Cancer Association of South Africa (CANSA)

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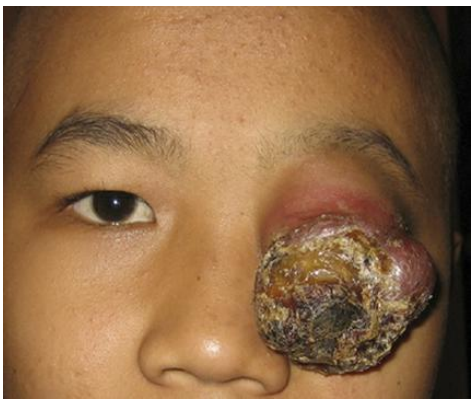
Fact Sheet
on
Adult Rhabdomyosarcoma and Pleomorphic Rhabdomyosarcoma

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.

Wang, J.N., Zhang, Q., Li, R.B., Sha, Y.J. & Wang, C.B. 2019.
Objective: This study aimed to explore the effect of perfluorooctanoate acid (PFOA) on the proliferation, migration and invasion of the human muscle rhabdomyosarcoma RD cell line and its related mechanisms.
Methods: RD cells were cultured and exposed to PFOA of different concentrations with 6-72 hours. The cell viability was assessed by cell counting kit-8 (CCK-8) assay. Wound healing and transwell filter assay were used to evaluated the migration and invasion ability of the RD cells respectively. The cell cycles were detected by Flow cytometry. Quantitative real-time PCR and Western blot were used to quantify the mRNA and protein expression difference of related genes, respectively.
Results: CCK-8 assay showed that, after treated the RD cell with different dose of PFOA for 72 h, low dose PFOA (1,10,50, 100 μmol/L) promotes the proliferation of RD cells while high dose PFOA (250, 500 mol/L) inhibits the proliferation (P<0.001). Flow cytometry showed that compared with the control group, there was no significant difference in G0/G1 phase, while cells in S phase deceased

and G2/M phase cells increased after treated with PFOA (50 μmol/L) for 72 h. The relative proportions of S and G2/M were significantly different between the two groups (P<0.01). The results of qPCR showed that the mRNA relative expression of CDK2 of the control group and the PFOA (50 μmol/L) group were 0.97±0.07 and 2.64±0.11 respectively, and there was a significant difference (t=12.60, P<0.001); The mRNA relative expression of cyclin E2 of the control group and the PFOA (50 μmol/L) group were 1.33±0.17 and 3.35±0.22 respectively, and there was a significant difference (t=7.42, P<0.001); The results of Western blot showed that the protein relative expression of CDK2 of the control group and the PFOA (50 μmol/L) group were 0.35±0.01 and 0.84±0.03 respectively, and there was a significant difference (t=14.60, P<0.001); The protein relative expression of cyclin E2 of the control group and the PFOA (50 μmol/L) group were 0.67±0.04 and 0.86±0.01 respectively, and there was a significant difference (t=4.88, P<0.01); There was no significant difference in the mRNA and protein expression of p21 and p53 between the PFOA and control group (P>0.05). The wound healing rate of the PFOA (50 μmol/L) group was faster than that of the control group, and the relative migration area of the PFOA group was larger accordingly (P<0.001). After PFOA (50 μmol/L) treated, the number of the cell through the membranes was much more than the control group (t=54.40, P<0.001), which means PFOA significantly stimulated the invasion ability of the RD cells. The results of qPCR showed that the mRNA relative expression of vimentin of the control group and the PFOA (50 μmol/L) group were 0.71±0.03 and 2.53±0.16 respectively, and there was a significant difference (t=11.00, P<0.001); The mRNA relative expression of MMP2 of the control group and the PFOA (50 μmol/L) group were 1.09±0.04 and 10.73±1.20 respectively, and there was a significant difference (t=8.04, P<0.001). The results of Western blot showed that the protein relative expression of vimentin of the control group and the PFOA (50 μmol/L) group were 0.55±0.06 and 0.81±0.01 respectively, and there was a significant difference (t=4.50, P<0.05). The protein relative expression of cyclin E2 of the control group and the PFOA (50 μmol/L) group were 0.64±0.04 and 1.03±0.13 respectively, and there was a significant difference (t=2.94, P<0.05).
Conclusions: Low dose PFOA (50 μmol/L) exposure promotes cell proliferation, migration and invasion in the human muscle rhabdomyosarcoma cell line through inducing the expressions of MMP2, vimentin and cell cycle related genes.

Kaseb, H., Kuhn, J. & Babiker, H.M. 2019.
"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 ."

Incidence of Rhabdomyosarcoma in South Africa
The outdated National Cancer Registry (2016) 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

Soffer, S., Amitai, M.M., Shimon, O., Ohana, O., Rozendorn, N., Barshack, I., Weitzen R. & Klang, E. 2019.

PURPOSE: Ki-67 is a marker of cellular proliferation that is commonly used for the assessment of rhabdomyosarcoma. The aim of this study was to investigate the associations between Ki-67 expression and primary tumor diameter with CT evidence of lymph node and solid organ metastatic spread in rhabdomyosarcoma.

MATERIALS AND METHODS: An institutional review board approval was granted for this study. A retrospective search for rhabdomyosarcoma patients was conducted. Pathology reports were examined for Ki-67 expression. Chest-abdomen CT was assessed for radiological evidence of lymph node and metastatic spread. The maximal primary tumor diameter (termed tumor size) was also measured in different modalities CT, MRI, PET-CT and US. Ki-67 levels and primary tumor maximal diameters were compared to CT evidence of lymph node and organ metastatic spread.

RESULTS: Twenty-four patients with rhabdomyosarcoma were included. CT evidence of lymph node spread was associated with Ki-67 levels (AUC = 0.896, p = 0.006) and to a lesser extent with tumor size (AUC = 0.790, p = 0.030). However, organ metastatic spread was associated only with tumor size (AUC = 0.854, p = 0.006) and not with Ki-67 levels (AUC = 0.604, p = 0.469). A combination of tumor size ≥50 mm and Ki-67 levels ≥60% was significantly associated with CT evidence of lymph node spread (p = 0.004).

CONCLUSION: In conclusion, this study demonstrates radiological-pathological correlation in RMS. Lymph node spread detected by radiological images is associated with Ki-67 values. Lymph node and metastatic spread are associated with primary tumor size.

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.

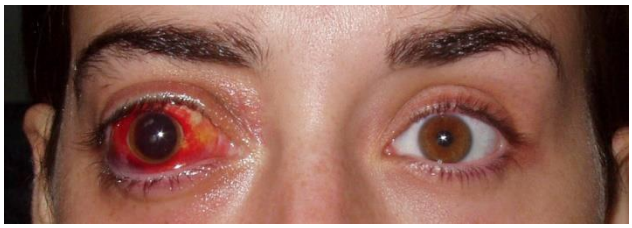
Liu, Y.T., Wang, C.W., Hong, R.L. & Kuo, S.H. 2019.
BACKGROUND: Adults with rhabdomyosarcoma (RMS) have a worse clinical outcome compared to pediatric cases. In the present study, the failure pattern and clinical outcome of adult patients with RMS who received multimodality treatment at our Institution 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

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 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."

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/

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