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# Rhabdomyosarcoma (RMS): Insights into Epidemiology, Molecular Classification, Therapeutic Advances, and Future Directions

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***Abstract***

*Rhabdomyosarcoma (RMS), the most common soft tissue sarcoma in children, represents a formidable challenge in pediatric oncology. This review article delves into the multifaceted landscape of RMS, combining clinical insights with molecular intricacies to provide a comprehensive overview.*

*RMS manifests in two major subtypes, alveolar RMS (ARMS) and embryonal RMS (ERMS), each propelled by distinct molecular mechanisms. While initial classification was based on histological features, fusion status now plays a pivotal role. Fusion-positive (FP) RMS, characterized by PAX3–FOXO1 or PAX7–FOXO1 translocations, presents unique clinical challenges, while fusion-negative (FN) RMS shares similarities with ERMS.*

*Accurate risk stratification, encompassing clinical, pathological, and molecular attributes, is imperative in tailoring therapeutic strategies. Current treatment modalities encompass surgical resection, ionizing radiation, and cytotoxic chemotherapy. These multidimensional approaches have significantly improved survival rates over the past three decades.*

*RMS continues to pose obstacles, particularly for patients with metastatic or recurrent disease. Treatment-related toxicities and long-term late effects further underscore the need for innovative therapeutic avenues and comprehensive survivorship care.*

*This review article provides a detailed portrait of RMS, from epidemiology to molecular subtypes, risk stratification, and treatment modalities. As research unveils RMS's biological intricacies through next-generation sequencing and advanced disease models, the path toward improved clinical outcomes becomes increasingly discernible.*

## Introduction

Rhabdomyosarcoma (RMS) stands as a formidable adversary within the domain of pediatric oncology [1]. This malignancy reigns as the most prevalent soft tissue sarcoma among children, characterized by the presence of malignant cells bearing a striking resemblance to skeletal myoblasts [2]. The battle against RMS has witnessed significant progress over the years, fueled by relentless clinical and scientific endeavors. This review endeavors to dissect the challenging mosaic of RMS, embarking on an expedition through its multifaceted dimensions, ranging from epidemiological insights to molecular subtypes, elusive risk factors, intricate disease classifications, evolving treatment paradigms, and the hopeful horizons of forthcoming research.

For decades, RMS has maintained its notoriety as a challenging adversary, necessitating an interdisciplinary approach and a deeper comprehension of its nuanced nature. The pursuit of unraveling RMS begins with an exploration of its epidemiological footprint, revealing both its rarity and the profound impact it has on the pediatric oncology landscape. As we delve into the core of RMS, the distinct molecular subtypes, alveolar RMS (ARMS), and embryonal RMS (ERMS), emerge as key players [3]. These subtypes, underpinned by fundamentally different molecular mechanisms, introduce unique clinical conundrums, and underscore the importance of precise disease classification.

Unveiling the enigmatic origins of RMS requires a glimpse into the cryptic world of risk factors. Although many mysteries enshroud the etiology of this malignancy, certain factors, such as in-utero radiation exposure, accelerated in-utero growth, and parental recreational drug use during pregnancy, have been implicated. RMS also casts its shadow over familial syndromes, such as neurofibromatosis, Noonan syndrome, Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and Costello syndrome, further deepening the complexity of its genesis [4-7].

In the clinical arena, RMS manifests diversely, affecting various anatomical sites in children. These clinical nuances necessitate sophisticated risk stratification, wherein clinical, pathological, and molecular features intertwine to guide therapeutic decisions. The treatment landscape for RMS encompasses a triad of surgical resection, ionizing radiation, and cytotoxic chemotherapy. The evolution of multidisciplinary treatment approaches has witnessed substantial improvements in patient outcomes over the past three decades.

Yet, RMS continues to stand as an unyielding adversary, especially for patients grappling with metastatic or recurrent disease. The toll of intensive therapies, fraught with treatment-related toxicities, underscores the urgency of innovative therapeutic avenues and comprehensive survivorship care. In this ever-evolving landscape, research endeavors unearth the molecular intricacies of RMS, ushering in a new era of understanding and illuminating promising avenues for improved clinical outcomes.

This comprehensive review embarks on a journey through the labyrinthine corridors of RMS, weaving together the threads of its epidemiology, molecular fabric, clinical challenges, and the tantalizing vistas of future research. As we traverse these intricate domains, a clearer picture of RMS emerges, offering hope and resilience in the ongoing battle against this pediatric malignancy.

## Epidemiology

Despite its rarity, RMS carries a substantial global disease burden, primarily affecting children. The overall incidence rate of RMS is estimated to be approximately 4.5 cases per million individuals aged under 20 years [8]. In the United States alone, this translates to approximately 350 new cases each year. Interestingly, the incidence of RMS exhibits regional variability, with higher rates reported in North America and Europe compared to certain Asian populations [9].

## Risk Factors

Understanding the factors that elevate the risk of developing RMS is pivotal. Recent research has shed light on genetic susceptibility and environmental factors that contribute to RMS development. Genetic syndromes such as Li-Fraumeni syndrome, Neurofibromatosis type I, Costello syndrome, Noonan syndrome, and others have been associated with an increased risk of RMS [4]–[6]. However, it's important to note that only a minority of RMS cases are linked to these syndromes. Environmental factors, including prenatal X-ray exposures and parental recreational drug use, have also been implicated in RMS risk [10].

## Molecular Subtypes

### Alveolar RMS (ARMS) and Embryonal RMS (ERMS)

RMS is not a singular entity but rather a group of tumors with diverse molecular characteristics. The two major subtypes, alveolar RMS (ARMS) and embryonal RMS (ERMS), were initially distinguished based on their histological features [11]. However, recent molecular investigations have revealed fundamental differences in their underlying mechanisms and clinical behavior [3].

## Rare RMS Variants

The World Health Organization (WHO) recognizes two rarer RMS subtypes: pleomorphic RMS and spindle cell/sclerosing RMS variants in children. These variants exhibit distinct clinical features and may carry specific somatic mutations, further complicating the RMS landscape [12].

## Fusion Proteins and Molecular Characterization

Molecular biology approaches and next-generation DNA and RNA sequencing have unveiled critical insights into RMS. ARMS-associated translocations generate fusion proteins involving paired box proteins PAX3 or PAX7 and forkhead box protein O1 (FOXO1). This molecular characterization provides a more precise framework for classifying RMS subtypes and guiding treatment strategies [13].

## Disease Classification and Risk Stratification

### RMS Subtype Refinement

The classification of RMS subtypes has evolved with our deepening molecular understanding of the disease. While initial subtyping relied on histological features, contemporary classification primarily hinges on fusion status. Although we predominantly refer to RMS subtypes based on fusion status, the terms ARMS and ERMS are still employed when referencing historical research and pathology reports [14], [15].

## Impact of Fusion Status

Fusion status, categorized as 'fusion positive' (FP) and 'fusion negative' (FN) RMS, has a profound influence on disease progression and management. Fusion proteins involving PAX3–FOXO1 or PAX7–FOXO1 are hallmark features of ARMS, whereas ERMS typically lacks these translocations [13]. It's noteworthy that a subset of ARMS cases may not harbor these translocations but share biological and clinical characteristics with ERMS [12].

## Risk Stratification

Precise risk stratification is crucial in tailoring treatment strategies for RMS patients. Risk assessment in pediatric RMS is a multifaceted process, incorporating clinical, pathological, and molecular features. This holistic approach aims to distinguish between low, intermediate, and high-risk groups, guiding the application of comprehensive therapy [16].

## Treatment Modalities

### RMS Therapeutic Advancements

Over the past three decades, significant strides have been made in treating RMS, marked by improved survival rates. Clinical trials conducted by cooperative groups across North America and Europe have played a pivotal role in advancing therapeutic strategies. Traditionally, RMS treatment has encompassed cytotoxic chemotherapy, surgery, ionizing radiation, or a combination of these modalities [17].

## Surgical Resection and Radiation

Control of the primary tumor through surgical resection and/or ionizing radiation remains a cornerstone of curative therapy. RMS can manifest in various anatomical sites, demanding tailored surgical approaches. The judicious use of radiation therapy has contributed to local tumor control, especially in cases where complete resection is challenging [17].

## Chemotherapy

Cytotoxic chemotherapy, administered as a crucial component of RMS treatment, targets both primary tumors and disseminat-

ed disease. Combination chemotherapy regimens have evolved to enhance efficacy while minimizing toxicity, marking a significant advancement in patient care [17].

## Quality of Life in Pediatric Rhabdomyosarcoma Survivors

In the past four decades, clinical trials in North America and Europe have predominantly concentrated on enhancing the survival rates of pediatric rhabdomyosarcoma (RMS) patients. While some consideration has been given to Quality of Life (QOL) concerns, like avoiding surgeries with potential form or function implications, comprehensive QOL data collection in these trials has been limited [18]. Given that a substantial portion of children diagnosed with RMS ultimately become long-term, disease-free survivors, it is vital to integrate QOL assessments during and after RMS therapy.

Children grappling with cancer frequently endure significant suffering and enduring symptom burdens stemming from both the disease itself and its treatments. Toxicity reporting in pediatric cooperative group studies typically relies on symptom descriptions documented by healthcare providers and subsequently extracted from medical records by researchers. However, these accounts may not fully encapsulate the genuine experiences of the patients themselves [18].

QOL evaluations in RMS survivors' post-therapy are pivotal, yet certain knowledge gaps endure. Genitourinary and sexual/reproductive health are two domains where issues may emerge in this population, although available QOL data are primarily derived from small-scale studies. For instance, one study examining the effects of proton therapy in pediatric patients with bladder and/or prostate disease included only five children who achieved disease-free status, presenting issues ranging from none to enuresis [18]. Another small study of four patients aged over 14 and previously treated for prostate or bladder RMS assessed sexual function using a modified International Erectile Function Index, revealing that two of the four patients achieved moderate or good quality scores after pelvic radiation therapy and cystectomy [19].

Given the ongoing debates concerning the optimal delivery of ionizing radiation, especially in cases involving large-field irradiation, such as pelvic RMS affecting the bladder and prostate, it is imperative to gather prospective data on bladder and sexual function. This becomes especially relevant when the likelihood of disease cure remains similar with or without radiation therapy. Such data can play a pivotal role in guiding treatment decisions for patients poised to achieve disease-free status [19], [20].

## Challenges and Future Directions

While substantial progress has been made in understanding and treating pediatric rhabdomyosarcoma (RMS), several formidable challenges continue to define the landscape of this malignancy. Patients grappling with widespread metastatic disease or experiencing disease recurrence still face daunting odds, underscoring the urgency of developing novel therapeutic strategies.

The aggressive multimodal treatments employed against RMS, including surgery, radiation, and chemotherapy, are essential in combating the disease [14]. However, these treatments can also impose life-threatening acute toxicities and pose the risk of long-term late effects, ranging from cardiac and pulmonary issues to fertility and growth impairments. As a result, comprehensive survivorship care programs are imperative to monitor and address these late effects, ensuring the well-being of RMS survivors [21].

To address these challenges and forge a brighter future for RMS patients, ongoing research endeavors are focusing on elucidating the intricate molecular mechanisms driving RMS.

Cutting-edge technologies, such as next-generation sequencing and patient-derived xenograft models, are providing unprecedented insights into the disease's biology. These advances hold the promise of not only improving survival rates but also mitigating the treatment-related burdens, ultimately enhancing the quality of life for young RMS survivors.

## Conclusion

Rhabdomyosarcoma (RMS) stands as a formidable adversary within the realm of pediatric oncology. With its prevalence as the most common soft tissue sarcoma in children and its capacity to affect various anatomical sites, RMS has demanded rigorous attention from clinicians, researchers, and healthcare providers. Over the years, an amalgamation of clinical insights and groundbreaking molecular research has reshaped our comprehension of this rare malignancy.

Two major subtypes, alveolar RMS (ARMS) and embryonal RMS (ERMS), initially classified based on histological features, have now pivoted towards a molecular framework. The advent of fusion-positive (FP) RMS, characterized by PAX3–FOXO1 or PAX7–FOXO1 translocations, has ushered in a distinct realm of clinical challenges. Simultaneously, fusion-negative (FN) RMS shares similarities with ERMS, illuminating the complexity of RMS classification.

Critical to navigating the intricacies of RMS is the precise stratification of risk, a multifaceted process that encompasses clinical, pathological, and molecular attributes. The fusion status, in particular, has emerged as a crucial determinant guiding therapeutic strategies. The current therapeutic arsenal against RMS includes surgical resection, ionizing radiation, and cytotoxic chemotherapy, collectively contributing to notable advancements in survival rates over the last three decades.

However, RMS leaves no room for complacency. For patients grappling with metastatic or recurrent disease, the challenges remain substantial. The therapeutic regimens, while effective, often take a toll in the form of treatment-related toxicities. Moreover, the long-term sequelae underscore the indispensable requirement for holistic survivorship care.

As we traverse this ever-evolving landscape, a relentless pursuit of innovative therapeutic avenues persists. Next-generation nucleic acid sequencing and sophisticated disease models have begun to shed new light on the intricacies of RMS biology. These advances serve as the beacon guiding us toward a future characterized by better treatments, diminished toxicities, and enhanced survivorship for RMS patients.

In closing, RMS continues to command our unwavering attention. Our journey from clinical observations to molecular rev-

elations has shaped a more nuanced understanding of this rare malignancy. Yet, this journey is far from over. The pursuit of improved clinical outcomes remains steadfast, fueled by the relentless exploration of RMS biology and the unyielding commitment to delivering the best possible care to those affected by this challenging adversary.

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