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Management and outcomes of children with rhabdomyosarcoma in a low-to-middle-income country: A first report from Chris Hani Baragwanath Academic Hospital, South Africa

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ABSTRACT

Background: Studies done in South Africa show that Rhabdomyosarcomas (RMS) comprises 6 % of childhood malignancies. Very few centres in South Africa (SA) have reported their management and outcomes of children with RMS, and as such, it is difficult to compare outcomes and come up with management protocols befitting our environment.

Aim: To describe the management and outcomes of children with RMS at Chris Hani Baragwanath Academic Hospital (CHBAH).

Setting: The Departments of Paediatric Surgery and Paediatric Oncology.

Methods: A retrospective review of clinical records of patients below 18 years of age with RMS, managed from 01 January 2008 to 31 December 2017.

Results: Fifty-eight patients had RMS, 77 % embryonal and 21 % alveolar subtypes. Primary tumour site was favourable in 48 %, and unfavourable in 45 %. Thirty-three patients (57%,) had surgery for the primary tumour, whilst 25 patients (43 %) did not have surgery. Post-operative clinical groups were 29 % group I, 9 % group II, 43 % group III, and 19 % group IV. The overall 5-year survival was 55%. Predictors for a good outcome included early disease stage at presentation, favourable site, embryonal subtype, and surgery for the primary tumour.

Conclusion: The 5-year survival of 55 % from this study is low when compared to high income countries but is comparable to middle income countries. The main factor contributing to mortality is patients presenting with unresectable advanced disease in unfavourable sites. Surgical resection plays a major role in improving outcomes.

Level of evidence: IV

Introduction

Soft tissue sarcomas are a group of malignant solid tumours derived from mesenchymal tissue, affecting structures such as muscle, bone, nerves, fibrous tissue, fat and vessels [1]. Rhabdomyosarcoma (RMS), a tumour arising from striated muscle, accounts for half of all soft tissue sarcomas and 4.5 % of all cases of childhood malignancy [2]. Studies in South Africa have found that RMS comprised 6 % of childhood malignancies [3], and that it is the second most common malignant solid tumour in children after Wilms tumour, when haematolymphoid, central nervous system and bone solid tumours were excluded [4]. No significant racial predilection has been noted [5]. RMS is diagnosed most frequently in the 0 – 4 age group in South Africa, with a male to female ratio of 1.4:1 [3]. There are both environmental and genetic risk factors for the development of RMS, with an increased risk of malignancy seen with certain familial syndromes such as Li Fraumeni and neurofibromatosis [2].

RMS is divided into two main histological subtypes, embryonal (ERMS) and alveolar (ARMS), with the former being more prevalent, accounting for 75 % of cases [2]. Molecular biology is now also being used to differentiate these two subtypes from each other and from other sarcomas, based on the chromosomal translocation which generates the

Abbreviations: ARMS, alveolar rhabdomyosarcoma; CHBAH, Chris Hani Baragwanath Academic Hospital; ERMS, embryonal rhabdomyosarcoma; IRSG, intergroup rhabdomyosarcoma study group; REDcap, research electronic data capture; RMS, rhabdomyosarcoma; SA, South Africa; USA, United States of America.

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PAX-FKHR fusion, found in about 80 % of ARMS [6]. Histologically, ERMS is further subdivided into leiomyomatous (spindle cell), botryoid and anaplastic variants [7]. The ARMS subtype can be further classified into classical and solid variants [8].

Patients with RMS are staged at diagnosis using the Intergroup Rhabdomyosarcoma Study Group (IRSG) staging criteria based on the size and location of the primary tumour, lymph node involvement and the presence of metastasis (Table 1). This is determined by pre-operative investigations and represents disease extent prior to intervention [2]. Favourable sites are where the primary tumours are in the orbital, non-parameningeal head and neck area, and the genitourinary tract (excluding bladder and prostate) and biliary tract. Unfavourable sites are where tumours originate in the bladder/prostate, parameningeal area (nasopharynx, nasal cavity, middle ear, paranasal sinuses & infratemporal/pterygopalatine fossae), trunk, peritoneum or extremities.

Treatment of patients with RMS is multi-disciplinary. Surgery, specifically complete resection with negative margins, is the primary treatment modality. Complete resection of the primary tumour has major implications for prognosis, and the recommended safe margin is from 0.5 - 2 cm, although this is difficult in paediatric patients where there should be a balance between obtaining negative margins, organ function preservation and avoiding mutilating surgery [2]. Complete surgical resection reduces the chance of recurrence, and the degree of residual tumour post resection determines the clinical grouping (Table 1), which is a major determinant of prognosis [9].

Neo-adjuvant and adjuvant chemotherapy and radiotherapy significantly enhance outcomes; however, these essential components of care may have detrimental long-term effects that need to be considered, as mortality rates in these patients are higher than that of the general population due to the toxic effects of chemotherapy and radiation and secondary malignancies [10].

Outcomes are more favourable in ERMS than ARMS [11]; Favourable sites are associated with better outcomes, whereas unfavourable sites confer a less favourable prognosis. Tumours confined to the anatomic site of origin, less than 5 cm, no evidence of regional lymph node disease or distant metastases at diagnosis, are more easily resected and therefore have a more favourable prognosis. Furthermore, patients older than 10 years have a poorer prognosis [12]. Overall, staging and clinical grouping, together with the histological subtype of the tumour, determine the risk group stratification. The risk group stratification system gives low, intermediate and high-risk categories, depending on the combination of parameters and therefore accurately predicts outcomes and the required intensity of treatment in patients with RMS [2]. A 78 % 5-year survival has been reported in the USA [2].

Relapse is seen more often in patients with ARMS, tumours larger than 5 cm, patients older than 10 years of age and in patients with metastatic spread [13]. In these cases, the duration of remission influences the prognosis of relapsed disease, with a shorter period of remission associated with worse outcomes. Second look operation with surgical resection is an important intervention in relapsed RMS and has been shown to improve survival [14].

There are very few centres in SA, and the broader African context, that have reported their management and outcomes of children with RMS, and no previous study has been done at Chris Hani Baragwanath Hospital (CHBAH). Studies in SA found that Rhabdomyosarcomas comprised 6 % of childhood malignancies, and that it is the second most common malignant extra cranial solid tumour after Wilms and therefore deserves attention [4]. Sarcomas have undergone a period of protocol revision in SA, which has shown an improved crude survival over time, 42 % pre-2003, 50 % between 2003 - 2005, and 61 % between 2005 – 2010. The improved survival was attributed to risk stratified chemotherapy regimens, especially increased intensity for high-risk patients, sophisticated radiotherapy techniques, on site CT and MRI, and improvements in surgical expertise to get local control in order to avoid radiotherapy [15].

Cancer mortality has been reported to be higher in sub-Saharan Africa due to poor health infrastructure and limited access to treatment modalities [16]. Poor governmental investment in public health has been a strong contributing factor [17]. Thus, this retrospective review aims to provide data on the management and outcomes of RMS in a group of South African paediatric patients from a single centre, to contribute to the national database, and aid in the formulation of a national protocol.

Table 1
Definitions of Intergroup Rhabdomyosarcoma Study Group (IRSG) clinical stages and post resection clinical groups.

	IRSG clinical stage	Post resection clinical group
I	Tumours occurring in favourable sites, regardless of size and lymph node status, provided there are no metastases	Complete resection of the tumour
II	Tumours in unfavourable sites with a size <5 cm, and no lymph node involvement	Microscopic residual tumour or involved nodes
III	Tumours in an unfavourable site with a size >5 cm or with positive nodes	Gross residual tumour
IV	Tumours with distant metastases, regardless of primary site	Distant metastases present

Methods

This study was a 10-year retrospective review of medical records from the Department of Paediatric Oncology at CHBAH. The sample population was exclusive to patients below 18 years of age diagnosed with RMS between 01 January 2008 and 31 December 2017. Patients with grossly incomplete clinical notes, or who were operated on at hospitals other than CHBAH and received no further surgical treatment from CHBAH, were excluded from the study.

Study data were collected and managed using the REDCap (Research Electronic Data Capture) electronic data capture tool hosted by the University of Witwatersrand.

Descriptive statistics were calculated using Microsoft Excel. Medcalc statistical software version 19.0.7 was used for chi-squared tests, statistical summaries and to generate survival curves. A chi-squared test was used to assess relationships between categorical variables. Survival curves were generated by the Kaplan-Meier method. A Logrank test was done to assess trends in survival between curves. Where relevant, P-values of less than 0.05 were considered significant. 95 % confidence intervals were included where applicable.

Ethical considerations: Ethical clearance was obtained from the University of Witwatersrand Human Research Ethics Committee (Medical). Being a retrospective review, consent from individual patients was not required. The clearance certificate number is M1811114.

Results

Demographics

There were 58 children with RMS identified. This comprised of 45 (77 %) children with ERMS, 12 (21 %) children with ARMS, and one child (2 %) with unconfirmed subtype (due to an inconclusive FNA result and the patient died before further testing could be done). Of the 45 children with ERMS, six had the spindle cell variant, one anaplastic, two had the botryoid variant, and the remaining 36 children had pure ERMS. Eleven children with ARMS had the classic subtype, with only one with the solid variant.

There was a male predominance with a male-to-female ratio of 2.2:1. For the subtypes, male to female ratios for ERMS and ARMS were 2.46:1 and 1.4:1 respectively.

For all subtypes, a peak in occurrence was found in the 2 to 4-year-old age group ($n = 15$) (Fig. 1).

The median age at diagnosis for RMS was 5.3 years (IQR 7.7 years). A median of 4.6 years (IQR 6.6 years) was observed for ERMS (Fig. 1).

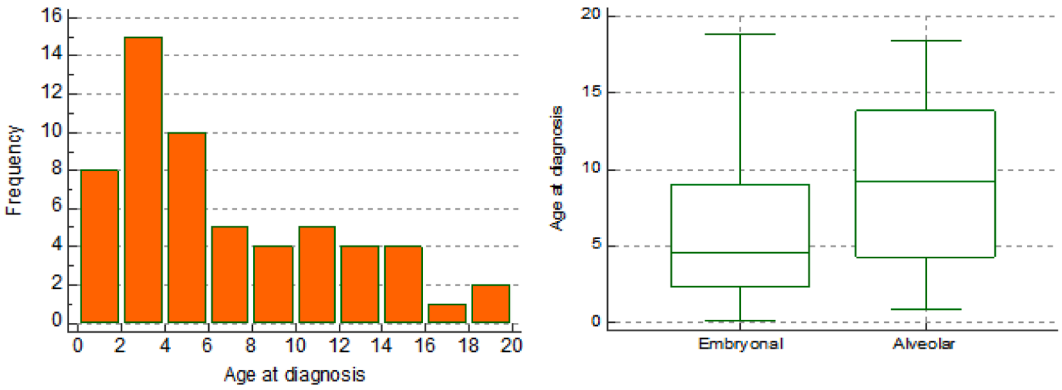

Fig. 1. Absolute number of patients per age at diagnosis for all subtypes of RMS (left) and Age at diagnosis ERMS vs. ARMS (right).

Patients with ARMS were relatively older with a mean age was 9.2 years (SD 5.7 years).

Investigations

Fifty-one (of 58) patients had imaging records found in their files. Thirty-eight patients had at least one documented CT scan (some patients had more than one CT scan), five had MRI scans and 37 bone scans were done. Biopsies were done for all 58 patients, and 40 patients has Bone Marrow Aspirates.

Primary tumour site

The primary site of RMS was favourable in 28 (48 %), unfavourable in 26 cases (45 %), and unknown in four (7 %) cases (Table 2). No relationship between histological subtype and the primary tumour site was found ($P = 0.89$).

Pre-treatment clinical staging information could only be retrieved from the files of 39 patients (67 %) and can be found in Table 3.

Surgical management

Thirty-three patients (57 %) had surgery for the primary tumour. Out of these 33 patients, 8 (24 %) had **primary Surgery**, and 25 (76 %) had **delayed Primary Surgery** after neo-adjuvant therapy. This neo-adjuvant therapy consisted of 14 patients who had chemotherapy alone, 1 radiotherapy alone, and 10 having both chemotherapy and radiotherapy. Post-surgery, 31 (94 %) patients went on to receive adjuvant therapy, 10 patients receiving chemotherapy alone, two had radiotherapy alone, and 19 having both chemotherapy and radiotherapy. Only one patient had a **second-look operation**, and only one had a **metastasectomy** for metastatic disease to the lung.

Table 2
Anatomical distribution of primary tumour sites.

Total sample ($n = 58$)					
Favourable Primary Tumour Site ($n = 28$) 48 %		Unfavourable Primary Tumour Site ($n = 26$) 45 %		Unknown Primary Tumour Site ($n = 4$) 7 %	
Head and Neck (excluding Parameningeal)	9	Parameningeal*	10	Primary Tumour Site Not Mentioned	2
Genitourinary (Non-bladder and Non-prostate)	11	Bladder/ Prostate	2	Tumour Clinically Noted as Systemic/ Metastatic	2
Orbit	8	Extremity Trunk & Peritoneum	4 10		

* Parameningeal - Nasopharynx, Nasal cavity, Middle ear, Paranasal sinuses & Infratemporal/Pterygopalatine fossae.

Clinical grouping could only be retrieved from the records for 21 (64 %) of the 33 patients who were treated surgically and is summarized in Table 4. Of these 21 patients, information regarding pre-treatment staging was only available for 19 of the patients, hence the discrepancy with Table 3.

Amongst all patients who had surgery, 21 (64 %) patients were known to still be alive at the end of the study period, six (18 %) were deceased, and six (18 %) were lost to follow up. There were four recurrences, of which two died and two survived.

Of eight patients who had primary surgery, six (75 %) were alive at the end of the study period. Two (25 %) were deceased of which one patient had a recurrence. Of the 25 patients who had delayed primary surgery, 15 (60 %) were confirmed to be alive at the end of the study period of which two patients had a recurrence. Four patients (16 %) were deceased of which one patient had a recurrence. Six (24 %) of these patients were lost to follow up.

Non-operative therapy

Twenty-five patients (43 %) did not have surgical resection of their primary tumour. Of these, 10 patients had chemotherapy only, one patient had radiotherapy only, 10 patients had both chemotherapy and radiation, and 4 patients did not receive any of the above. The reasons for not having surgery were: death within six weeks of diagnosis (11), and advanced stage disease (12) and two, who had no residual disease after treatment, therefore did not need surgery.

In this group, only three patients (12 %) were **confirmed to be alive** at the end of the study period, 19 (76 %) were deceased, and three (12 %) were lost to follow up. Thus, 76 % of this group were known to have died at the end of the study period.

Chemotherapeutic regimen used and radiation therapy dosing

For neo-adjuvant chemotherapy, IVAD (Ifosfamide, Vincristine, Actinomycin, Doxorubicin) was the most commonly used regimen ($n = 14$) while VAC (Vincristine, Adriamycin, Cyclophosphamide) was the second most common ($n = 9$). The mean duration was 18 weeks (SD 7 weeks).

For adjuvant chemotherapy, VAC was the most common regimen ($n = 17$), and IVAD was the second most common ($n = 12$). The median duration was 25.5 weeks (IQR 29.5 weeks)

Among the patients who did not have surgery, VAC was the most common chemotherapy regimen ($n = 13$), while IVAD was the second most common ($n = 10$). The median duration of chemotherapy for this group was 7.5 weeks (IQR 9 weeks).

Another uncommon regimen used was VICE (vincristine, ifosfamide, carboplatin, etoposide).

The median dose for any patient receiving radiotherapy was 45 Gy (IQR 9 Gy). The median duration of treatment was five weeks (IQR 4

Table 3
Number of patients, percentage and clinical grouping (CG) per pre-treatment stage.

Pre-Treatment Stage	Number of patients ($n = 39$)	Percentage	CG 1	CG 2	CG 3	CG 4	CG not available	Surgery not done
I	11	28 %	5	0	3	0	2	1
II	3	8 %	0	0	2	0	1	0
III	12	31 %	0	2	3	1	4	2
IV	13	33 %	0	0	0	3	0	10

Table 4
Number of patients and percentage per clinical group.

Clinical Group	Number of patients ($n = 21$)	Percentage
I	6	29 %
II	2	9 %
III	9	43 %
IV	4	19 %

weeks).

Survival trends

For all subtypes, the 3-year predicted survival was 60.2 % (95 % CI 73.2–47.2) and the 5-year survival was predicted to be 55.0 % (95 % CI 68.8–41.2) (Fig. 2A)

A significant difference in 5-year survival was observed between cases with a favourable site, compared to an unfavourable site (71.2% vs. 37.9 %, $p = 0.03$) as shown in Fig. 2B. A considerable difference in 5-year survival between ERMS as compared to ARMS at 62.1% vs. 36.4 % respectively was noted ($p = 0.18$) (Fig. 2C), although this did not reach statistical significance.

Those patients that had surgical resection of the primary tumour had a significant difference in 5-year survival, compared to those who did not have surgical resection (79.3% vs. 21.9 %, $p < 0.0001$) (Fig. 2D).

Lastly, patients presenting with early-stage disease (stage I and II) had a significant difference in 5-year survival, compared to those presenting with late-stage disease (stage III and IV) (90% vs. 40.7 %, $p = 0.0067$) (Fig. 2E).

Discussion

The average number of RMS patients presenting to CHBAH was 5.8 per year between 2008 and 2017 in contrast to an average of 3.8 per year reported in a similar study in Cape Town done at Red Cross War Memorial Children's Hospital (1990–2010) [15]. This may be influenced by CHBAH being a referral hospital for a larger population (3.6 million people) [18]. The study found a relative frequency of ERMS of 78 % and

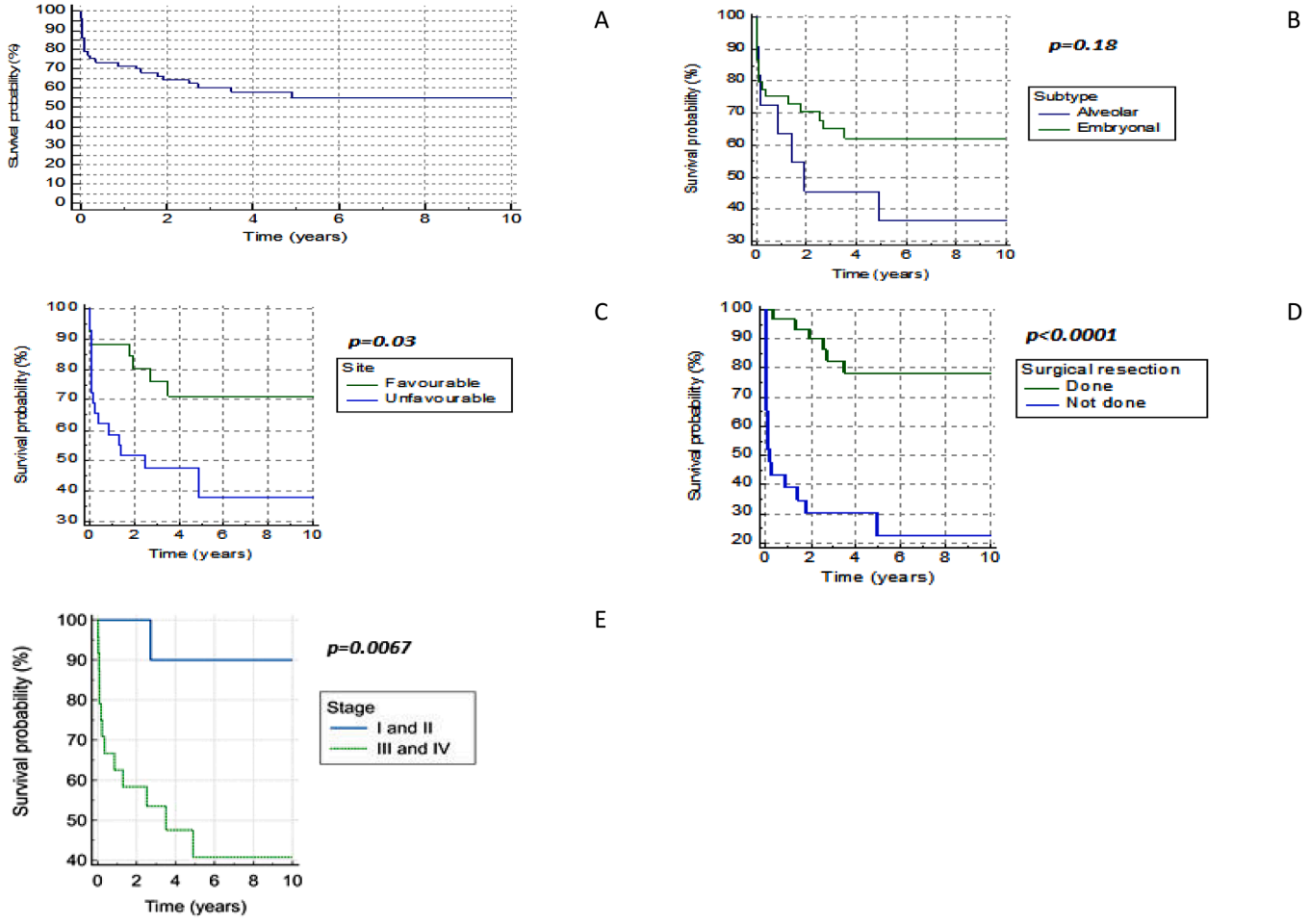

Fig. 2. Survival curves for (A) all patient, (B) favourable and unfavourable primary tumour site, (C) ARMS vs. ERMS, (D) regarding surgical resection for the primary tumour, (E) early (stage I and II) vs. advanced stage disease (stage III and IV).

ARMS 21 %. This is a similar distribution to that (ERMS 75 %, ARMS 25 %) classically described in the literature [2]. A male-to-female ratio of 2.2:1 was noted, which is higher than the male to female ratio of 1.4:1 observed in a study from the South African Children's Tumour Registry in 2015 [3], however there was a very significant difference in the sample sizes (58 vs. 711). We found a peak occurrence in the 2–4-year age group age range, however no bimodal age distribution, as is described in literature, was observed in our cohort [2]. Children with ARMS (mean 9.2 years) were relatively older than those with ERMS (median 4.2 years), consistent with international literature [2].

While anatomical predilections for ERMS in the head/neck and genitourinary tract, and ARMS in the trunk and the extremities have been described [2], we did not find a relationship between histological subtype and favourability of the primary tumour site ($P = 0.89$). There was a relatively equal distribution between favourable and unfavourable sites (48 % and 45 % respectively). While a significant difference in 5-year survival was observed between cases with a favourable site at 71.2 %, compared to an unfavourable site at 37.9 % ($p = 0.03$), no statistically significant difference in 5-year survival was noted between ERMS at 62.1 % and ARMS at 36.4 % ($p = 0.18$). These results, however, do demonstrate that patients with primary tumours in favourable sites and embryonal histology had better outcomes, although a favourable primary tumour site was a stronger predictor of 5-year survival than histological subtype ($P = 0.03$ vs. $P = 0.18$).

As this was a retrospective study, there were gaps in the information collected. All patients in the study had a biopsy done, 66 % had at least one documented CT scan, 8 % had MRI scans, 64 % had bone scans and 69 % had bone marrow aspirates. None of our patients during the study period had a PET scan. These results may be inaccurate, as the preliminary workup for patients with suspected RMS should comprise of a biopsy, a CT scan or MRI scan of the primary tumour, CT scan of the abdomen and retro peritoneum, CT scan of the chest, a bone scan, and bilateral bone marrow aspirate and biopsy [19], as well as a PET/CT scan. Thus, it would have been expected that all patients would have had these investigations done. A possible reason for these findings is that eleven patients died within six weeks of admission and may have demised before comprehensive investigations could be performed. Additionally, the absence of a standardised clinical data collecting tool/system and missing records may have contributed to these findings.

In our study, of the patients with known staging, one third presented with low stage disease I and II, two thirds presented with advanced stage disease III and IV, and this resonated with a similar study from Cape Town done at Red Cross War Memorial Children's Hospital (1990–2010) [15]. These results indicate that delayed presentation is a problem in South Africa as a whole.

Only 57 % (33) of patients had surgery in this cohort. In this group of patients 24 % had primary surgery, and 76 % had delayed primary surgery after neo-adjuvant therapy. This neo-adjuvant therapy consisted of 56 % of patients who had chemotherapy alone, 4 % radiotherapy alone, and 40 % having both chemotherapy and radiotherapy. Post-surgery, 94 % of these patients had some form of adjuvant therapy (32 % chemotherapy, 7 % radiotherapy, and 61 % both). Our study found that only one patient had a second look operation, and only one a metastastectomy. This translates to a 3 % metastastectomy rate and 3 % second look rate which are surprisingly very low. Further studies would be helpful to confirm the accuracy and/or reason of this finding. No clear relationship between pre-treatment staging and post-surgical clinical grouping for stages I-III was observed, however all patients with stage IV disease were either clinical group IV or not operated on. Future research with larger sample sizes may contribute to further understanding of the link between staging and clinical grouping in our population/centre.

Twenty-five of the total patients (43 %) were not treated surgically. Reasons for not having surgery included death within six weeks of diagnosis and advanced stage disease at presentation. There was a significant mortality in those who did not have surgery (as described below), contributing to the sub-optimal overall survival in patients in our centre. Of these 25 patients 40 % were treated with only chemotherapy, 4 % with only radiotherapy and 40 % with both modalities. There were, however two patients who did not need surgery following cure by primary chemotherapy and/or radiation therapy of their head and neck tumours. In this group of patients, survival was not affected by not having had surgery.

Our study found that IVAD & VAC were the most common used chemotherapy regimens at our centre. We observed that neo-adjuvant chemotherapy had a mean duration of 18 weeks (SD 7 weeks) and Adjuvant chemotherapy had a median duration of 26 weeks (IQR 30 weeks). The median dose of radiotherapy was 45 Gy, and the median duration was 5 weeks (IQR 4 weeks).

We observed a recurrence rate of 7 %. This figure is comparable to larger studies from North America reporting that 9 % of patients experienced relapses after five years post-treatment [19]. However, a similar study from Cape Town done at Red Cross War Memorial Children's Hospital (1990–2010) had an average of 38 % relapse or progression on treatment, 62 % before 2005 and 38 % after 2005 [15]. This discrepancy may be influenced by the longer study period (20 years) of the above-mentioned study and may also be contributed to by the authors of the study considering relapse and progression of disease together. Additionally, some patients in our cohort may have been lost to follow up and thus recurrences not reported.

The study found a 5-year survival of 55 % for RMS in the unit. This figure is significantly lower than the 5-year-survival of 78 % reported in the USA [2]. This disparity may be due to resource limitations in CHBAH compared to hospitals in North America and may be somewhat confounded by advanced tumour stage at presentation as our patients did present with later stage disease than their patients. A large study in the USA ($n = 1062$) found that 25 % of patients presented with metastatic disease [20], whereas in our cohort 33 % of patients had metastases at presentation.

Nonetheless, our results were comparable to other studies done in low- and middle-income countries and in South Africa. A similar study in Cape Town done at Red Cross War Memorial Children's Hospital (1990–2010) reported a similar 5-year survival of 58.7 % [15]. Furthermore, our 5-year survival of 55 % was higher than a 44 % 4-year survival rate for RMS found in a study done in Central America [21]. The Cape Town study mentioned above described an improvement in outcomes over time due to intensified risk-based treatment, sophisticated radiotherapy techniques, on site CT and MRI, and improvements in surgical techniques [15]. Evaluation of outcome trends over time was beyond the scope of this study but could be valuable in future research.

A significantly strong trend to survival was observed in patients who had surgery (79.3 %) than those who did not have surgery (21.9 %). However, it must be considered that a number of patients died before the possibility of surgery, or at diagnosis were initially not eligible for surgery due to advanced disease that was not amenable to resection. Therefore, the survival curve of patients without surgery does not accurately represent the cohort of patients that were 'treated with intent to cure' without surgery. However, the results do show that if a patient qualifies for and has surgery, their chance of survival after five years is significantly higher. Furthermore, a significant difference in 5-year survival was found between patients presenting with early-stage disease (stage I, II), compared to those presenting with late-stage disease (stage III, IV) (40.7 vs. 90 %). This finding emphasizes the need for early diagnosis and referral of patients with suspected RMS.

Conclusion

The 5-year survival of 55 % from this study is low when compared to high income countries. However, it is comparable to middle income or other SA national studies. The main factors contributing to mortality are patients presenting with unresectable advanced disease in unfavourable sites. Surgical resection, be it primary or delayed, plays a major role in improving outcomes of children with RMS, thereby emphasizing the

need for paediatric oncological surgeons. Neo-adjuvant chemotherapy and radiotherapy played an important part in improving resectability of these tumours, as well as for post-operative control in the higher stage/group disease, however, there needs to be more aggressive second look surgery for residual disease, and metastasectomy for distant disease.

This study, being a single centre retrospective review of 58 patients comes with its limitations; however it does contribute to the national statistics and current outcomes of rhabdomyosarcoma in children in South Africa. It emphasises the need for early referral and large national collaborative studies, both in public and private hospitals and will hopefully contribute to the implementation of a South African National Protocol with standardised reporting for children with RMS, to improve outcomes.

Authors' contributions

J.M.J. (principal investigator) was involved in the conceptualization, data curation, formal analysis, investigation, methodology, project administration, visualization, original draft writing as well as reviewing and editing. J.C.J. (investigator) was involved in the writing, reviewing and editing of this manuscript as well as data curation and formal analyses. S.M. (second supervisor) provided supervision from the study's inception through data curation until its writing and assisted with formal analysis, validation and reviewing and editing. D.S.H. (main supervisor) was invloved in conceptualization, provided supervision from the study's inception through data curation, formal analysis and investigation, validation, reviewing and editing and provided final approval of this manuscript.

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Disclaimer

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CRediT authorship contribution statement

Jonathan Jacobson: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Julia Jamieson:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Sithandweyinkosi Mushunje:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Derek Harrison:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

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