidney profiles. The overall survival, (time from date of diagnosis until date of death or last follow up), disease free survival (DFS time from date of complete response until time of documented radiological and clinical relapse) and complications of treatment were assessed according to the WHO criteria [1] and statistically analyzed. Correlation between various prognostic factors with survival and disease free survival (DFS) was done.

The response to treatment was assessed whether complete response, CR (complete resolution of the original disease), partial response, PR (>50% reduction of the original disease), stable disease and disease progression.

*Statistical Methods:*

The Kaplan Meier method was used to estimate overall survival and disease free survival. Assessment by uni- and multi-variant analyses the most important prognostic factors affecting treatment and prognosis. The log rank test was applied to compare the different groups (*p*-value is significant at 0.05 level) [14].

## RESULTS

This study included 55 cases of pediatric rhabdomyosarcoma and we found that; the most common age was between 1 and 9 years old (36/55, i.e. 65.5%). In addition, it has been found that this disease is significantly higher in boys (35/55, i.e. 63.6%) than girls (20/55, i.e. 36.4%). Concerning the site of the primary tumor it was found to be highest in the head and neck (20/55, i.e. 36.4%) followed by abdominal sites (23.6%) excluding the genitourinary system (13/55, i.e. 23.6%) which was classified separately because it included the pelvis and the abdomen. Pathologically, embryonal type was the commonest statistically (48/55, i.e. 87.3%) compared to the alveolar type (7/55, i.e. 12.7%). The size of the tumor was found to be ≤5cm in 25 cases (45.5%) and >5cm in 30 cases (54.5%). Regarding the various stages, this disease was diagnosed in most of the cases in early stages (40/55, i.e. 72.7%) versus late stages (15/55, i.e. 27.3%). This is because the most common site here in this study was the head and neck, which causes early parental notification (Table 2).

Concerning treatment, Table (1) mentioned earlier showed the classification according to surgical procedures. Added to that, 19/55 (34.5%) were treated by radiotherapy.

*Regarding Response to Treatment:* 41/55 (74.5%) were responders in the form of 28 (50.9%) achieving a complete response and 13 (23.6%) with partial response. While disease progression was reported in 12 cases (21.8%). Out of those responders 20/41 (48.8%) showed relapse during the 5 years of follow up. Mainly within the first 30 months post treatment: 15 as local failure and 5 as distant metastasis.

Table (2): Demographic data of the study group.

Factor	Number	Percentage
<i>Age:</i>		
<1 year	3/55	5.4
1-9 years	36/55*	65.5
≥10 years	16/55	29.1
<i>Sex:</i>		
Male	35/55	63.6
Female	20/55	36.4
<i>Site of tumor:</i>		
<i>Head and neck:</i>		
Nasopharynx	20/55*	36.4
Orbit	8/55	14.5
Nose	4/55	7.3
Ear	3/55	5.4
Parotid	3/55	5.4
<i>Abdominal:</i>	13/55	23.6
Retroperitoneal	7/55	12.7
Trunk	3/55	5.4
GIT	3/55	5.4
Genitorurinary	13/55	23.6
Peripheral	9/55	16.3
<i>Tumor size:</i>		
≤5cm	25/55	45.5
>5cm	30/55	54.5
<i>Pathological:</i>		
Embryonal	48/55*	87.3
Alveolar	7/55	12.7
<i>Stages:</i>		
<i>Early:</i>		
I	40/55*	72.7
II	2	3.6
II	38	69.1
<i>Late:</i>		
III	15/55	27.3
IV	12	21.8
IV	3	5.4
<i>Risk:</i>		
Low	12/55	21.8
High	43/55	78.2
<i>Surgical:</i>		
Biopsy	23/55	41.8
Incomplete (removed but residual in margins or LNs)	17/55	30.9
Complete	15/55	27.3
Adjuvant radiotherapy	19/55	34.5
<i>Response:</i>		
Complete response (CR)	28/55	50.9
Partial response (PR)	13/55	23.6
Stationary disease (SD)	2/55	3.6
Disease progression (DP)	12/55	21.8
<i>Relapse:</i>		
Local	15	27.3
Distant	5	9

\* $p < 0.05$  between this factor and the rest of the following rows.

The estimated 5-year disease free actuarial survival (DFS) for the entire study was 68% [n=55; 95% confidence interval (CI), 63% to 73%], and the estimated 5-year overall actuarial survival (OS) rate was 74% (95% CI, 69% to 79%). Twenty cases experienced relapse during the 5 years follow up (i.e 36.4%). There was no lost follow-up cases in the selected group of children studied (Fig. 1). In addition, only 3 cases showed distant metastasis at the onset of the study.

#### *Uni-Variant Analysis of Total Actuarial Survival:*

On the other hand, according to grouping, it has been found that survival in group I (at 30 months) was found to be 100% (CI=100%), 89% in group II (CI=84-94%) and 79% in group III (CI=75-83%) with a statistically significant difference between the three groups (Fig. 2). On the other hand, total actuarial survival according to pathological type and groups showed statistically higher survival for embryonal type compared to alveolar type. I.e. children with embryonal histology and treated by complete surgical excision with free surgical margins and -ve LNs showed the highest survival (100%) compared to the rest. However, if surgical margins or LNs showed microscopical residual as seen in group II or III, the embryonal histology showed statistically higher values of survival compared to those with alveolar histology (95%, CI=93-97% and 83%, CI=79-87% respectively versus 83%, CI=79-87% and 77%, CI=71-83%) ( $p < 0.05$ ) (Figs. 3,4).

#### *Uni-Variant Analysis of Failure Free Survival:*

According to grouping, it has been found that FFS was statistically higher in group I (FFS 95%, CI=90-100%) compared to group II (FFS 85%, CI=81-89%) ( $p < 0.05$ ) and group III (FFS 65%, CI=55-73%) ( $p < 0.001$ ). On comparing group II and III, the  $p$  value was  $< 0.01$  (Fig. 5).

On the other hand, when histological types were added to the grouping, it was found that the failure rate increased in the three groups with the note that, in group I; it was of marginal statistical difference between the embryonal type (FFS 96%, CI=92-100%) and alveolar type (FFS 85%, CI=79-91%) ( $p = 0.05$ ), whereas, it was statistically higher for group II (FFS

90%, CI=82-95% versus FFS 77%, CI=69-82% and  $p < 0.01$ ), for group III the difference was insignificant (FFS 78%, CI=74-82% versus FFS 72%, CI=67-77% respectively, and  $p > 0.05$ ). Meanwhile, the difference between the FFS for group II and III was insignificant in the embryonal histology but it was statistically significant in the alveolar type (Figs. 6,7).

**Radiotherapy and Children of Groups II & III:**

Nineteen cases of both groups had been treated with conventional radiotherapy and it had been found that radiotherapy had no effect on the total actuarial survival when compared with those children not treated with radiotherapy (OS 85%, CI=78-92% versus OS 79%, CI=69-89%; and  $p > 0.05$ ). On the other hand, radiotherapy affected the failure free survival period where the incidence of failure was statistically higher in patients not treated with radiotherapy (FFS for those treated with radiation was 84%, CI=80-88% versus 69% for the non-irradiated, CI=64-74%,  $p < 0.05$ ) (Figs. 8,9).

**Relapse and End Point Results:**

It has been found that failure affected survival significantly in such a way that local failure made a significant drop in total actuarial survival from 90% (CI=87-93%) to 80% (CI=75-85%) (with  $p < 0.001$ ) with a further statistical significant drop in total actuarial survival with distant metastasis to be 44% (CI=39-49%) ( $p < 0.001$ ) (Fig. 10).

**Multivariate Analysis:**

Multivariate analysis showed that the most predictable favorable factors in the management of rhabdomyosarcoma were, type of surgery (grouping in this study), histology, staging of the disease and favorable primary sites (head and neck, and genitourinary tumors). This can be summarized in Table (3).

From the above table, children of group I with embryonal histology and favorable primary sites showed the highest overall survival of 88% (CI=85-91%), and survival significantly dropped to 74% when the cases had unfavorable sites of disease (70-78%). Similarly, survival significantly dropped in children with alveolar histology. What is more important that the unfavorable sites affected significantly children of group III who suffered a significant drop in survival in both histology types, from a survival of 74% and 62% to 38% and 25% respectively.

**For Failure Free Survival, Multivariate Analysis Showed:**

The most important predictive favorable factors for FFS included a tumor size less than 5cm, ( $p = 0.001$ ) early stages, (I and II) ( $p = 0.01$ ), favorable primary sites, (of head and neck and genitourinary) ( $p = 0.001$ ) and radiotherapy treatment ( $p = 0.01$ ). On the other hand age, ( $p = 0.44$ ) sex, ( $p = 0.90$ ), and histology ( $p = 0.30$ ) were not predictive of FFS.

Table (3): The most predictable criteria of actuarial survival.

Histology lry site	Group I	p1	Group II	p2	Group III	p3
<i>Embryonal:</i>						
Fvorable	88% (85-91%)	=0.05	78% (73-83%)	>0.05	74%@ (68-80%)	<0.01
Unfavorable	74%* (70-78%)	<0.01	55%* (47-63%)	<0.05	38%* (30-46%)	<0.001
p4	<0.05		<0.01		<0.001	
<i>Alveolar:</i>						
Favorable	83% (78-88%)	=0.05	72% (66-78%)	<0.05	62%@ (53-71%)	<0.0001
Unfavorable	58%* (51-65%)	<0.05	44%* (36-52%)	<0.01	25%** (20-30%)	<0.001
p5	<0.01		<0.01		<0.001	

p1 between group I and II, p2 between group II and III, p3 between group I and III, p4 between favorable and unfavorable of embryonal (first and second rows), similarly p5 for alveolar (third and fourth rows).

\* $p < 0.05$  on comparing between unfavorable embryonal and alveolar histology in the same column except the last item which shows  $p (**)$  <0.01. @ $p < 0.01$  on comparing between the favorable embryonal and alveolar histology in group III.

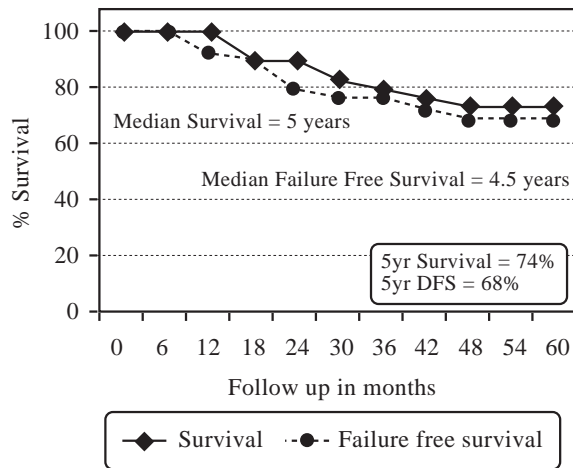


Fig. (1): Total actuarial survival and failure free survival of all cases.

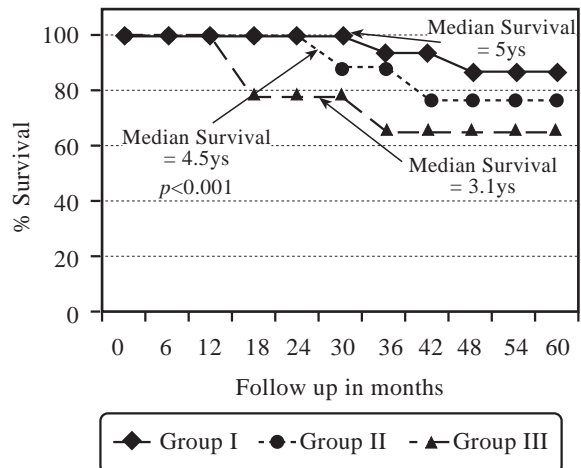


Fig. (2): Total actuarial survival according to patients groups.

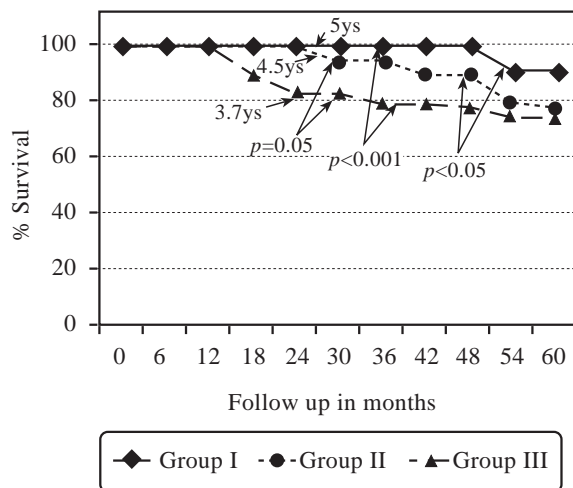


Fig. (3): Total actuarial survival according to patients groups with embryonal histology.

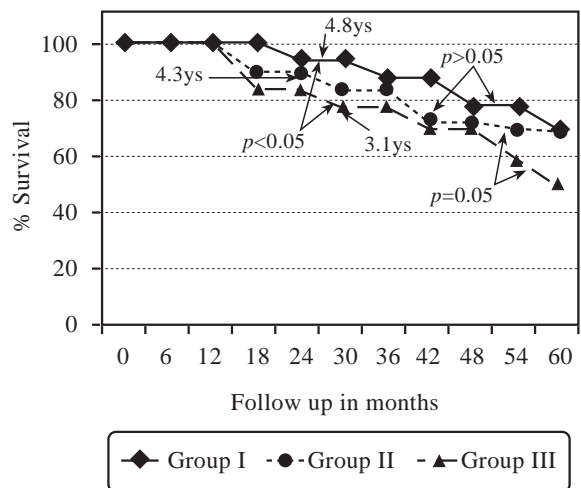


Fig. (4): Total actuarial survival according to patients groups with alveolar histology.

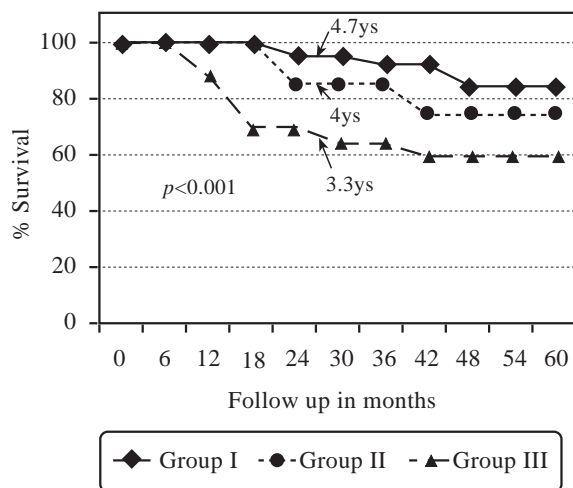


Fig. (5): Failure free actuarial survival according to patients groups.

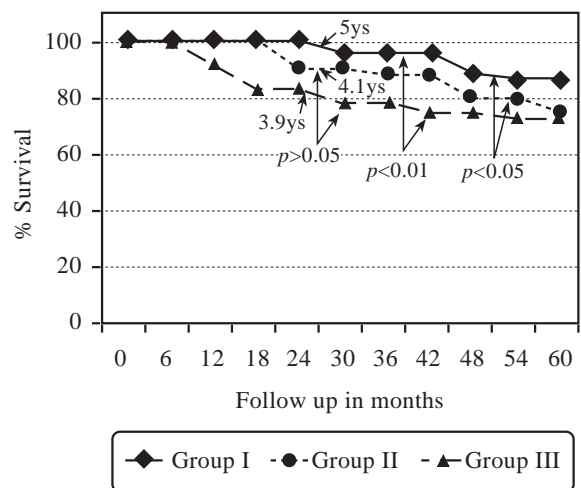


Fig. (6): Failure free actuarial survival according to patients groups with embryonal histology.

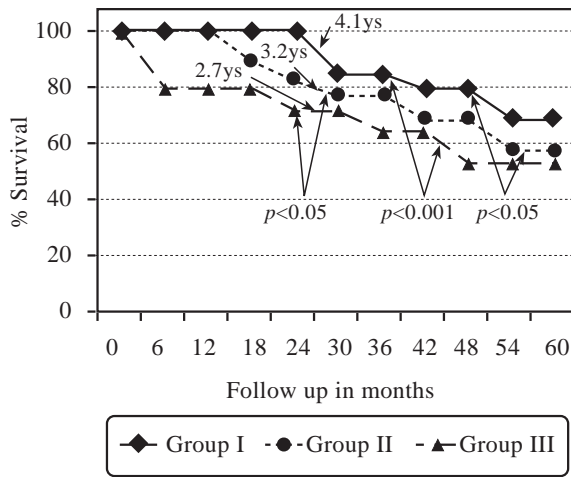


Fig. (7): Failure free actuarial survival according to patients groups with alveolar histology.

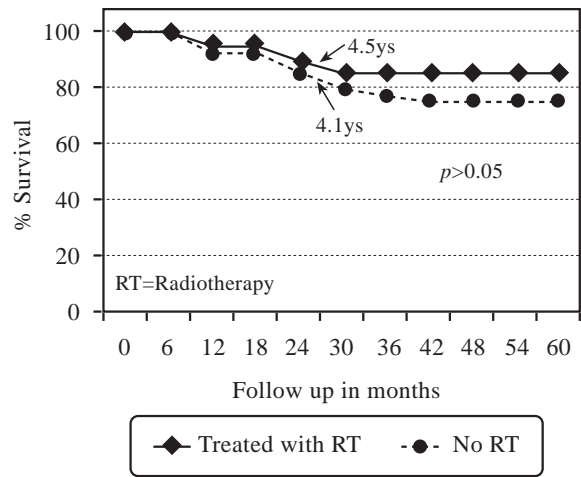


Fig. (8): Total actuarial survival of patients of groups II and III according to treatment with or without radiotherapy.

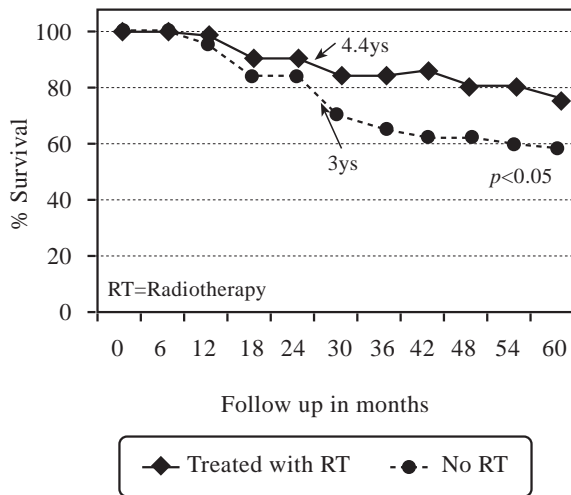


Fig. (9): Failure free survival patients of groups II and III according to treatment with or without radiotherapy.

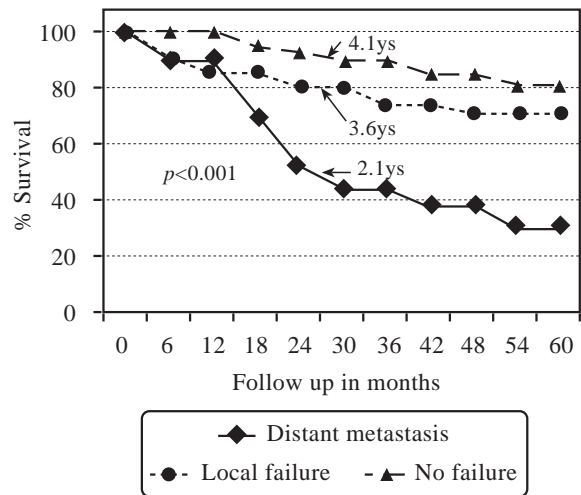


Fig. (10): Total actuarial survival according to presence or absence of relapse and its site.

### DISCUSSION

In our current study; males constituted 63.6% of the cases (35 cases) and females constituted 36.4% of the cases (20 cases) and history of consanguinity was present in 5.45% of the cases (3 cases). These results are close to the work of Ruymann and Groves where males constituted 71.4% of the cases and females 28.6% of the cases; and history of consanguinity was present in only 9% of the cases [15].

In the present study the most common site of involvement was the head and neck 36.4% (20/55), followed by the abdomen and the genitourinary tract, which each had the same inci-

dence of 23.6% (13/55), and finally the extremities 16.3% (9/55). This contradicts the work of Akyuz and associates where the pelvi-abdominal area was the most common site of involvement (29%), followed by the extremities (15%), and then the trunk and the lung (5%) [16]. Moreover, Nakada found that the most common site of involvement was the pelvis (27.3% of cases), then the abdomen (23.8%), and then the head and neck (21.4% of cases) [17]. This observation could be explained by differences in sample size between the two studies.

In our present study stage I cases constituted about 3.6% of the cases (2 cases), stage II 69.1%

(38 cases), stage III 21.8% (12 cases) and stage IV 5.4% of the cases (3 cases). Contrary to that, Raje and Raosr who performed a similar study stated that stage I cases constituted about (10%) of the cases, stage II cases (62.7%), stage III cases (20.2%) and stage IV cases (7.1%) [18].

In the present study, embryonal histology constituted about 87.3% of the cases (48 cases) and alveolar histology 12.7% of the cases (7 cases). Unsimilar to the work of Callender et al., where embryonal histology constituted about (43.2%) of the cases, alveolar histology (40.5%) of the cases, mixed histology (2.7%), and unclassified histology in (13.5%) of cases [19].

In the present study stage I, II orbital and stage I paratesticular disease cases with favorable histology; received 32 weeks of vincristine, and actinomycin-D. Other sites received 52 weeks of chemotherapy VAC, VAI or VIE. On the other hand radiation therapy was given on week 13 with 4140cGy for stage I & II, and 5040cGy for stage III & IV by conventional fractionation radiation therapy (CFT) and the treatment volumes included the tumor bed and a 2cm safety margin at least [9,10]. This coincides with the work of Crest and associates, where early stage orbital and para-testicular area disease received vincristine and actinomycin-D, other stages received VAC, VAI or VIE, radiation therapy was also given at a dose of 35-54 cGy according to stage [20].

In the present study the 5-year overall survival was 74% and disease free survival was 68%, in comparison to the work of Crist et al., where the 5-year survival was 77% and 4-year DFS was 76% [20]. Also, with the work of Flamant et al., who attained a 5-year overall survival of 68% and a 5-year DFS of 55% [21].

In our present study the 5-year, overall survival for embryonal histology was 80.6% and 65% or alveolar histology; these results correlate with the work of Pappo et al., where the 5-year survival for embryonal histology was 64%, and for alveolar histology, it was 26% [22].

The 3-year overall survival for patients with ages less than 10 years was 55.7% and for those more than 10 years it was 45.5%. These figures were similar to the work of La Quaglia and colleagues [23] and the work of Arndt and associates [24]; where the age of the patient whether

less than 10 years or more than 10 years had an impact on the 3-year survival. All the studies agreed that patients aged 1-9 years had the best 5-year survival (with results ranging from 81-98%). This work also resembles the work of Crist et al. [20] where patients with paratesticular primaries had poorer outcomes if they were more than 10 years of age. The 3-years DFS was 63% for patients older than 10 years; versus 90% for patients less than 10 years of age. This work also coincides with the work of Chin and Wei [25] who stated that long-term survival was noticed with patients younger than 10 years of age. The work coincides with the work of Simon et al., who stated that patients younger than 11 years of age have the best overall survival [26].

In our present study, the 3-year overall survival and DFS for favorable sites was 51% and 50%. Whereas, it was 23.08% and 20% for unfavorable sites respectively. This goes with the work of Flamant et al. [21] where the 5-year survival for favorable sites was 86% and the 5-year DFS was 52%. In addition, Akyuz et al., found that the overall 10-year survival for pediatric rhabdomyosarcoma patients was 42% and the best results were obtained in patients with orbital and genitourinary sites, especially with stages I-II and 1 to 5 years of age cases [16]. Contradictory to our results was the work of Ruymman and Grovas where they found no significant difference in survival among patients with favorable and unfavorable sites [15].

In the present study the 5-year overall survival and DFS for groups I, II, and III was 86%, 77% and 65% respectively; this coincides with the work of Neville and colleagues [27] where the 5-year survival for group I RMS was 70%, for group II it was 65% and for group III it was 55%. In addition, the work coincides with the work of Akyuz et al., who reported the best survival results for patients with stages I and II [16].

In our present study, the 5-year survival for patients receiving radiotherapy was 84%, and for patients receiving no radiation therapy it was 74%. This resembles the work of Oberlin et al. [28] who stated that there is no difference in overall survival regarding the implementation of radiation therapy as a part of initial treatment. However, Wolden et al. [9] who conducted a pediatric rhabdomyosarcoma study; stated that

patients with alveolar histology who received radiation therapy had a greater 10-year survival (82%) versus those who did not receive radiation therapy (52%). These contradictory opinions for the value of use of loco-regional radiotherapy need to be evaluated accurately by using bigger sample sizes and further extension and prolongation of the follow-up periods to obtain a sound statistical value.

In our present study, the 5-year survival for local relapse was 70% and for distant failure, it was 30%. This is similar to the work of Pappo and Anderson [22] where the 5-year survival for local relapse was 65% and for distant failure, it was 25%.

In the present study complete remission occurred in 28 cases (50.9%), partial response in 13 cases (23.6%), stable disease in 2 cases (3.6%) and disease progression in 12 cases (21.8%). This contradicts the work of Frascella et al., where 2 patients achieved complete remission, 41 patients showed partial remission and 3 cases showed disease progression [29].

In the present study relapse occurred in 20 cases (36.4%). Fifteen cases relapsed locally (27.3%) and 5 cases relapsed metastasizing distantly (9%), this coincides with the work of Wolden et al., where 6% of the failure sites were local, 6% were regional and 7% were distant [9].

In the present study grade (I) hematological toxicity was present in 100% of the cases, 30% of the cases experienced grade III leucopenia and 20% experienced grade II thrombocytopenia. Mucositis occurred in 20% of the cases and infections in 10% of the cases. This coincides with the work of Stewart et al., where toxicity was mainly hematological, mucositis and infections were not severe. No toxic deaths were reported [30].

#### *Conclusion:*

Despite the advances in the therapy of rhabdomyosarcoma nearly 30% of the pediatric cases with rhabdomyosarcoma experience progressive or relapsing disease, which eventually have a fatal end.

The factors determining the 3-year survival after relapse at the time of initial diagnosis include histological subtype, disease risk group

including age and stage. We also believe that high risk rhabdomyosarcoma cases treatment protocols results are unsatisfactory regarding the complete remission rates and the survival indices; so further treatment intensification, may be newer drugs should be taken into consideration to manage those patients.

In addition to this, we believe that the role of radiation therapy on an adjuvant basis needs to be further investigated. These findings will form the basis of a multi-institutional risk adapted protocol for new cases of childhood rhabdomyosarcoma patients and protocols for relapsing patients.

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