Cancer Association of South Africa (CANSA)

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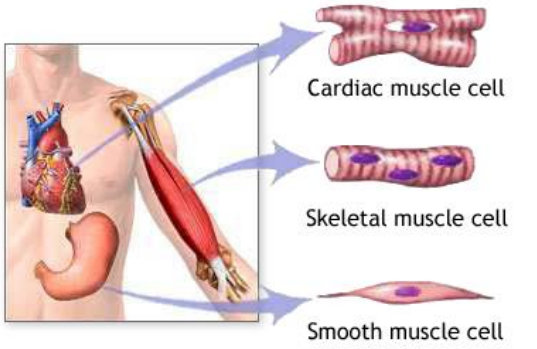
Fact Sheet
on
Childhood Rhabdomyosarcoma

Introduction

There are three (3) kinds of muscle cells in the body: smooth muscle cells in smooth muscles which control involuntary activities – meaning one cannot control these muscles at will - skeletal muscle cells found in those muscles that perform voluntary activities and are under voluntary human control – and heart muscle cells found only in the heart.



[Picture Credit: Muscle Cells]

Rhabdomyosarcoma (RMS) is a malignant cancer (tumour) that arises from a normal skeletal muscle cell. Not very much is known about why normal skeletal muscle cells become cancerous. Because skeletal muscle cells are found in virtually every site of the body, RMS can develop in almost any part of the body.

Childhood Rhabdomyosarcoma

Rhabdomyosarcoma is a type of soft tissue sarcoma (STS) that begins in mesenchymal cells, which are immature cells that normally become muscle. This disease develops in a type of muscle called striated muscle. Striated muscles are the skeletal voluntary muscles, which are those muscles that people can control.

[Picture Credit: Rhabdomyosarcoma]

Rhabdomyosarcoma can occur anywhere in the body:

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- Head and neck: about 39% of all rhabdomyosarcoma cases. This includes:
    - parameningeal sites (near the membranes covering the brain) - 24%; eye socket - 8%; and other head and neck locations - 7%
- Urinary or reproductive organs - 29%
- Arms or legs - 15%
- Other sites: about 17% of cases. This includes the trunk (torso), intrathoracic (inside the lung and/or chest), biliary tract, retroperitoneal, pelvic, and perineal sites (close to the anus, vagina, and urinary structures).

Slemmons, K.K., Yeung, C., Baumgart, J.T., Juarez, J.O.M., McCalla, A. & Helman, L.J. 2020.
"Rhabdomyosarcoma is the most common childhood soft-tissue sarcoma, yet patients with metastatic or recurrent disease continue to do poorly, indicating a need for new treatments. The SRC family tyrosine kinase YES1 is upregulated in rhabdomyosarcoma and is necessary for growth, but clinical trials using single agent dasatinib, a SRC family kinase inhibitor, have failed in sarcomas. YAP1 (YES-associated protein) is highly expressed in rhabdomyosarcoma, driving growth and survival when the upstream Hippo tumor suppressor pathway is silenced, but efforts to pharmacologically inhibit YAP1 have been unsuccessful. Here we demonstrate that treatment of rhabdomyosarcoma with DNA methyltransferase inhibitor (DNMTi) upregulates Hippo activators RASSF1 and RASSF5 by promoter demethylation, activating canonical Hippo signaling and increasing inactivation of YAP1 by phosphorylation. Treatment with DNMTi decreased rhabdomyosarcoma cell growth and increased apoptosis and differentiation, an effect partially rescued by expression of constitutively active YAP (S127A), suggesting the effects of DNMTi treatment are, in part, due to Hippo-dependent inhibition of YAP1. In addition, YES1 and YAP1 interacted in the nucleus of rhabdomyosarcoma cells, and genetic or pharmacologic suppression of YES1 resulted in cytoplasmic retention of YAP1 and decreased YAP1 target gene expression, suggesting YES1 regulates YAP1 in a Hippo-independent manner. Combined treatment with DNMTi and dasatinib targeted both Hippo-dependent and Hippo-independent regulation of YAP1, ablating rhabdomyosarcoma cell growth *in vitro* and trending toward decreased tumor growth *in vivo*. These results show that the mechanisms regulating YAP1 in rhabdomyosarcoma can be inhibited by combinatorial therapy of DNMTi and dasatinib, laying the groundwork for future clinical investigations. SIGNIFICANCE: This study elucidates the signaling pathways that regulate the oncogenic protein YAP1 and identifies a combination therapy to target these pathways in the childhood tumor rhabdomyosarcoma."

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

Types of Childhood Rhabdomyosarcoma (RMS)
Each rhabdomyosarcoma tumour is classified as either favourable or unfavourable based on its histology, which is what the cells look like under a microscope. The terms "favourable" and "unfavourable" refer to the appearance of the cancer cells. In general, the more cancer cells look like normal cells, the more "favourable" they are and the greater the chance that treatment will be successful.

Favourable histology tumours include the following:

- Embryonal RMS.This is the most common type of RMS, frequently found in the head and neck and in the reproductive and urinary organs

    - Botryoid RMS. This is one subtype of embryonal RMS, found most often in hollow organs, such as the bladder or a girl's vagina
    - Spindle RMS. This is another subtype of embryonal RMS, found most often in the area around a boy's testicles

Unfavourable histology tumours include the following:

- Alveolar RMS. This is a more aggressive type of RMS, found most often in an arm, leg, or the trunk of the body
- Pleomorphic and undifferentiated RMS. These are the rarest types of RMS, found most commonly in an arm, leg, or the body's trunk

RMS is most often found in children and young adults.

Genetic Risk for Rhabdomyosarcoma

Although the overwhelming majority of cases of RMS occur sporadically, between 10-33% of children who develop RMS are thought to have an underlying genetic risk factor. The development of RMS has been associated with a number of rare familial "cancer syndromes" such as the Li-Fraumeni syndrome (LFS), which includes familial clustering of RMS and other soft tissue tumours in children, with adrenocortical carcinoma and early-onset breast carcinoma in adult relatives. The LFS has been associated with germline mutations of the p53 tumour suppressor gene.

RMS has also been seen in association with Beckwith-Wiedemann syndrome, a foetal overgrowth syndrome associated with abnormalities on 11p15, where the insulin-like growth factor II (IGFII) gene is located.

Studies of children with Costello's syndrome, likely an autosomal dominant disorder characterised by postnatal growth retardation, typical coarse faces, loose skin and developmental delay, have noted an increased risk for development of solid tumours, most commonly rhabdomyosarcoma.

Cortes Barrantes, P., Jakobiec, F.A. & Dryja, T.P. 2019.

"Rhabdomyosarcoma (RMS) is the most common sarcoma of childhood and adolescence. Approximately 10% arise in the orbit, where the embryonal type is most common variant. The alveolar variant is less frequent and has a worse prognosis. Cytogenetic studies have revealed that most alveolar rhabdomyosarcomas have translocations involving the PAX and the FOX01 genes, giving rise to fusion genes that contribute to lack of differentiation and proliferation of the tumor cells. However, approximately 20% of alveolar rhabdomyosarcomas lack translocations and have been found to behave more similarly to embryonal cases. Histopathology remains the basis of diagnosis, but cytogenetic features and molecular signatures are becoming part of the routine analysis of RMS, since they determine not only prognosis, but also management and treatment regimens. A comprehensive review of the recent published literature in relation to orbital rhabdomyosarcomas and their cytogenetic features as well as clinical and therapeutic implications will be discussed."

Signs and Symptoms of Childhood Rhabdomyosarcoma (RMS)
RMS usually manifests as an expanding mass. Tumours in superficial locations may be palpable and detected relatively early, but those in deep locations (e.g., retroperitoneum) may grow large before causing symptoms.

The symptoms that occur depend on where the cancer forms. Other conditions may cause the same symptoms.

Typical presentations of non-metastatic disease, by location, are as follows:
- Orbit: Proptosis (Exophthalmos, also called exophthalmia, is a bulging of the eye anteriorly out of the orbit)
- Dysconjugate gaze (failure of the eyes to turn together in the same direction)
- Paratesticular: Painless scrotal mass
- Prostate: Bladder or bowel difficulties
- Uterus, cervix, bladder: Menorrhagia (abnormally heavy and prolonged menstrual period at regular intervals) or metrorrhagia (excessive uterine bleeding at irregular intervals, particularly between the expected menstrual periods)
- Vagina: Protruding polypoid mass (botryoid, meaning a grapelike cluster)
- Extremity: Painless mass
- Parameningeal (ear, mastoid, nasal cavity, paranasal sinuses, infratemporal fossa, pterygopalatine fossa): Upper respiratory symptoms or pain

Metastatic disease may cause the following symptoms:
- Bone pain
- Respiratory difficulty (secondary to lung nodules or to pleural effusion)
- Anaemia
- Thrombocytopenia
- Neutropenia

A doctor should be consulted if any of the following problems occur:
- A lump or swelling that keeps getting bigger or does not go away. It may be painful
- Bulging of the eye
- Headache
- Trouble urinating or having bowel movements
- Blood in the urine
- Bleeding in the nose, throat, vagina, or rectum

Diagnosis of Rhabdomyosarcoma (RMS)
The following tests and procedures may be used:

Physical exam and 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. 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.

CT scan (CAT scan) - a procedure that makes a series of detailed pictures of areas inside the body, such as the abdomen or pelvis, 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.

MRI (magnetic resonance imaging) - a procedure that uses a magnet, radio waves, and a computer to make a series of detailed pictures of areas inside the body. This procedure is also called nuclear magnetic resonance imaging (NMRI).

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 and is detected by a scanner.

Lumbar puncture - a procedure used to collect cerebrospinal fluid (CSF) from the spinal column to check for cancer cells. This is done by placing a needle between two bones in the spine and into the spinal column to remove a sample of CSF. This procedure is also called an LP or spinal tap.

Ultrasound examination - a procedure in which high-energy sound waves (ultrasound) are bounced off internal tissues or organs and make echoes. The echoes form a picture of body tissues called a sonogram.

Biopsy-the removal of cells or tissues so they can be viewed under a microscope by a pathologist to check for signs of cancer. The biopsy is done after imaging tests are done. If RMS is found, the pathologist will determine the type. Because treatment depends on the type of RMS, patients should ask to have biopsy samples checked by a pathologist who has experience in diagnosing RMS.

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.

Light and electron microscopy - a laboratory test in which cells in a sample of tissue are viewed under regular and high-powered microscopes to look for certain changes in the cells.

Immunohistochemistry study - a laboratory test in which a substance such as an antibody, dye, or radioisotope is added to a sample of cancer tissue to test for certain antigens. This type of study is used to tell the difference between different types of cancer.

Factors that Affect Prognosis (Chance of Recovery) and Treatment Options

The prognosis (chance of recovery) and treatment options depend on the following:

- Where in the body the tumour started
- The size of the tumour at the time of diagnosis
- Whether the tumour has been completely removed by surgery

- Whether the tumour has spread to nearby lymph nodes or distant parts of the body
- The type of RMS
- The patient's age and general health
- Whether the tumour has just been diagnosed or has recurred (come back)

For patients with recurrent cancer, prognosis and treatment depend on the following:
- Where in the body the tumour recurred (came back)
- How much time passed between the end of cancer treatment and when the cancer recurred

Staging of Childhood Rhabdomyosarcoma (RMS)
Childhood RMS is staged by using three different ways to describe the cancer:
- A staging system
- A grouping system
- A risk group

The staging system is based on the size of the tumour, where it is in the body, and whether it has spread to other parts of the body:

Stage 1
In stage 1, cancer is any size, has not spread to lymph nodes, and is found in only one of the following 'favourable' sites:
- Eye or area around the eye.
- Head and neck (but not in the tissue next to the brain and spinal cord).
- Gallbladder and bile ducts
- In the testes or vagina (but not in the kidney, bladder or prostate)

RMS that occurs in a 'favourable' site has a better prognosis (outcome). If the site where cancer occurs is not one of the favourable sites listed above, it is said to be an 'unfavourable' site.

Pea, peanut, walnut, and lime show tumour sizes.

Stage 2
In stage 2, cancer is found in any one area not included in stage 1. The tumour is 5cm or smaller and has not spread to lymph nodes

Stage 3
In stage 3, cancer is found in any one area not included in stage 1 and one of the following is true:
- The tumour is 5cm or smaller and cancer has spread to nearby lymph nodes
- The tumour is larger than 5cm and cancer may have spread to nearby lymph nodes

Stage 4
In stage4, the tumour may be any size and cancer may have spread to nearby lymph nodes. Cancer has also spread to distant parts of the body such as the lung, bone marrow, or bone

The grouping system is based on whether the cancer has spread and how much cancer remains after surgery to remove the tumour:

Group I
Cancer was found only in the place where it started and it was completely removed by surgery. Tissue was taken from the edges of where the tumour was removed. The tissue was checked under a microscope by a pathologist and no cancer cells were seen.

Group II
Group II is divided into groups IIA, IIB, and IIC.

- IIA: Cancer was removed by surgery but cancer cells were seen when the tissue, taken from the edges of where the tumour was removed, was viewed under a microscope by a pathologist
- IIB: Cancer had spread to nearby lymph nodes and the cancer and lymph nodes were removed by surgery
- IIC: Cancer had spread to nearby lymph nodes and the cancer and lymph nodes were removed by surgery. Tissue was taken from the edges of where the tumour was removed. The tissue was checked under a microscope by a pathologist and no cancer cells were seen

Group III
Cancer was partly removed by surgery and there are cancer cells (a lump or mass) remaining that can be seen by X-ray or other imaging test. Cancer has not spread to distant parts of the body.

Group IV
Cancer had spread to distant parts of the body at the time of diagnosis.

The risk group is based on the staging system and the grouping system and is used to plan treatment.

The risk group describes the chance that RMS will recur (come back). The following risk groups are used:

Low-risk childhood RMS
Low-risk childhood RMS is one of the following:

- An embryonal tumour of any size that is found in a 'favourable' site. There may be tumour remaining after surgery that can be seen without a microscope. The cancer may have spread to nearby lymph nodes. The following areas are 'favourable' sites:
    - Eye or area around the eye.
    - Head or neck (but not in the tissue next to the brain and spinal cord)
    - Gall bladder and bile ducts
    - In the testes or vagina (but not in the kidney, bladder, or prostate)
- An embryonal tumour of any size that is not found in one of the 'favourable' sites listed above. There may be tumour remaining after surgery that can be seen only with a microscope. The cancer may have spread to nearby lymph nodes.

Intermediate-risk childhood RMS

Intermediate-risk childhood RMS is one of the following:

- An embryonal tumour of any size that is not found in one of the 'favourable' sites listed above. There is tumour remaining after surgery, that can be seen with or without a microscope. The cancer may have spread to nearby lymph nodes
- An alveolar tumour of any size in a 'favourable' or 'unfavourable' site. There may be tumour remaining after surgery that can be seen with or without a microscope. The cancer may have spread to nearby lymph nodes.

High-risk childhood RMS

High-risk childhood RMS may be the embryonal type or the alveolar type. It may have spread to nearby lymph nodes and has spread to one or more distant parts of the body.

Treatment of Childhood Rhabdomyosarcoma (RMS)

The treatment of childhood RMS often includes surgery, radiation therapy, and chemotherapy. The order that these treatments are given depends on where in the body the tumour started, the size of the tumour, the type of tumour, and whether the tumour has spread to lymph nodes or other parts of the body.

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."

Slemmons, K.K., Yeung, C., Baumgart, J.T., Juarez, J.O.M., McCalla, A. & Helman, L.J. 2020

"Rhabdomyosarcoma is the most common childhood soft-tissue sarcoma, yet patients with metastatic or recurrent disease continue to do poorly, indicating a need for new treatments. The SRC family tyrosine kinase YES1 is upregulated in rhabdomyosarcoma and is necessary for growth, but clinical trials using single agent dasatinib, a SRC family kinase inhibitor, have failed in sarcomas. YAP1 (YES-associated protein) is highly expressed in rhabdomyosarcoma, driving growth and survival when the upstream Hippo tumor suppressor pathway is silenced, but efforts to pharmacologically inhibit YAP1 have been unsuccessful. Here we demonstrate that treatment of rhabdomyosarcoma with DNA methyltransferase inhibitor (DNMTi) upregulates Hippo activators RASSF1 and RASSF5 by promoter demethylation, activating canonical Hippo signaling and increasing inactivation of YAP1 by

phosphorylation. Treatment with DNMTi decreased rhabdomyosarcoma cell growth and increased apoptosis and differentiation, an effect partially rescued by expression of constitutively active YAP (S127A), suggesting the effects of DNMTi treatment are, in part, due to Hippo-dependent inhibition of YAP1. In addition, YES1 and YAP1 interacted in the nucleus of rhabdomyosarcoma cells, and genetic or pharmacologic suppression of YES1 resulted in cytoplasmic retention of YAP1 and decreased YAP1 target gene expression, suggesting YES1 regulates YAP1 in a Hippo-independent manner. Combined treatment with DNMTi and dasatinib targeted both Hippo-dependent and Hippo-independent regulation of YAP1, ablating rhabdomyosarcoma cell growth *in vitro* and trending toward decreased tumor growth *in vivo*. These results show that the mechanisms regulating YAP1 in rhabdomyosarcoma can be inhibited by combinatorial therapy of DNMTi and dasatinib, laying the groundwork for future clinical investigations. SIGNIFICANCE: This study elucidates the signaling pathways that regulate the oncogenic protein YAP1 and identifies a combination therapy to target these pathways in the childhood tumor rhabdomyosarcoma."

Gesche. J., Beckert, S., Neunhoeffer, F., Kachanov, D., Königsrainer, A., Seitz, G. & Fuchs, J. 2019. "Advanced and relapsed intraperitoneal rhabdomyosarcomas in young children represent an oncological challenge and options for local tumor control are limited. Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is commonly used in advanced peritoneal tumors in adults. However, no studies are available regarding CRS and HIPEC in young children.

"We report our experiences treating six patients with intraperitoneal rhabdomyosarcoma with CRS and HIPEC using cisplatin and doxorubicin focusing on safety and outcomes. No procedure-associated mortalities occurred and no major short- or long-term toxicities were recorded. All patients showed no evidence of disease after 12-month median (7-41) follow-up."

RMS of the brain and head and neck

- For tumours of the brain: Treatment may include surgery to remove the tumour, radiation therapy, and chemotherapy.
- For tumours of the head and neck that are in or near the eye: Treatment may include chemotherapy and radiation therapy. If the tumour remains or comes back after treatment with chemotherapy and radiation therapy, surgery to remove the eye and some tissues around the eye may be needed.
- For tumours of the head and neck that are near the brain and spinal cord but not in or near the eye: Treatment may include radiation therapy and chemotherapy.
- For tumours of the head and neck that cannot be removed by surgery: Treatment may include chemotherapy and radiation therapy.
- For tumours of the larynx (voice box): Treatment may include chemotherapy and radiation therapy. Surgery to remove the larynx is usually not done, so that the voice is not harmed.

RMS of the arms or legs

- Surgery to remove the tumour. If the tumour was not completely removed, a second surgery to remove the tumour may be done.
- For tumours of the hand or foot, radiation therapy and chemotherapy may be given. The tumour may not be removed because the function of the hand or foot would be lessened.
- Lymph node dissection (one or more lymph nodes are removed and a sample of tissue is checked under a microscope for signs of cancer).

    - For tumours in the arms, lymph nodes near the tumour and in the armpit area are removed.
    - For tumours in the legs, lymph nodes near the tumour and in the groin area are removed
- Chemotherapy
- Radiation therapy

RMS of the chest, abdomen, or pelvis

- For tumours in the chest or abdomen (including the chest wall or a abdominal wall): Surgery (wide local excision) may be done. If the tumour is large, chemotherapy, and sometimes radiation therapy, is given to shrink the tumour before surgery
- For tumours of the pelvis: Surgery (wide local excision) may be done. If the tumour is large, chemotherapy, and sometimes radiation therapy, is given to shrink the tumour before surgery. Some pelvic tumours may be treated with biopsy, rather than wide local excision, followed by radiation therapy
- For tumours of the diaphragm: A biopsy of the tumour is followed by chemotherapy and radiation therapy to shrink the tumour. Surgery may be done later to remove any remaining cancer cells
- For tumours of the gallbladder or bile ducts: Surgery is done to remove as much of the tumour as possible, followed by chemotherapy and radiation therapy
- For tumours of the muscles or tissues around the anus or between the vulva and the anus or the scrotum and the anus: Surgery is done to remove as much of the tumour as possible and some nearby lymph nodes, followed by chemotherapy and radiation therapy

RMS of the kidney

- Surgery to remove as much of the tumour as possible

RMS of the bladder and prostate

- For tumours that are only at the top of the bladder: Surgery (wide local excision) is done
- For tumours of the prostate or bladder (other than the top of the bladder):
    - Chemotherapy and radiation therapy are given first to shrink the tumour. If cancer cells remain after chemotherapy and radiation therapy, the tumour is removed by surgery. Surgery may include removal of the prostate, part of the bladder, or pelvic exenteration without removal of the rectum. (This may include removal of the lower colon and bladder. In girls, the cervix, vagina, ovaries, and nearby lymph nodes may be removed)
    - Chemotherapy is given first to shrink the tumour. Surgery to remove the tumour, but not the bladder or prostate, is done. Internal radiation therapy is given after surgery

RMS of the area near the testicles

- RMS of the testicular area is usually treated with surgery to remove the testicle and spermatic cord
- The lymph nodes in the back of the abdomen may be checked for cancer, especially if the lymph nodes are enlarged or the child is older than 9 years. Radiation therapy may be given if the tumour cannot be completely removed by surgery. CT scans may be done every 3 months after surgery to see if the cancer is growing in nearby lymph nodes

RMS of the vulva, vagina, uterus or ovary

- For tumours of the vulva and vagina: Treatment may include chemotherapy followed by surgery to remove the tumour. Internal or external radiation therapy may be given after surgery
- For tumours of the uterus: Treatment may include chemotherapy with or without radiation therapy. Sometimes surgery may be needed to remove any remaining cancer cells
- For tumours of the cervix: Treatment may include chemotherapy followed by surgery to remove any remaining tumour.
- For tumours of the ovary: Treatment may include combination chemotherapy followed by surgery to remove any remaining tumour

Metastatic RMS

- Radiation therapy may be given for tumours that have spread to the brain, spinal cord, or lungs
- Treatment is also given to the site where the tumour first formed.

Ramadan, F., Fahs, S., Ghayad, S.E. & Saab, R. 2020.
"Rhabdomyosarcoma (RMS) is an aggressive childhood mesenchymal tumor with two major molecular and histopathologic subtypes: fusion-positive (FP)RMS, characterized by the PAX3-FOXO1 fusion protein and largely of alveolar histology, and fusion-negative (FN)RMS, the majority of which exhibit embryonal tumor histology. Metastatic disease continues to be associated with poor overall survival despite intensive treatment strategies. Studies on RMS biology have provided some insight into autocrine as well as paracrine signaling pathways that contribute to invasion and metastatic propensity. Such pathways include those driven by the PAX3-FOXO1 fusion oncoprotein in FPRMS and signaling pathways such as IGF/RAS/MEK/ERK, PI3K/AKT/mTOR, cMET, FGFR4, and PDGFR in both FP and FNRMS. In addition, specific cytoskeletal proteins, G protein coupled receptors, Hedgehog, Notch, Wnt, Hippo, and p53 pathways play a role, as do specific microRNA. Paracrine factors, including secreted proteins and RMS-derived exosomes that carry cargo of protein and miRNA, have also recently emerged as potentially important players in RMS biology. This review summarizes the known factors contributing to RMS invasion and metastasis and their implications on identifying targets for treatment and a better understanding of metastatic RMS."

Mandeville, H.C. 2019.
"Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood, comprising over 50% of cases. It is considered to be an embryonal tumour of skeletal muscle cell origin, frequently occurring at genitourinary and head and neck sites, although it can arise throughout the body and at sites where there is no skeletal muscle. For most cases, multimodality therapy is required to achieve the best results, incorporating induction ifosfamide, vincristine and actinomycin D-based chemotherapy and local therapy (radiotherapy and/or surgery). Recent reports from the European Paediatric Soft Tissue Sarcoma Group (EpSSG) RMS 2005 study have shown significant improvements in outcomes; high-risk rhabdomyosarcoma having a 3-year event-free survival and overall survival of about 68% and 80%, respectively. The more routine use of radiotherapy is considered to be a contributing factor to these improved results, but does also often result in significant long-term sequelae for survivors. Despite an increasing number of rhabdomyosarcoma treated with advanced radiotherapy techniques, including protons, brachytherapy and rotational intensity-modulated radiotherapy, in an effort to reduce the frequency of late complications, there remain a number of unanswered questions. Future planned collaborative group studies, such as the EpSSG Frontline and

Relapsed Rhabdomyosarcoma (FaR-RMS) study, are looking to address these questions, investigating the potential benefits of preoperative radiotherapy, dose escalation and the irradiation of metastatic sites."

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/

Medical Disclaimer

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Muscle Cells
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