DELAYED RADIATION THERAPY IN THE TREATMENT OF EMBRYONAL RHABDOMYOSARCOMA: A CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Background: Rhabdomyosarcoma (RMS) is a rare malignancy, accounting for 3% of all cancers in children, as the most common primary site for RMS is in the head and neck region. The most common histology in children is the embryonal subtype. The diagnosis of embryonal rhabdomyosarcoma in the head and neck region is primarily based on histopathology, following biopsy of the tumor. Despite the improved outcome based on the EFS and OS using the three different treatment modalities-chemotherapy, radiotherapy and surgical treatment, the survival of patients depends on their IRS groups pathological and surgical.

Case presentation: We present a clinical case of a nine-year-old male with initial complaints of painful mass in the region near the left parotid gland**.** Clinical and paraclinical investigations were conducted for diagnostic purposes. The postoperative histopathology report given at the centre of primary wide excision and cervical neck dissection was embryonal rhabdomyosarcoma. The patient then was treated with adjuvant chemotherapy. The strategy of concurrent chemo-radiotherapy was not implemented, and radiotherapy was delayed for 4 months due to the patient's refusal of the treatment.

Results: The combination of surgery, chemotherapy and local control with radiotherapy achieved a good result in our patient.

Conclusions: Rhabdomyosarcoma (RMS) is a predominantly pediatric malignancy which can present throughout the body including the head and neck region. The use of radiation therapy is an important part of multimodality treatment for rhabdomyosarcoma.

Keywords: Embryonal rhabdomyosarcoma; pediatric cancer; chemoradiotherapy; head and neck cancer; delay treatment.

1. INTRODUCTION

Rhabdomyosarcoma (RMS) is a highly malignant soft tissue tumor derived from primitive embryonal mesenchymal tissue that differentiates into striated skeletal muscle. It is the most common soft tissue sarcoma

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in children, accounting 3-4% of all childhood malignancies with an annual incidence of 4.4 per million people under 20[1,2]. There are two main subtypes of RMS, distinguished by histopathology: embryonal subtype, alveolar subtype with difference clinical characteristics and prognosis. The most common in children (70-80%) is the embryonal subtype which predominates in head and neck regions and has better prognosis compared with alveolar ones. A multimodality approach involving surgical treatment, chemotherapy and radiotherapy is necessary in the treatment of pediatrics with RMS. According to the patient's individual risk group assignment, the optimal timing and intensity of these three treatment modalities must be evaluated with taking into consideration prognostic factors but also the late effects of treatment. Generally, the multimodal approach seemed to be the ideal management of RMS with good outcome in localised stage but poor prognosis in extensive, metastatic disease.

We report a case of rhabdomyosarcoma with an advanced stage located near the left parotid gland. The standard treatment plan was not implemented due to several factors. This report reflects our clinical experience and contributes to the understanding of this disease.

2. CASE PRESENTATION

A 9-year-old male patient with no remarkable medical history was admitted to our hospital because of painful mass in the region near the left parotid gland over the past few weeks. Clinical examination revealed no abnormalities except for a tumor near the left parotid gland, measuring 5 cm, which was tender to palpation. The head and neck MRI was performed, which showed a mass measuring about 54 mm located mainly near the left parotid gland that displaced the medial pterygoid muscle anteriorly. It showed hypointensity in the T1-weighted (T1W) image, hyperintensity in the both T2W and T2FS, heterogeneous enhancement postcontrast (Figure 1). The addition CT confirmed that the tumour invaded the apex of the ipsilateral petrous bone but no intracranial invasion was seen. The chest and abdominal computed tomography (CT), whole body scan, showed no evidence of metastasis was seen.

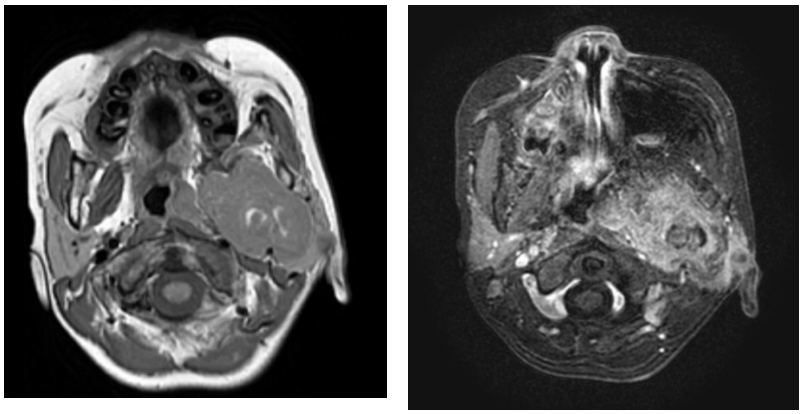
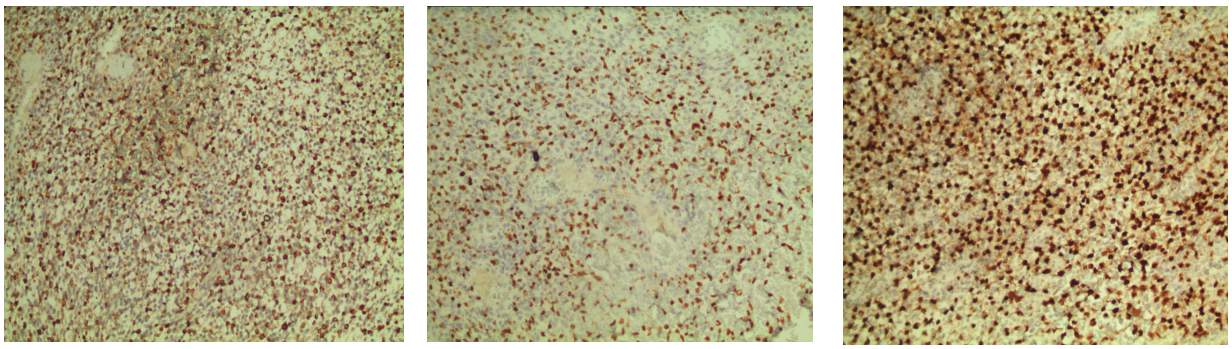


Figure 1. The MRI imaging in axial T1 (left) and axial postcontrast (right) at time of diagnosis

The patient underwent the wide excision of the primary site of tumor and the ipsilateral neck dissection. Incomplete resection with gross residual disease was performed. In addition, the entire left parotid gland and the level II cervical lymph nodes were dissected. Postoperative pathology and immunohistochemistry (IHC) were consistent with embryonal rhabdomyosarcoma with 16/16 negative lymph nodes (Figure 2). The genetic mutation testing showed no evidence of FOXO1 gene rearrangements.



Desmin 2 (+) MyoD1 (+) Myogenin (+)

Figure 2. The immunohistochemistry results

The final diagnosis was embryonal rhabdomyosarcoma, group F – High risk group (according to Cooperative Weichteilsarkom Study-CWS). Based on the CWS protocol, our patient was planned to receive 9 cycles of chemotherapy with I2VA (Ifosfamide, Vincristine, Actinomycin-D) for every 3 weeks, combined with concurrent chemoradiotherapy starting from week 13. After 4 cycles of chemotherapy, the disease showed a complete response (Figure 2). However, due to economic constraints and difficulties in patient transportation, the patient refused to receive the planned radiotherapy and continued with the additional 9 cycles of chemotherapy at a local hospital near his house. The patient refused radiotherapy and was discharged with no evidence of disease after 13 cycles of chemotherapy.

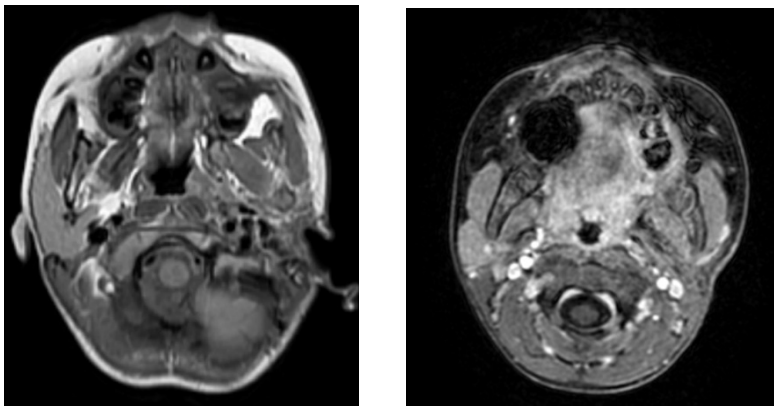


Figure 3. The MRI imaging after 13 cycles of chemotherapy

The patient returned to our hospital after 4 months with progressive lesions at the surgical site. After a multidisciplinary consultation, we decided to proceed with radiotherapy for this patient. The patient then received the adjuvant radiotherapy in 28 fractions with a total dose of 50.4 Gy for tumor bed (Five fractions per week) using VMAT technique. No significant toxicity was recorded during and at the end of treatment. The patient recovered well and achieved complete response (CR) after two months in the both clinical and paraclinical examination (Figure 5).

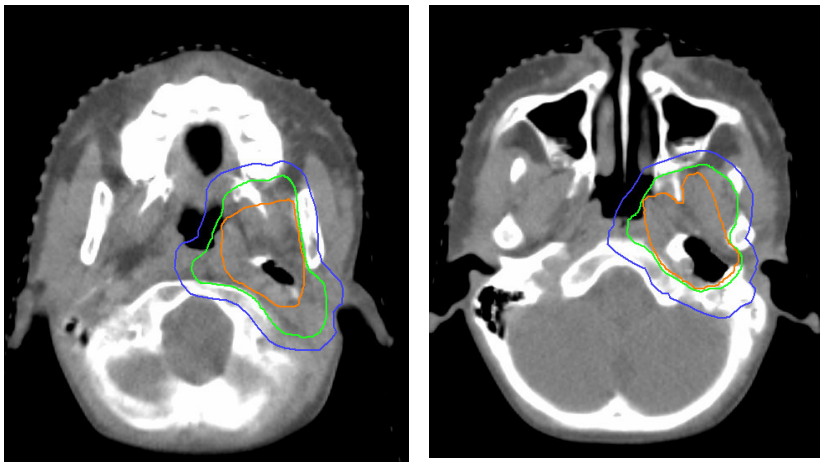


Figure 4. The patient's target volumes (Orange contour: Tumor bed; green contour: CTV 50.4; blue contour: PTV 50.4)

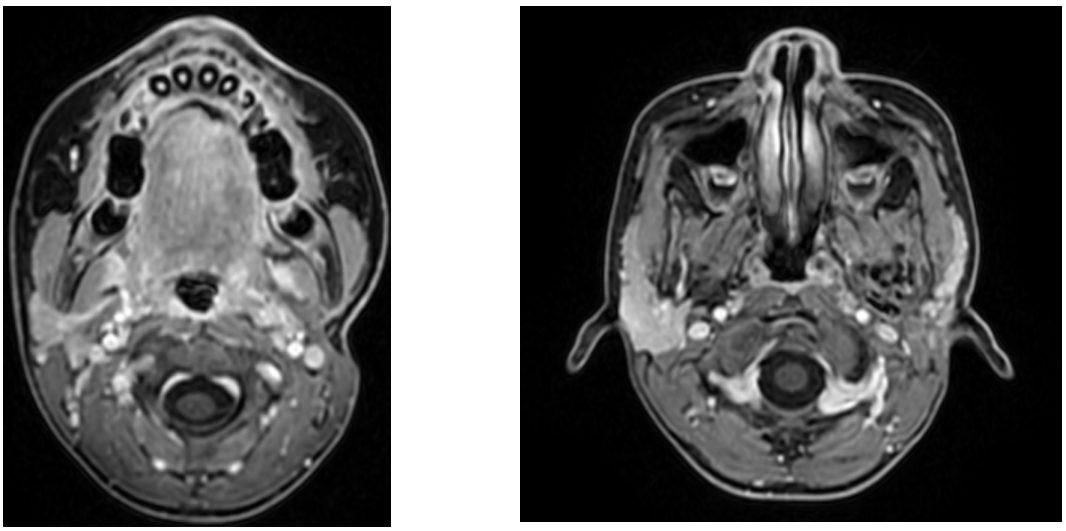


Figure 5. The MRI imaging after two months of radiotherapy

3. DISCUSSION

Rhabdomyosarcoma is the most common pediatric soft tissue sarcoma but relatively rare in adults. Although these tumors can occur anywhere in the body, the most common sites are the head and neck (accounting for nearly 40%), the urinary tract (20%), the extremities (20%), and other locations (20%).[3,4] Rhabdomyosarcoma in children is commonly found in the head and neck region, whereas in adults, it is more frequently located in the extremities. Head and neck RMS (HNRMS) is divided into three anatomic subsites based on prognosis and location: parameningeal (50%), orbital (25%), and other head and neck (25%). Parameningeal RMS comprise 16% of all of cases and include those tumors specifically arising from the nasal cavity/nasopharynx, paranasal sinuses, parapharyngeal space, pterygopalatine/ infratemporal fossa, and mastoid/middle ear[4].

Histopathology and immunohistochemistry plays the critical role for diagnosing rhabdomyosarcoma. It is expressed in immunohistochemistry with markers including Desmin, Myogenin, CD 56, muscle-specific actin, Myoglobin, Vimentin, and VioD1. Differential diagnoses include Ewing's sarcoma, lymphoma, neuroblastoma, nasopharyngeal carcinoma, among others. Regarding histopathology, the WHO classification from 2013, as well as the update version in 2020, divides rhabdomyosarcoma into four main subtypes: Embryonal rhabdomyosarcoma (ERMS), Alveolar rhabdomyosarcoma (ARMS), Pleomorphic rhabdomyosarcoma (PRMS) and Spindle Cell/Sclerosing rhabdomyosarcoma (SRMS). Embryonal and alveolar rhabdomyosarcoma are the most common types in children. Embryonal rhabdomyosarcoma is more frequently seen in younger children and has a good prognosis, whereas alveolar rhabdomyosarcoma can occur in both children and adults, with a poor prognosis with hight propensity of recurrent or metastasises. Among all the subtypes of rhabdomyosarcoma, alveolar rhabdomyosarcoma is the only one associated with translocation mutations. Approximately 80% of cases of alveolar rhabdomyosarcoma carry mutations in the FOXO1 and PAX3 (or PAX7) genes. Skapek et al.'s study showed that PAX3-FOXO1 or PAX7-FOXO1 mutations significantly reduce both overall survival (OS) and event-free survival (EFS)[5].

The decision about the appropriate therapeutic protocol for RMS is preceded by a complex classification process that includes clinical staging and evaluation of the completeness of the primary surgical procedure. The staging of embryonal rhabdomyosarcoma is commonly assessed using the IRSG (The Intergroup Rhabdomyosarcoma Study Group) classification. Stage is based on the anatomic site (favorable versus unfavorable), tumor size, nodal involvement, and presence or absence of distant metastases. While the post-surgical 'Group' is based on whether the tumor was completely resected before chemotherapy, it helps guide the radiotherapy strategy (Table 1 and 2)[6]. For all available information, our patient was classified into Group 3. The EpSSG (European Paediatric Soft Tissue Sarcoma Study Group) risk classification for non-metastatic rhabdomyosarcoma is divided into 4 risk groups, based on histopathology, post-surgical staging, location, lymph node involvement, tumor size, and the patient's age (Table 3). Our patient herein belongs to high-risk group E due to the tumor's location near the meninges (in the infratemporal fossa) and the tumor size >5cm. Risk stratification not only helps in disease prognosis but also in determining the intensity of treatment. Patients with low risk, where the tumor was completely resected, are treated with 8 cycles of VA chemotherapy at a lower dose, while other groups are treated with 9 cycles. The intermediate-risk group is treated with 4 cycles of IVA (ifosfamide, vincristine, actinomycin D), followed by 5 cycles of VA, whereas the high-risk group is recommended to receive 9 cycles of IVA [7, 8].

The multimodal approach seemed to be the ideal management of RMS including surgery, chemotherapy and radiotherapy. For head and neck regions, considering functional preservation, cosmetics and the complex structures, the role of surgery was limited to biopsy. Radiotherapy is indicated for all patients who do not achieve R0 resection, thus, almost all rhabdomyosarcomas in the head and neck region are indicated for radiotherapy. Radiotherapy may begin earlier if the patient has symptoms from the tumor or intracranial invasion, but rhabdomyosarcoma is chemosensitive, so radiotherapy is typically delayed until the 13th week[9]. The available guideline suggest the dose for primary tumor is 50.4Gy, 36Gy for micrometastasis. Primary positive lymph nodes should receive 50.4Gy and 41.4Gy is enough for post neck dissection. The prophylactic neck irradiation should not be recommended. CTV was created by expanding 0.5-1cm in all directions from GTV[1,9]. Previously, patients with tumors near the meninges received concurrent chemoradiotherapy,

with whole-brain radiotherapy starting on day 0. In recent decades, due to a better understanding of the risk factors for meningeal invasion, whole-brain radiotherapy is no longer used[10].

Our patient belongs to the IRS III group. The patient did not receive concurrent chemoradiotherapy starting from week 13 according to the CWS guidelines due to several factors. Although the disease showed a complete response after 13 weeks of chemotherapy, the recurrence rate remains very high if radiotherapy is not included in the initial treatment. For head and neck rhabdomyosarcoma, when the primary tumor is not completely resected, radiotherapy and chemotherapy were the mainstay treatment. In this condition, although the disease responded well to chemotherapy, it showed a tendency to progress when radiotherapy was delayed. We decided to administer radiotherapy after chemotherapy with a dose of 50.4 Gy in 28 fractions to the tumor bed, which is higher than the CWS guidelines (Table 4) due to the the delay of treatment and lack of concurrent chemotherapy. Regarding radiotherapy techniques, in Vietnam, 3D radiotherapy, IMRT, and VMAT are commonly used. With more advanced techniques, IMRT and VMAT minimize the impact on surrounding organs, thereby reducing side effects compared to the 3D technique. Our patient received radiotherapy using the VMAT technique, and after 28 fractions, there were virtually no significant side effects from radiotherapy. After evaluating the treatment results two months later, the disease showed a complete response.

Table 1. The stage of rhabdomyosarcoma according to IRSG

Stage	Site	Tumor size	Nodal Involvement	Metastatic Spread
I	Favorable	Any	Any	No
II	Unfavorable	< 5cm	No	No
III	Unfavorable	< 5cm	Yes	No
		> 5cm	Any	No
IV	Any	Any	Any	Yes

Table 2. IRS clinical grouping classification

IRSG grouping	Description
Group I	**Localized disease with microscopic margin-negative (RO) resection** A-Confined to muscle/organ of presentation B-Extension beyond muscle/organ of presentation
Group II	**Gross total resection** A-Margin-positive resection (R1) B-Regional lymph node involvement with RO resection of nodal disease C-Regional lymph node involvement with R1 resection of nodal disease
Group III	**Gross residual disease following resection** A-Biopsy only B->50% resection completed
Group IV	**Distant metastatic disease at presentation**

Table 3. Risk Stratification for RMS according to EpSSG

Risk group	Subgroups	Pathology	Post surgical stagc	Site	Node stage	Size & age
Low-risk	A	Favourable	I	Any	NO	Favourable
Standard-risk	B	Favourable	I	Any	NO	Unfavourable
	C	Favourable	II, III	Favourable	NO	Any
	D	Favourable	II, III	Unfavourable	NO	Favourable
High-risk	E	Favourable	II, III	Unfavourable	NO	Unfavourable
	F	Favourable	II, III	Any	NI	Any
	G	Unfavourable	I, II, III	Any	NO	Any
Very High-risk	H	Unfavourable	I, II, III	Any	NI	Any

Pathology: Favourable = All embryonal, spindle cells, botryoid RMS, Uníavourablc = Alí alveolar RMS (including the solid-alveolar variant); **Post surgical stage:** Group I = Primary complete resection (RO), Group II = Microscopic residual (RI) or primary complete resection but NI, Group III = Macroscopic residual (R2); **Site:** Favourable = Orbit, genitourinary non-bladder prostate (i.e., paratesticular and vagina/uterus) and non-parameningeal head and neck, Unfavourable = all other sites (parameningeal, extremities, genitourinary bladder-prostate and "othersites"; **Node stage:** NO = No clinical or pathological node involvement, N1 = Clinical or pathological nodal involvement; **Size & Age:** Favourable = Tumor size (maximum dimension) < 5 cm and age < 10 y, Unfavourable = All others (/>., size >5 cm or age > 10 y).

Table 4. Radiation doses used in CWS

IRS group	Resection and response	Embryonal RMS (RME)	Alveolar RMS (RMA)
1		No RTX	41.4 Gy; 23 F
II		41.4 Gy; 23 F	41.4 Gy; 23 F
III	Secondary complete resection (RO) prior to (or atter) RTX	36 Gy; 20 F (good response) 41.4 Gy; 23 F (poor response) Subgroup C: omittance of RTX only in case of íavourable size and age.	41.4 Gy; 23 F
III	Incomplete secondary resection (R1 or R2)	50.4 Gy; 28 F	50.4 Gy; 28 F
III	Clinical complete remission, no secondary resection	41.4 Gy; 23 F	50.4 Gy; 28 F
III	Partial remission, no secondary resection or no RO expected	50.4 Gy; 28 F Orbit and PR (>2/3): 45 Gy; 25 F	50.4 Gy; 28 F
III	Poor response, Progressive disease, no secondary resection	50.4 Gy; 28 F	50.4 Gy; 28 F (+ optional boost: 5.4 Gy; 3 F)

4. CONCLUSIONS

Head and neck rhabdomyosarcoma is a uncommon, complex condition with a variable prognosis based upon the subsite of presentation and the histologic and molecular subtype. The diagnosis should be based on based on the precise physical investigation, past medical history, radiological imaging, histology, laboratory and molecular tests. The treatment strategy for rhabdomyosarcomas of the head and neck involves strict multidisciplinary cooperation. Radiotherapy plays a crucial role in the group of diseases manifesting in the head and neck region difficulty to achieve R0 resection and it's radiosensitive.

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