Cancer Association of South Africa (CANSA)

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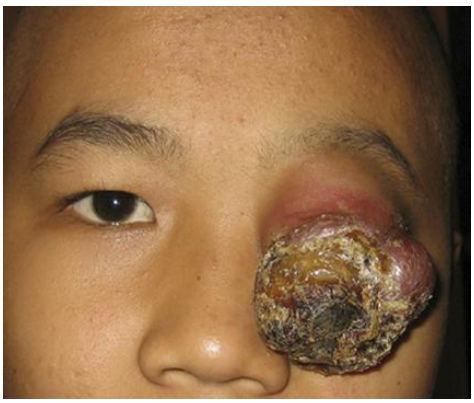
Fact Sheet
on
Adult Rhabdomyosarcoma
and Pleomorphic Rhabdomyosarcoma

Introduction

Sarcomas are cancers that develop from connective tissues in the body, such as muscles, fat, bones, the linings of joints, or blood vessels. There are many types of sarcomas.



[Picture Credit: Rhabdomyosarcoma]

Rhabdomyosarcoma (RMS) is a cancer made up of cells that normally develop into skeletal muscles. The body has 3 main types of muscles.

- Skeletal (voluntary) muscles are muscles that we control to move parts of our body.
- Smooth muscle is the main type of muscle in internal organs (except for the heart). For example, smooth muscles in the stomach and intestines push food along as it is digested. We do not control this movement.
- Cardiac muscle is the main muscle type in the heart.

About 7 weeks into the development of an embryo, cells called *rhabdomyoblasts* (which will eventually form skeletal muscles) begin to form. These are the cells that can develop into RMS. Because this is a cancer of embryonal cells, it is much more common in children, although it does sometimes occur in adults – more than 50% of cases are diagnosed before the age of 10.

Kaseb, H., Kuhn, J. & Babiker, H.M. 2020.
"Rhabdomyosarcoma (RMS) is a primitive pediatric malignant soft tissue sarcoma of skeletal muscle phenotype that originates from a primitive mesenchymal cell. Most cases are diagnosed in children under the age of 6. The etiology and risk factors remain largely unknown. Most cases of rhabdomyosarcoma are sporadic; however, the disease is associated with familial syndromes. Rhabdomyosarcoma types include embryonal rhabdomyosarcoma (approximately 60%), alveolar (approximately 20%), pleomorphic (approximately 10%), and spindle/sclerosing (approximately 10%). The survival of rhabdomyosarcoma patients has improved, especially in the last decade, mainly due to interprofessional disease management approaches."

Schneider, K.W., Cost, N.G., Schultz, K.A.P., Svihovec, S.& Suttman, A. 2020.
"Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma of children and adolescents. The fusion-positive (FP)-RMS variant expressing chimeric oncoproteins such as PAX3-FOXO1 and

PAX7-FOXO1 is at high risk. The fusion negative subgroup, FN-RMS, has a good prognosis when non-metastatic. Despite a multimodal therapeutic approach, FP-RMS and metastatic FN-RMS often show a dismal prognosis with 5-year survival of less than 30%. Therefore, novel targets need to be discovered to develop therapies that halt tumor progression, reducing long-term side effects in young patients. Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that regulates focal contacts at the cellular edges. It plays a role in cell motility, survival, and proliferation in response to integrin and growth factor receptors' activation. FAK is often dysregulated in cancer, being upregulated and/or overactivated in several adult and pediatric tumor types. In RMS, both in vitro and preclinical studies point to a role of FAK in tumor cell motility/invasion and proliferation, which is inhibited by FAK inhibitors. In this review, we summarize the data on FAK expression and modulation in RMS. Moreover, we give an overview of the approaches to inhibit FAK in both preclinical and clinical cancer settings."

Incidence of Rhabdomyosarcoma in South Africa

The outdated National Cancer Registry (2017) does not provide any information regarding the incidence of Rhabdomyosarcoma in South Africa.

Diagnosis of Rhabdomyosarcoma

The following may be used in the diagnosis of Rhabdomyosarcoma in adults:

- X-rays
- Computed Tomography (CT) scab
- Magnetic Resonance Imaging (MRI) scan
- Bone scan
- Positon Emission Tomography (PET) scan
- Ultrasound
- Biopsy
    - Surgical biopsy
    - Needle biopsy
    - Core needle biopsy
    - Fine needle biopsy
    - Bone marrow aspiration and biopsy
- Lumbar puncture
- Blood tests
- Blood chemistry

Leiner, J. & Le Loarer, F. 2020.

"Rhabdomyosarcomas are malignancies associated with a rhabdomyoblastic phenotype which can be demonstrated morphologically or by immunohistochemistry for MYOD1 and myogenin. Rhabdomyosarcomas are currently subdivided into 4 types in the 2013 WHO classification of tumors of soft tissue and bone, including embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma, spindle cell/sclerosing rhabdomyosarcoma, and pleomorphic rhabdomyosarcoma. Recent studies have significantly impacted this classification with the emergence of three distinct new subtypes of rhabdomyosarcomas, namely rhabdomyosarcoma with MYOD1 mutations, rhabdomyosarcoma with TFCP2 fusions, and rhabdomyosarcoma with VGLL2/NCOA2 fusions. Although all these tumors share the terminology "rhabdomyosarcoma," their morphology, clinical behavior, and underlying

molecular alterations are dramatically different. Finally, the presence of a rhabdomyoblastic phenotype within a tumor is by no means a diagnostic of a rhabdomyosarcoma, as this may be seen in many other mesenchymal malignancies, such as mesenchymal chondrosarcomas, malignant peripheral nerve sheaths tumors, and biphenotypic sinonasal sarcomas. In this review, we present the main clinical, morphological, and molecular features of these tumors and discuss the evolution of the current classification."

Casey, D.L., Wexler, L.H., Pitter, K.L., Samstein, R.M., Slotkin, E.K.& Wolden, S.L. 2020.
Purpose: Increased availability of next-generation sequencing has allowed for the genomic characterization of a variety of pediatric tumors, although genomic determinants of response to treatment remain largely unknown. We sought to evaluate the genomic landscape and genomic determinants of clinical outcomes in rhabdomyosarcoma (RMS).
Experimental design: Of 29,067 patients who underwent genomic profiling at our institution using a 468-gene oncopanel with complete records, 87 had RMS, of whom 22 were fusion positive. The 10 most common genetic alterations were associated with locoregional control (LC), disease-free survival (DFS), and overall survival (OS). Tumor mutational burden (TMB), defined as the total number of somatic nonsynonymous mutations normalized to the number of sequenced megabases, was also associated with clinical outcomes.
Results: Median age at diagnosis was 16.4 years and median follow-up, 2.1 years. Patients with fusion-negative RMS had more genomic alterations and a higher TMB than those with fusion-positive RMS (mean number of genomic alterations, 6.0 vs. 2.9; $P = 0.007$ and mean TMB, 2.6 vs. 1.0; $P = 0.01$). Genetic alterations in *TP53* were associated with worse OS ($P = 0.03$). High TMB (defined as the top quartile ≥ 2.8) was associated with worse LC ($P = 0.05$), DFS ($P = 0.04$), and OS ($P = 0.01$), with significance retained on multivariable analysis after controlling for risk group, fusion status, and receipt of chemotherapy as per pediatric protocols.
Conclusions: High TMB was associated with worse clinical outcomes in patients with RMS. With further validation, TMB and other genomic classifiers may be combined with traditional clinicopathologic risk factors to guide risk stratification and ultimately treatment decisions.

Rhabdomyosarcoma in Adults
Rhabdomyosarcoma (RMS) is a paediatric sarcoma rarely occurring in adults. More than 50% of Rhabdomyosarcoma cases are diagnosed before the age of 10. Males are affected slightly more than females. Adults with RMS have worse outcomes.

Rhabdomyosarcomas can occur anywhere in the body but occur more commonly near muscular structures – e.g., around the intestines, around the ocular muscles and in the cardiac muscle in tuberous sclerosis. The most common locations of rhabdomyosarcomas are:

- Head and neck (35-40%).
- Bladder (20%).
- Muscles, limbs, chest and abdominal wall (15-20%).
- Other sites – e.g., testes.

Rhabdomyosarcomas are highly malignant and grow rapidly. They are, however, potentially curable.

Liu, Y.T., Wang, C.W., Hong, R.L. & Kuo, S.H. 2019.

BACKGROUND: Adults with rhabdomyosarcoma (RMS) have a worse clinical outcome compared to pediatric cases. In the present study, the failure pattern and clinical outcome of adult patients with RMS who received multimodality treatment at our Institution was assessed.

PATIENTS AND METHODS: Data were retrospectively recorded and analyzed from 20 adult patients, aged 19 years or more, who were treated for RMS at our Institution between 2004 and 2015. Disease-free (DFS) and overall (OS) survival after starting treatment were calculated using the Kaplan-Meier method. The relationship of these outcome measures with the following variables was then assessed: Primary site, tumor stage, lymph node involvement, histological subtype, radiotherapy (RT), and duration of chemotherapy.

RESULTS: Sixteen patients had localized RMS, and four had metastatic disease. For the whole patient cohort, the 3-year DFS and OS rates were 20%, and 45%, respectively. Patients with alveolar histological subtype had a better 3-year OS than those with other subtypes (p=0.038). The median OS rates for those with localized and metastatic disease were 53.2 (95% confidence interval(CI)=14.7-91.8) months, and 21.7 (95% CI=0-45.7) months, respectively (p=0.047). In patients with localized RMS, those who received RT (n=13) had a better median DFS (24.6 versus 6.0 months, p=0.009) and OS (53.2 versus 11.4 months, p=0.009) than those who did not (n=3). For patients receiving RT, concurrent chemotherapy with vincristine and cyclophosphamide (n=11) was associated with better 3-year DFS (36.4% versus 0%, p<0.001) and OS (81.8% versus 0%, p<0.001) compared with RT alone (n=2). Administration of chemotherapy for more than 19 weeks significantly correlated with better 3-year DFS (44% versus 0%, p=0.001) and OS (53.3% versus 0%, p<0.001) in those with localized RMS.

CONCLUSION: In addition to staging and histological subtype, our results indicate that concurrent chemoradiotherapy and longer duration of chemotherapy were associated with significantly improved DFS and OS in adult patients with localized RMS.

Contributory Causes of Rhabdomyosarcoma (RMS)

The exact causes of Rhabdomyosarcoma remains unclear, although genetic syndromes and various other factors are associated with this condition. Factors that are associated with Rhabdomyosarcoma may include:

- Smoking – This is included in our Risk Factors because most of the cancers are induced by smoking.
- Radiation – This can cause a change or mutation in normal cells
- Drug Abuse – studies have shown that the use of illegal drugs are connected with adults who have Rhabdomyosarcoma

PDQ Pediatric Treatment Editorial Board. 2020.

Risk factors for rhabdomyosarcoma include having the following inherited diseases:

- Li-Fraumeni syndrome
- Dicer1 syndrome
- Neurofibromatosis type 1 (NF1)
- Costello syndrome
- Beckwith-Wiedemann syndrome
- Noonan syndrome
- Children who had a high birth weight or were larger than expected at birth may have an increased risk of embryonal rhabdomyosarcoma.

In most cases, the cause of rhabdomyosarcoma is not known.

Diagnosis of Rhabdomyosarcoma

The diagnostic tests that are done depend in part on where the cancer forms. The following tests and procedures may be used **PDQ Pediatric Treatment Editorial Board.** 2020:

Physical examination and health history: An exam of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

X-ray: An x-ray of the organs and bones inside the body, such as the chest. An x-ray is a type of energy beam that can go through the body and onto film, making a picture of areas inside the body.

CAT scan: A procedure that makes a series of detailed pictures of areas inside the body, such as the chest, abdomen, pelvis, or lymph nodes, taken from different angles. The pictures are made by a computer linked to an x-ray machine. A dye may be injected into a vein or swallowed to help the organs or tissues show up more clearly. This procedure is also called computed tomography, computerized tomography, or computerized axial tomography.

Magnetic resonance imaging (MRI): A procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas of the body, such as the skull, brain, and lymph nodes. This procedure is also called nuclear magnetic resonance imaging (NMRI).

Pet scan (positron emission tomography scan): A procedure to find malignant tumor cells in the body. A small amount of radioactive glucose (sugar) is injected into a vein. The PET scanner rotates around the body and makes a picture of where glucose is being used in the body. Malignant tumor cells show up brighter in the picture because they are more active and take up more glucose than normal cells do.

Bone scan: A procedure to check if there are rapidly dividing cells, such as cancer cells, in the bone. A very small amount of radioactive material is injected into a vein and travels through the bloodstream. The radioactive material collects in the bones with cancer and is detected by a scanner.

Bone marrow aspiration and biopsy: The removal of bone marrow, blood, and a small piece of bone by inserting a hollow needle into the hipbone. Samples are removed from both hipbones. A pathologist views the bone marrow, blood, and bone under a microscope to look for signs of cancer.

Lumbar puncture: A procedure used to collect cerebrospinal fluid (CSF) from the spinal column. This is done by placing a needle between two bones in the spine and into the CSF around the spinal cord and removing a sample of the fluid. The sample of CSF is checked under a microscope for signs of cancer cells. This procedure is also called an LP or spinal tap.

If these tests show there may be a rhabdomyosarcoma, a biopsy is done. A biopsy is the removal of cells or tissues so they can be viewed under a microscope by a pathologist to check for signs of cancer. Because treatment depends on the type of rhabdomyosarcoma, biopsy samples should be checked by a pathologist who has experience in diagnosing rhabdomyosarcoma.

One of the following types of biopsies may be used:

- Fine-needle aspiration biopsy: The removal of tissue or fluid using a thin needle.
- Core needle biopsy: The removal of tissue using a wide needle. This procedure may be guided using ultrasound, CT scan, or MRI.
- Open biopsy: The removal of tissue through an incision (cut) made in the skin.

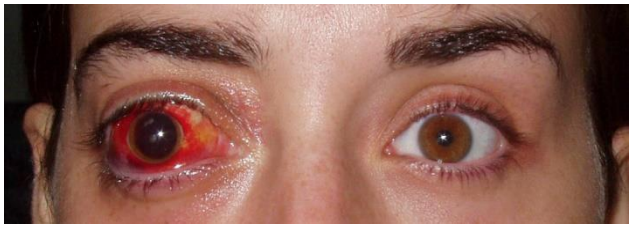
- Sentinel lymph node biopsy:: The removal of the sentinel lymph node during surgery. The sentinel lymph node is the first lymph node in a group of lymph nodes to receive lymphatic drainage from the primary tumor. It is the first lymph node the cancer is likely to spread to from the primary tumor. A radioactive substance and/or blue dye is injected near the tumor. The substance or dye flows through the lymph ducts to the lymph nodes. The first lymph node to receive the substance or dye is removed. A pathologist views the tissue under a microscope to look for cancer cells. If cancer cells are not found, it may not be necessary to remove more lymph nodes. Sometimes, a sentinel lymph node is found in more than one group of nodes. Sentinel lymph node biopsy may be used for patients with rhabdomyosarcoma of the limbs or trunk when enlarged lymph nodes are not found with imaging or physical exam.

Staging and Prognosis

Staging of RMS is determined by the tumour size and local invasion, lymph nodes involvement, and metastasis.

Pleomorphic Rhabdomyosarcoma

Pleomorphic Rhabdomyosarcoma (PRMS) is an extremely infrequent, but highly malignant 'skeletal muscle' tumour of the soft tissues.



[Picture Credit: Adult Orbital Alveolar Pleomorphic Rhabdomyosarcoma]

Incidence of Pleomorphic Rhabdomyosarcoma

- Even though Pleomorphic Rhabdomyosarcoma is observed across all ages; a majority of them are noticed in adults over 40 years, with a peak in the 50-60 year age range. Young children are hardly affected
- Males are affected more than females
- There is no ethnic/racial preference noticed

Signs and Symptoms of Pleomorphic Rhabdomyosarcoma

The presentations are based on the location of PRMS. Signs and symptoms of Pleomorphic Rhabdomyosarcoma include:

- In the initial growing phase of the tumours, they are normally asymptomatic
- As the tumour grows rapidly, its presence is felt by pain and a sensation of mass. The mass can cause compression on the body region, resulting in obstruction of adjacent organs
- Most lesions occur in the legs (in 45% of the cases) followed by the hands. Occasionally, it is found in the abdomen and on the chest wall too
- Functional impairment of organs may occur owing to the large size of the tumour (5-15cm), due to mass effect

Treatment of Rhabdomyosarcoma

Miwa, S., Yamamoto, N., Hayashi, K., Takeuchi, A., Igarashi, K. & Tsuchiya, H. 2020.
"Rhabdomyosarcoma, the most common soft tissue sarcoma noted in childhood, requires multimodality treatment, including chemotherapy, surgical resection, and/or radiation therapy. The majority of the patients with localized rhabdomyosarcoma can be cured; however, the long-term outcomes in patients with metastatic rhabdomyosarcoma remain poor. The standard chemotherapy regimen for patients with rhabdomyosarcoma is the combination of vincristine, actinomycin, and cyclophosphamide/ifosfamide. In recent clinical trials, modifications of the standard chemotherapy protocol have shown improvements in the outcomes in patients with rhabdomyosarcoma. In various type of malignancies, new treatments, such as molecular targeted drugs and immunotherapies, have shown superior clinical outcomes compared to those of standard treatments. Therefore, it is necessary to assess the benefits of these treatments in patients with rhabdomyosarcoma. Moreover, recent basic and clinical studies on rhabdomyosarcoma have reported promising therapeutic targets and novel therapeutic approaches. This article reviews the recent challenges and advances in the management of rhabdomyosarcoma."

PDQ Pediatric Treatment Editorial Board. 2020
Some treatments are standard (the currently used treatment), and some are being tested in clinical trials. A treatment clinical trial is a research study meant to help improve current treatments or obtain information on new treatments for patients with cancer. When clinical trials show that a new treatment is better than the standard treatment, the new treatment may become the standard treatment.
Because cancer in children is rare, taking part in a clinical trial should be considered. Some clinical trials are open only to patients who have not started treatment.

Treatment of Pleomorphic Rhabdomyosarcoma
Treatment measures for Pleomorphic Rhabdomyosarcoma may include the following:

- Wide surgical excision of PRMS with removal of the entire lesion; this is essentially followed by radiation and/or intensive chemotherapy
- If possible, sometimes chemotherapy/radiotherapy is given prior to the operation, to shrink the tumour
- Arterial embolization of the tumour is used to provide temporary relief from the symptoms, and reduce blood loss during 'tumour removal' surgical procedure
- When PRMS is at an inaccessible location, or is unsafe for a surgical intervention; non-invasive procedures are adopted
- Post-operative care is important: Minimum activity level is to be ensured until the surgical wound heals. Follow-up care with regular screening and check-ups are important

Kim, J.K., Verma, N., McBride, S., Riaz, N., Boyle, J.O., Speilsinger, D., Sabol, C., Waldenberg, T., Brinkman, T., Alektiar, K., Lee, N.Y. & Tsai, C.J. 2019.
OBJECTIVES/HYPOTHESIS: We used the National Cancer Database to identify the patterns of care and prognostic factors in adult patients with head and neck soft-tissue sarcoma (HNSTS).
STUDY DESIGN: Retrospective cohort analysis.
METHODS: Using the National Cancer Database, we identified patients age ≥ 18 years who were diagnosed with HNSTS between 2004 and 2013. Both χ^2 and multivariate logistic regression were

used to identify factors associated with radiation therapy (RT) utilization. Kaplan-Meier methods were used to estimate overall survival (OS) and Cox proportional regression was used to determine significant contributors to OS.
RESULTS: Our final cohort included 1,282 patients (682 treated with surgery only, 199 treated with RT only, and 401 treated with surgery and RT). Patients with younger age, poor tumor grade, rhabdomyosarcoma histology, and chemotherapy treatment were more likely to receive RT alone without surgery. Among the 1,083 surgical patients, RT utilization was associated with positive margins (odds ratio [OR]: 2.18, 95% confidence interval [CI]: 1.36-3.48), poor grade (OR: 2.92, 95% CI: 1.95-4.38), and chemotherapy use (OR: 1.78, 95% CI: 1.15-2.76). Radiotherapy utilization among surgical patients was not affected by demographic factors (age, sex, or ethnicity) or treatment institution (academic or community). For surgical patients, poor grade, large tumor size, and rhabdomyosarcoma histology were associated with worse OS on multivariate analysis.
CONCLUSIONS: In this analysis of HNSTS, younger patients with poor tumor grade and rhabdomyosarcoma histology were more likely to receive RT without surgery. Among surgical patients, adjuvant RT was more likely to be used for positive margins and poor grade, with no demographic disparities identified. Poor grade and rhabdomyosarcoma histology were negative prognostic factors for surgical patients.

Yohe, M.E., Heske, C.M., Stewart, E., Adamson, P.C., Ahmed, N., Antonescu, C.R., Chen, E., Collins, N., Ehrlich, A., Galindo, R.L., Gryder, B.E., Hahn, H., Hammond, S., Hatley, M.E., Hawkins, D.S., Hayes, M.N., Hayes-Jordan, A., Helman, L.J., Hettmer, S., Ignatius, M.S., Keller, C., Khan, J., Kirsch, D.G., Linardic, C.M., Lupo, P.J., Rota, R., Shern, J.F., Shipley, J., Sindiri, S., Tapscott, S.J., Vakoc, C.R., Wexler, L.H. & Langenau, D.M. 2019.
"Overall survival rates for pediatric patients with high-risk or relapsed rhabdomyosarcoma (RMS) have not improved significantly since the 1980s. Recent studies have identified a number of targetable vulnerabilities in RMS, but these discoveries have infrequently translated into clinical trials. We propose streamlining the process by which agents are selected for clinical evaluation in RMS. We believe that strong consideration should be given to the development of combination therapies that add biologically targeted agents to conventional cytotoxic drugs. One example of this type of combination is the addition of the WEE1 inhibitor AZD1775 to the conventional cytotoxic chemotherapeutics, vincristine and irinotecan."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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