

# Fusion Partner has no Implication on Survival in TFCP2 Mutated Intraosseous Rhabdomyosarcoma of Head and Neck Region: An Embrasive Review of 27 cases from Literature

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## ABSTRACT

**Background:** Intraosseous rhabdomyosarcoma (I-RMS) with unique unique TFCP2 mutation is a recently described entity with an aggressive clinical course. The present review aimed to summarize and analyse the available data on head and neck I-RMS with TFCP2 mutation to update the current cognizance about the pathology for nobler diagnostic and therapeutic purposes.

**Methodology:** Electronic databases were searched, and data were extracted for age, gender, location, histopathology of primary lesion, tumor cell type, necrosis and mitosis, immunohistochemical markers, mutation, follow-up and overall survival.

**Results:** 27 cases were included and showed a mean age of  $28.1 \pm 16.84$  years (median- 22.5 years; Range 11-74 years). There was no definitive gender preponderance. Undisputedly, mandible was the most common affected site. Histologically, I-RMS show predominantly spindle and epithelioid morphology with rare rhabdoid differentiation. CK, desmin, MyoD1 and ALK are useful immunohistochemical markers. The fusion partner does not seem to affect the survival in I-RMS

**Conclusion:** I-RMS is rare malignancy with limited information available in literature. Molecular characterization should be done for all cases with adequate follow-up. TPCP2 could also be an attractive target for therapies.

**Keywords:** EWSR1; FUS; intra-osseous; rhabdomyosarcoma; TFCP2

## INTRODUCTION

The latest WHO classification of head and neck tumors released in 2022 included intraosseous rhabdomyosarcoma (I-RMS) with TFCP2 mutation as a separate entity.<sup>1</sup> The pioneer three cases at various sites were reported by Watson *S et al* in the year 2018, with unique EWSR1/FUS-TFCP2 rearrangement and grave outcome.<sup>2</sup> A number of cases and studies have been published thereafter, broadening the spectrum of the disease sufficient enough to be included in the latest classification.<sup>3-10</sup> TFCP2 is a transcription factor that belongs to TFCP2/Grainyhead family of transcription factors, and plays a significant role in hematopoiesis, cell cycle control, lineage-specific gene expression and regulation of immune-related and cytochrome P450 genes.<sup>11-12</sup> It is believed that this transcription factor family has a very ancient origin and can be ubiquitously found in Metazoa and fungi.<sup>13</sup> Owing to the characteristic immunoglobulin-like structure of DNA-binding domains akin to TP53- tumor suppressor gene, they are sometimes referred to as 'ancestor of TP53'.<sup>14</sup>

TFCP2 plays a versatile role in oncogenesis; while it acts as a pro-oncogenic factor in malignancies of liver, pancreas and breast, it acts as a tumor suppressor in cutaneous melanoma inhibiting the growth.<sup>11</sup> Also, it may be important in cervical carcinogenesis and in colorectal cancer. Epithelial-mesenchymal transition (EMT) and increased angiogenesis have also been attributed to TFCP2.

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Intra-osseous RMS with signature TFCP2 mutation is a clinically and morphologically distinct high-grade malignancy with spindle cell/ epithelioid morphology with rare rhabdoid phenotype. Additionally, the expression of immunohistochemical markers is variable but there is consistent TFCP2 rearrangement with FUS or EWSR1 as the most common translocation partners. Most recently, mutation is UBP1 gene has been reported<sup>15</sup>, which shares 88% identical amino acid sequences with TFCP2<sup>14</sup>, however, involvement of UBP1 is not as widely studied in carcinogenesis as TFCP2.<sup>11</sup>

The present review was formulated to summarize and analyse the available data on head and neck I-RMS with TFCP2 mutation in order to elucidate and update the current understanding of the disease process in a nutshell for nobler diagnostic and therapeutic purposes. Further, characterization was done based on translocation partner to compare and contrast the biological behaviour of site specific entities.

**MATERIALS AND METHODS**

Two investigators (DP and RPK) independently explored PubMed, Medline, SCOPUS, Web of Science, EMBASE and Google Scholar for the following keywords singly or in combination: ‘intra-osseous rhabdomyosarcoma’, ‘intra-osseous rhabdomyosarcoma TFCP2’, ‘intraosseous rhabdomyosarcoma head and neck’, ‘Bone rhabdomyosarcoma TFCP2-EWSR1’, ‘rhabdomyosarcoma TFCP2-FUS’, ‘rhabdomyosarcoma mandible TFCP2’, ‘rhabdomyosarcoma maxilla TFCP2’, and ‘rhabdomyosarcoma bone TFCP2’. All the articles were scrutinized and ensuing citations were identified through the reference lists of the included papers. Bibliographical linkages were also included.

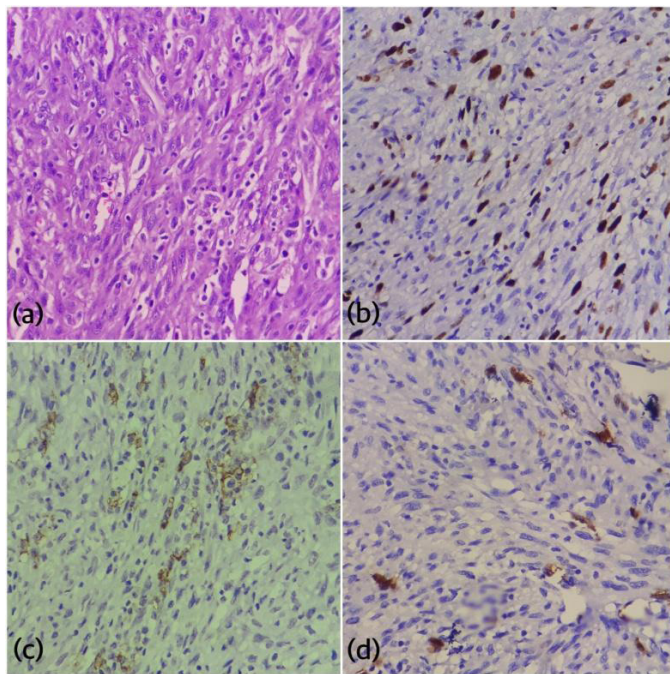
**Inclusion and exclusion Criteria:** All the papers pertaining to head and neck intraosseous rhabdomyosarcoma with proven TFCP2 mutation, irrespective of the translocation partner, published till 2022 were included in the present review. Reviews and mini-reviews were excluded from the study. Papers which were published languages other than English and articles where full text could not be obtained, were not included. The cases of soft tissue rhabdomyosarcoma were excluded. At instances, single case was published more than once, care was

taken to consider only one paper to avoid synthesis of duplicate data. The extracted data were analyzed and tabulated for the following parameters: age, gender, location, histopathology of primary lesion, tumor cell type, necrosis and mitosis, immunohistochemical markers, mutation, follow-up and overall survival. The data were presented on Microsoft excel spreadsheet 2021. Descriptive statistics were done for frequency counts. Death was considered as an event of interest. IBM SPSS statistics software version 26 (IBM Analytics, Armonk, New York, U.S.) was used to analyze the data. Kaplan-Meier survival plot was used to estimate and compare the survival.

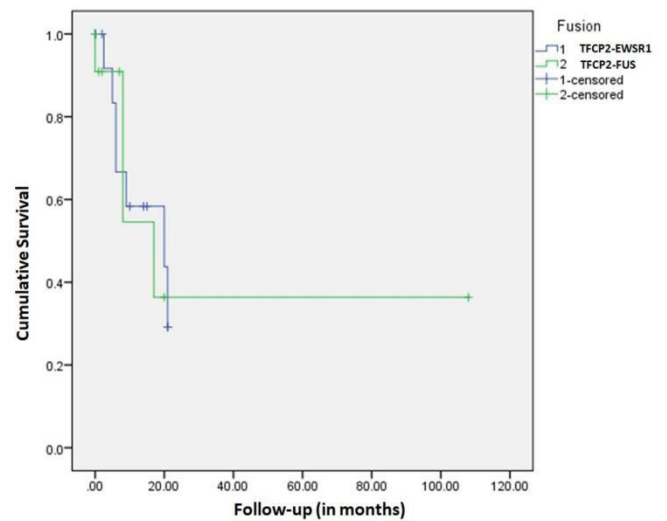
**RESULTS AND DISCUSSION**

**Clinico-demographic profile**

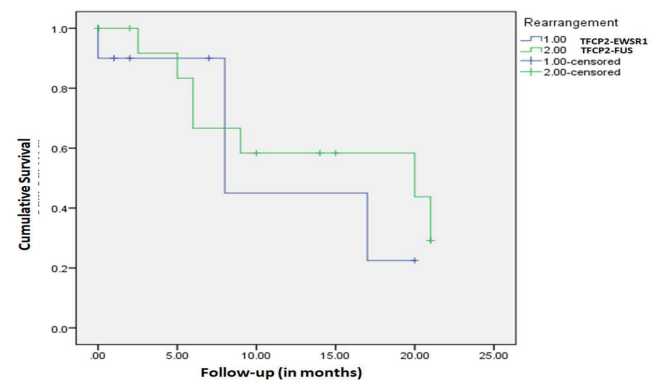
In total, 27 cases were included for review.<sup>3-10,16,17</sup> Excluding one case where the exact age was not mentioned<sup>7</sup>, the mean age was 28.1±16.84 years (median- 22.5 years; Range 11-74 years). The only detail provided for the aforementioned case was that the patient was in 20s-30s. Including this case, a peak incidence was found in 3rd and 4th decade of life, with only four cases seen after 40 years of age. This age predilection is similar to



**Fig1.** Photomicrograph from an archival case which showed histological and immunohistochemical characteristics similar to I-RMS, however, gene testing was not done. **A.** H and E stained section showing proliferation of malignant spindle cells with increased mitoses (40X). **B.** ki-67 IHC showing proliferation of >50% (40X). **C.** EMA positivity in tumor cells (40X). **D.** Desmin positivity (40X)



**Fig 2.** Kaplan-Meier curve for overall survival stratified by molecular signature for all included cases



**Fig 3.** Kaplan-Meier curve for overall survival stratified by molecular signature excluding one case with a survival of 108 months.



previously published literature.<sup>8,9</sup> I-RMS is clearly a lesion of young adults. No definite gender preponderance was noted (M:F::0.93:1). Jaw bones were undisputedly the most commonly affected (17 cases) followed by skull bone (n=8), neck (1 case) and nasal region (1 case). Mandibular cases outnumbered any other site (11 cases). It has been previously established and accepted that RMS with TFCP2 shows a marked predilection for bones, making it a unique entity to be included in latest WHO classification of head and neck tumors.<sup>1</sup> One case involved in the present review showed lesions in two contiguous bones (one lesion in neck and other in the inter-trochanteric area), with no clear evidence of primary or secondary lesion.<sup>6</sup> This case was thus considered to avoid dilution of the data. Ignoring the fact that we included intraosseous cases with known TFCP2 mutations, most intra-osseous rhabdomyosarcoma showed a predilection for craniofacial bones even if not molecularly characterized. There are reported cases of soft tissue rhabdomyosarcoma with specific mutations but were not considered in the present review. It is noteworthy that I-RMS is an aggressive lesion and tend to destroy the cortical plates to involve the adjacent soft tissues.

The three main histopathological criteria were retrieved viz., cell type/differentiation, mitoses, and necrosis. These have been considered to be the most fruitful parameters in determining the prognosis and therapeutic management for soft tissue sarcomas (STS).<sup>18</sup> Noteworthy, majority of the cases were biphasic, consisting predominantly of spindle and epithelioid tumor cells (48.15%, 13 cases) followed by monophasic (purely spindle- 6 cases and epithelioid-3 cases) and mixed population of cells. Despite a tumor of skeletal muscles origin, rhabdoid differentiation was rarely encountered. Thus, a plethora of neoplasms fall in the histological differential diagnosis including undifferentiated tumors, odontogenic neoplasms, or lesions of fibrogenic, smooth muscle, epithelial, or vascular origin.<sup>19</sup> Odontogenic carcinosarcoma or oral spindle cell squamous cell carcinoma invading the bone could be difficult diagnosis. Primary gnathic intraosseous epithelioid hemangioma, fibrosarcoma and leiomyosarcoma are even rare. I-RMS is high grade malignancy and all cases where information was available the mitotic count per 10 HPF was high. Brisk mitotic activity with presence of necrosis seems to be another diagnostic clue and necrosis was noted in 44.4% of cases, at least focally. In a previous study, presence and volume of necrosis on FDG PET/CT were proven to be independent adverse prognosticators in limb and girdle sarcomas.<sup>20</sup> In line with histological grading of STS, we opine that for reporting I-RMS these three parameters must be considered, and most appear to be Grade 3 using this classification system. Previous studies have shown that, irrespective of the grading system applied, the grade is the most important prognostic factor and not differentiation alone. Other studies however, support inclusion of tumor size, vascular/bony invasion and tumor depth.<sup>18</sup> Application of grading in sarcomas also bears significance in therapeutic decision making, with Grade 3 tumors responding best to chemotherapeutic drugs. The usage of these drugs seems inefficient in Grade 1 sarcomas.

As aforementioned I-RMS rarely demonstrates rhabdoid differentiation thus, there should be high degree of suspicion while an intraosseous spindle cell neoplasm is encountered. Many markers have been used and we found that application

of few markers could be of great importance in saving time. Wherever the information was available, cytokeratin (CK) expression was noted (at least focally) in 20/23 cases, desmin in 24/27 cases, MyoD1 in 24/27 cases and ALK in 22/24 cases. The expression pattern of myogenin was highly variable. Thus, we suggest that for any case histologically demonstrating malignant spindle cell neoplasm with increased mitoses and necrosis, particularly in cranio-facial bones, ALK must be included in the primary panel which in the absence of molecular characterization could give a possibility of I-RMS in conjunction with CK, desmin and MyoD1 positivity (Figure 1).

### Genetic analysis and Impact on survival

Of 27 cases included in the present review, FUS was the more common translocation partner with TFCP2 (16/27) than EWSR1 (11/27). Only single reported case showing EWSR1-UBP1 mutation was noted however, to avoid generation of heterogeneous data, this case wasn't included.<sup>15</sup> TFCP2 has been widely and extensively studied in hepatocellular carcinoma (HCC) and over expression has been linked to aggressiveness, more proliferation, disease progression, increased angiogenesis and higher metastatic potential.<sup>11</sup> Analysis of TFCP2 characterization could be a potential factor for targeted therapy. Previously regarded as 'undruggable' owing to lack of ligand-binding domain and intrinsic enzymatic activities, recent advancement opens options to target such chemically intractable through small molecule inhibitors. In contrast to oncogenic role in HCC, pancreatic cancer, oral squamous cell carcinoma, and various GI malignancies, TFCP2 has a protective role in malignant melanoma.<sup>11,21</sup>

One patient had a longer survival of 108 months<sup>5</sup>, including this patient the overall survival (OS) was 41.024 months. This patient showed EWSR1 as fusion partner.<sup>5</sup> Thus, based on fusion partner I-RMS was divided into two groups as Group 1: TFCP2-EWSR1 and Group 2: TFCP2-FUS. The overall survival for Group 1 (45.273 months) was significantly higher (p value: 0.004) than Group 2 (14.482 months) (Figure 2), but this is attributable to one extreme value (108 months). When this patient was excluded, the survival time did not show any significant difference between two groups (OS: 13.758 months, Group 1: 11.925 months, Group 2: 14.482 months, p value: 0.440) (Figure 3). Thus, genetic characterization does not seem to alter the course of the disease. Previous studies have shown 20% risk of regional nodal metastasis and 50% for distant metastasis.<sup>10</sup> Similar molecular signature has been reported in RMS of the soft tissues.

### CONCLUSION

In conclusion, I-RMS is an extremely rare aggressive malignancy which shows a predilection for jaw bones. The list of histological mimickers is vast and correct diagnosis is essential as this tumor bears poor outcome despite treatment. A set of immunohistochemical markers including pan-CK, desmin, MyoD1 and ALK may help in faster diagnosis particularly for tumors showing spindle/epithelioid morphology, with brisk mitoses and necrosis. Molecular characterization should be done for all cases with adequate follow-up. TFCP2 could also be an attractive target for therapies.



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