Introduction
A sarcoma is a soft tissue, connective tissue or a bone cancerous malignant tumor. They can occur in either children or adults. For children under 20, 15% of cancer cases are sarcomas.1

Rhabdomyosarcoma (RMS) is a type of sarcoma that is caused by a disruption in the pathway of primitive mesenchymal stem cells directed towards myogenesis.2 Although RMS is a very rare form of cancer, it is the most common pediatric sarcoma, primarily affecting children before the age of 5, yet is very rare in adults.3 From the year 2006 to 2010 there has been 295 cases of children diagnosed with RMS in Canada, with 43 mortalities from the year 2008 to 2012.4 RMS is 1.4 times more likely in males than females, and it is not different among different races of ethnicities.5 There are 4 major types of RMS. Embryonal rhabdomyosarcoma (ERMS) is the most common type of RMS representing 70% of cases, and it usually affects children under 10 years of age. The other three types include alveolar rhabdomyosarcoma (ARMS), pleomorphic rhabdomyosarcoma (PRMS), and sclerosing/spindle cell Rhabdomyosarcoma, which comprise the remaining 30%.6 We have summarized the distribution of different RMS subtypes in Figure 1.

Keywords: Rhabdomyosarcoma, Childhood cancer, Cancer therapy.
genetic patterns. For example, in the case of ERMS there are typically gains and losses of chromosomal regions, whereas in patients diagnosed with ARMS there are generally amplifications in the regions of the genome. Treatment of patients diagnosed with RMS involves a multi-step plan consisting of surgery, radiotherapy, and chemotherapy. From 1971 to the year 2000 the 5-year survival rate has gone up from 25% to 60%. Treatment failures occur due to many reasons, the most common ones being drug resistance and metastatic diseases.

**Biology**

Morphological and biological studies have revealed that RMS is a malignant neoplasm originating from immature myoblasts. Although the origins of RMS are not clear, RMS occurs when there is a disruption within the genetic differentiation pathway in myogenic precursor cells, so that RMS cells display features of undifferentiated fetal myoblasts. Consistent with this observation RMS cells have been shown to upregulated fetal genes such as FGFR4 (fibroblast growth factor receptor 4), NOTCH2 (neurogenic locus notch homolog protein 2), UBE2C (ubiquitin-conjugating enzyme E2 C), UHRF1 (ubiquitin-like, containing PHD and RING finger domains 1), and YWHAB genes. These observations led to the hypothesis that disruption in myocyte differentiation is an oncocgenic process contributing to the development of RMS.

In most cases of patients diagnosed with RMS there is a genetic or chromosomal alteration involved. In 80% of ARMS cases patients have a gene fusion involving either PAX3 (paired box 3) or PAX7 (paired box 7) and FOXO1 (forkhead box protein O1) created by a chromosomal translocation, t(2;13)(q35;q14) and t(1;13)(p36;q14) respectively. The resulting PAX3-FOXO1 or PAX7-FOXO1 fusion genes creates potent transcription factors that prevents myoblast differentiation and the expression of the MyoD family of muscle regulatory factors (MRF).

In addition, a previous study revealed that ARMS tumors have fewer copy number variants than cases that were studied with ERMS tumors. Most ERMS tumors involve chromosomal region gains and losses, such as gains in TYROBP (TYRO protein tyrosine kinase-binding protein), HCST (hematopoietic cell signal transducer), LRFN3 (leucine rich repeat and fibronectin type III domain containing 3), and ALKBH6 (AlkB Homolog 6) (19q13.12), whereas most ARMS cases have amplified regions in their chromosomes such as the following genes, CDK4 (cyclin dependent kinase 4), MYCN (v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog), GLI, MDM2 (mouse double minute 2 homolog), FGFR1, and FGFR.

**Diagnosis**

Early diagnosis of RMS in children is an important step towards improving their survival rate and quality of life. The primary step for diagnosing RMS is radiography, then in the case of a positive test result, further steps are considered. Referral of the patient to a pediatric tertiary hospital, where they can finalize the diagnosis of RMS with a complete team of pediatrics, general and orthopedic surgeons, oncologists, radiologists, and pathologists. Complete primary evaluation of the bone or soft tissue are usually done through 2 techniques: (1)
magnetic resonance imaging or MRI, and (2) computed tomography or CT scan. For a more conclusive diagnosis, it is recommended that the imaging includes the entire long bone and its adjacent joints. The primary sites of RMS tumour has been summarized in Figure 2. For diagnosis of metastatic RMS different steps should be considered, such as whole body nuclear bone scan and CT of the patient's chest, in order to determine whether the cancer has reached other sites on the body or not, so further action can be considered.

After the initial steps, such as primary bone and soft tissue examination in a tertiary care centre and a whole body nuclear bone scan, “staging” of the cancer should be considered in order to determine the extent of the initial and whether or not it has spread throughout the body. Conventional staging processes are consistent of tumor, lymph node, and metastases or better known as TNM.

A modified version of this conventional method is used in the staging of RMS to indicate the advancement of the disease on a scale of 1 to 4. These stages are associated with group assignments that subsumes their initial surgical approaches, for example a group I is a patient with a localized tumor and no metastatic diseases, where the tumor can be located and completely resected. Whereas in a group IV patient a distant metastatic disease is in existence.

Thus, the entire process of diagnosis of RMS involves the pathological diagnosis, histological subtypes where the subtype (PRMS, ARMS, ERMS, and SRMS) of the RMS is indicated, followed by determining disease's primary site. The final step in the diagnosis of RMS is staging and grouping where the extent of the disease and the advancement of the tumor is identified.

Treatment

After RMS diagnosis, staging and grouping the patient's condition, the patients’ treatment immediately begins. RMS treatment includes a multiple step strategies, starting from a surgical treatment following with chemical and radiation stages.

Surgical: Resecting the original tumor site to gather all of the macro remnants of the malignant tumor is the first step toward treating a patient with RMS. Benefits of the surgical procedures are evident in patients with a group I or the localized tumor RMS, as their survival rate dramatically increase in those who have gone under the procedure, compared to the group III and IV patients that have distant metastatic diseases. A surgeon's goal is to rid the body from the neoplastic cells as much as possible whilst trying to avoid amputation.

Numerous complications may be caused by a surgical procedure that could compromise a person's daily functioning, therefore a new standard has been set by the COG and the North American RMS study group that states a surgical procedure shall not alter or compromise the form nor the functionality of an organ. Through careful considerations scientists have concluded that in case of a patient whose tumor cannot be resected during the initial stages, the resection should be delayed for 12 weeks during which the patient goes through chemotherapy. The reason for why this chemotherapeutic period makes a difference is yet to be learnt.

Radiation: through radiotherapy the cancerous cells are damaged or broken down by using high energy particles such as x-rays, gamma rays, electron beams, or protons. This approach is usually considered as a post-surgical method that eradicates any microscopic amounts of neoplastic particles that are still present in the body after the resection.

In RMS diagnosed patients an ionizing radiation is considered to be the best method to liberate the body from the cancerous cells, which is advised throughout the first 12 weeks of recovery after the surgery for patients diagnosed as a group I RMS; though, COG has recently reveal in a study that patients at an intermediate level of risk can go through a 4-week radiotherapy treatment plan.

Chemotherapy: In order to stop the growth and the dividing of the cancerous cells another therapeutic method is used by exposing the body to chemical substances. In the case of RMS, cytotoxic chemotherapy is the most commonly used therapy. For an RMS patient to be treated chemically a combination of vincristine, actinomycin-D, and cyclophosphamide is necessary, but in some cases where the patient is considered as a low risk to an intermediate patient the combination of vincristine and actinomycin-D alone should be sufficient although it is often received by the patient with low doses of cyclophosphamide. Other supplementary drugs have been discovered to be helpful in lowering the chances of failure in the process, but their impact in long term is not known yet. Chemotherapy can also be done through oral medications such as temozolomide. Temozolomide is a drug that is often used to treat types of brain tumors called glioblastoma multiforme or anaplastic astrocytoma. It is an alkylating agent that stops the cancerous cells from making new DNAs, so the cancer cannot grow. Temozolomide can be added to vincristine and actinomycin-D to help stop the cancer from progressing, but the results are still inconclusive. Furthermore, temozolomide resistant RMS has been reported in the literature, but the extent of this observation or the clinical consequences of resistance has not yet been determined.

Conclusion

Over the past decades there has been an appreciable elevations in diagnosis and treatment of RMS, where early diagnosis with improved and advanced techniques, improved categorizing the disease, and the discovery of more effective cytotoxic chemicals, has resulted in a better survival rate for RMS patients from 25% to 60%. However, additional researches and clinical trials are needed, especially in ARMS where survival rate remains markedly low, in order to minimize the devastating consequences of the pediatric cancer.
Ethical Approval
Not applicable.

Competing Interests
Authors declare that they have no competing interests.

References:
4. Statistics Canada. CANSIM Table 102-0522 - Deaths bc, Chapter II: Neoplasms (C00 to D48), age group and sex, Canada, annual (number). http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=1020522.