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REVIEWER'S REPORT

Manuscript No.: IJAR- 58256

Title: Pediatric Parameningeal Rhabdomyosarcoma in a Developing Country: Treatment Outcomes With Chemotherapy and VMAT-Based Radiotherapy,

Recommendation:
Accept after minor revision

Rating	Excel.	Good	Fair	Poor
Originality		✔		
Techn. Quality			✔	
Clarity			✔	
Significance	✔			

Reviewer's ID: Bilqees Hamza

Detailed Reviewer's Report

Article Overview and Significance

The manuscript titled *"Pediatric Parameningeal Rhabdomyosarcoma in a Developing Country: Treatment Outcomes With Chemotherapy and VMAT-Based Radiotherapy"* offers a valuable and highly relevant clinical analysis of a challenging therapeutic area within a resource-constrained healthcare setting. Focusing on a specific subgroup of head and neck rhabdomyosarcomas, the study investigates the management and early outcomes of pediatric patients treated at a single, prominent radiation oncology center in Rabat, Morocco. Parameningeal rhabdomyosarcomas are historically associated with a poor prognosis due to their deep anatomical locations, their proximity to critical intracranial structures, and the high risk of meningeal and skull-base invasion. By evaluating patients treated between 2020 and 2024, the author addresses a significant gap in the literature regarding how advanced, highly conformal radiation techniques like Volumetric Modulated Arc Therapy can be successfully operationalized in middle-income countries to optimize local control while minimizing debilitating toxicities in children.

The primary scholarly value of this study lies in its realistic, real-world documentation of multimodal treatment protocols implemented outside of high-resource Western or East Asian academic medical centers. The author effectively contextualizes the dual challenges faced by clinicians in developing countries: the imperative to deploy modern, highly sophisticated therapeutic technologies alongside systemic obstacles such as diagnostic delays, logistical barriers, and resource limitations. By tracing the clinical pathways of nine pediatric patients who received systemic chemotherapy according to standard

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European-style regimens paired with VMAT, the manuscript demonstrates that high-quality, protocol-driven oncological care is both feasible and effective in an LMIC setting. The encouraging early survival data and manageable acute toxicity profiles presented in this study offer a reassuring benchmark for regional centers striving to modernize their pediatric sarcoma workflows.

Methodological and Clinical Strengths

A major strength of this manuscript is its clear, concise description of the treatment protocols and the consistency with which they were applied across the patient cohort. All nine patients received uniform local therapy consisting of VMAT delivering a total dose of 50.4 Gy in standard 1.8-Gy daily fractions. This dose selection is perfectly aligned with international consensus guidelines for the definitive treatment of gross residual or unresectable parameningeal disease. Furthermore, the systemic treatment utilized the ifosfamide, vincristine, and actinomycin D backbone, occasionally supplemented by doxorubicin, which accurately mirrors the established European pediatric soft-tissue sarcoma study group frameworks. By maintaining adherence to these internationally validated treatment regimens, the center ensures that its clinical data can be reliably compared with global registries, thereby strengthening the validity of its reported outcomes.

Additionally, the manuscript provides an insightful and highly practical discussion on the spatial and technical advantages of VMAT over older, conventional radiotherapy modalities within the context of head and neck malignancies. The author accurately highlights that parameningeal targets are routinely surrounded by critical organs at risk, including the optic chiasm, brainstem, cochleae, pituitary gland, and developing craniofacial bones. Through precise target delineation and inverse planning, the utilization of VMAT in this cohort represents a vital technological bridge. While proton beam therapy remains the gold standard for sparing healthy tissues in pediatric skull-base tumors, its extreme cost and scarcity render it inaccessible across most developing countries. The author's defense of VMAT as a highly conformal, socioeconomically viable, and technologically realistic alternative in low- and middle-income countries is a compelling and pragmatic argument that elevates the clinical utility of the paper.

Areas for Improvement and Detailed Critiques

Despite its clinical relevance, the manuscript contains several methodological and structural limitations that must be addressed to enhance its scholarly rigor before formal publication. The most prominent limitation is the exceptionally small sample size, consisting of only nine patients, combined with a short median follow-up period of twelve months. While the author acknowledges these constraints in the limitations section, the short follow-up duration significantly weakens the conclusions regarding overall survival and progression-free survival. In pediatric rhabdomyosarcoma, late relapses and, more importantly, long-term radiation-induced sequelae—such as neurocognitive decline, growth hormone

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deficiencies, facial asymmetry, and secondary malignancies—often take several years to manifest. The author should temper the assertions regarding the safety and long-term efficacy of the protocol, explicitly stating that a twelve-month snapshot is insufficient to evaluate late-onset toxicities or durable local control.

Furthermore, the data collection and analysis would benefit from a deeper exploration of the socioeconomic and clinical correlations underlying the observed outcomes. The author notes that one patient experienced disease progression and another died during treatment, which are significant events in a small cohort. However, the manuscript fails to provide granular details regarding these specific cases. It would be highly beneficial to know if the patient who progressed exhibited high-risk features at baseline, such as intracranial extension or an unfavorable histological variant, or if their treatment was compromised by systemic delays. Similarly, the paper should clarify whether the death that occurred during treatment was due to rapid, uncontrollable local tumor progression or secondary to systemic treatment toxicity, such as neutropenic sepsis. Dissecting these failures is critical for identifying areas where supportive care or patient selection can be optimized.

Another critical gap in the manuscript is the total absence of molecular stratification data, specifically the FOXO1 fusion status. Modern risk stratification for pediatric rhabdomyosarcoma has fundamentally shifted away from a purely histology-based approach toward a molecularly driven framework, where alveolar tumors lacking the FOXO1 fusion are treated similarly to embryonal variants, and fusion-positive tumors require aggressive treatment escalation. While the author briefly mentions the lack of molecular data as a limitation, the discussion should expand on the practical challenges of integrating molecular pathology into routine diagnostic workflows in developing countries. Discussing the financial, logistical, and technical barriers to establishing fluorescence in situ hybridization or next-generation sequencing in regional laboratories would add substantial depth to the paper, transforming a simple acknowledgment of a limitation into a constructive commentary on infrastructure development.

Structurally, the section addressing acute toxicities requires refinement to improve its academic utility. The author mentions that radiomucositis and radiodermatitis were the most frequent acute toxicities observed during treatment, emphasizing their potential impact on oral intake, hydration, and nutritional status. However, the text lacks a standardized grading system, such as the Common Terminology Criteria for Adverse Events. Without specific grading, it is impossible for readers to discern whether these toxicities were mild and transient or severe enough to necessitate hospitalization, feeding tube placement, or temporary interruptions in radiotherapy. The author should review the medical records to assign formal toxicity grades to these events. Additionally, a detailed description of the institutional supportive care

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protocols implemented to manage severe mucositis in a pediatric population would significantly enhance the manuscript's value for other clinicians operating in similar resource-limited environments.

Finally, the forward-looking recommendations outlined in the discussion section, while noble, tend to be overly generalized. The author lists several priorities for improving care, such as faster access to diagnostic imaging, the establishment of multidisciplinary tumor boards, and the reinforcement of psychosocial support networks. To make these recommendations truly impactful, the author should anchor them in concrete, regional strategies. For example, instead of broadly calling for earlier recognition of symptoms, the author could propose specific educational initiatives targeting primary care physicians and pediatricians to help distinguish parameningeal tumor symptoms from benign conditions like persistent sinusitis or otitis media. Providing a brief overview of how a national or regional pediatric sarcoma network could realistically be structured in Morocco would elevate the paper from a descriptive institutional report to a strategic framework for systemic healthcare reform.

Conclusion and Review Decision

In conclusion, this manuscript provides an encouraging and highly necessary perspective on the management of pediatric parameningeal rhabdomyosarcoma within a developing country's healthcare infrastructure. The center's success in delivering complex, highly conformal VMAT plans to a vulnerable pediatric cohort while achieving an estimated twelve-month overall survival rate of 87.5% is a commendable achievement that underscores the progress of radiation oncology in the region. The paper effectively argues that advanced radiotherapy techniques can be safely integrated into multimodal pediatric protocols even when facing the distinct socioeconomic and logistical challenges characteristic of low- and middle-income countries.

The methodological limitations, including the small cohort size and limited follow-up duration, are inherent to institutional studies of rare pediatric malignancies and do not diminish the baseline value of the report. However, the manuscript requires targeted revisions to maximize its scholarly contribution. These include providing specific details on the clinical failures, incorporating a standardized grading schema for acute toxicities, expanding the discussion on the systemic barriers to molecular testing, and offering more actionable, localized strategies for early detection and network development. Addressing these points will significantly improve the analytical depth and structural clarity of the text. Consequently, this manuscript is recommended for publication in the journal, subject to Minor Revision.