Ewing Sarcoma of the Oral and Maxillofacial Region: Current Concepts in Pathogenesis, Diagnosis, and Multidisciplinary Management—A Comprehensive Review

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ABSTRACT

Ewing sarcoma (ES) is an aggressive malignant small round cell sarcoma that primarily affects children and adolescents and represents the second most common primary malignant bone tumor after osteosarcoma. The disease is molecularly characterized by recurrent chromosomal translocations involving the EWSR1 gene, most commonly the EWSR1–FLI1 fusion, which functions as an aberrant transcription factor driving tumorigenesis. Although ES most frequently arises in the long bones and pelvis, involvement of the head and neck region is uncommon, accounting for only 1–9% of all cases, with the mandible being the most frequently affected craniofacial site. Owing to its rarity and nonspecific clinical and radiographic presentation, Ewing sarcoma of the oral and maxillofacial region is often misdiagnosed as odontogenic infection, osteomyelitis, or other malignant small round cell tumors, resulting in delayed diagnosis and treatment[1-4].

Recent advances in molecular diagnostics, including fluorescence in situ hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS), have substantially improved diagnostic precision through the identification of characteristic EWSR1 rearrangements. Furthermore, the integration of neoadjuvant chemotherapy, surgery, and radiotherapy has significantly improved survival in patients with localized disease. Nevertheless, metastatic and recurrent Ewing sarcoma remain associated with poor clinical outcomes despite intensive multimodal treatment. Emerging therapeutic strategies targeting the molecular drivers of Ewing sarcoma, including epigenetic modulation, insulin-like growth factor-1 receptor (IGF-1R) inhibition, poly(ADP-ribose) polymerase (PARP) inhibition, and immunotherapy, have shown encouraging results and may further improve future patient outcomes[5-8].

This review comprehensively summarizes the current evidence regarding the epidemiology, molecular genetics, pathogenesis, clinicopathological characteristics, imaging features, histopathology, immunohistochemical profile, molecular diagnosis, differential diagnosis, treatment modalities, prognostic factors, and emerging therapeutic advances in Ewing sarcoma, with particular emphasis on lesions involving the oral and maxillofacial region.

Keywords: Ewing sarcoma; Oral and maxillofacial region; EWSR1-FLI1; Small round cell tumor; Mandible; Molecular pathology; Immunohistochemistry; Targeted therapy.

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INTRODUCTION

Ewing sarcoma (ES) is a highly aggressive malignant mesenchymal neoplasm belonging to the family of undifferentiated small round cell sarcomas. Since its first description by James Ewing in 1921, the understanding of this disease has evolved considerably from a morphologically defined bone tumor to a genetically characterized malignancy driven by

recurrent chromosomal translocations involving the EWSR1 gene. Today, ES is recognized as a distinct molecular entity characterized by fusion oncogenes, most commonly EWSR1–FLI1, which are considered the principal drivers of tumor initiation and progression. These fusion proteins function as aberrant transcription factors that dysregulate multiple cellular pathways involved in proliferation, apoptosis, differentiation, angiogenesis, and metastatic dissemination. Consequently, molecular characterization has become the cornerstone of diagnosis and has significantly improved the distinction of ES from other morphologically similar small round cell malignancies[9-12].

Ewing sarcoma represents the second most common primary malignant bone tumor after osteosarcoma, accounting for approximately 10–15% of all primary malignant bone neoplasms worldwide. The annual incidence is estimated at approximately 2–3 cases per million population, with the highest frequency occurring during the second decade of life. Nearly 80% of patients are diagnosed before the age of 20 years, and the disease demonstrates a slight male predominance with a male-to-female ratio of approximately 1.3–1.5:1. Marked ethnic variation has also been documented, with ES occurring predominantly in individuals of European ancestry and being relatively uncommon among African and East Asian populations. These epidemiological observations suggest that inherited genetic susceptibility may contribute to disease development in addition to the acquired chromosomal rearrangements responsible for tumorigenesis[13-16].

The majority of Ewing sarcomas arise within the medullary cavity of long bones, particularly the femur, tibia, humerus, and fibula, followed by the pelvis, ribs, vertebrae, and scapula. Extraskeletal Ewing sarcoma, originating in soft tissues without primary osseous involvement, constitutes approximately 15–20% of all cases and demonstrates clinicopathological characteristics largely similar to those of skeletal ES. In contrast, involvement of the head and neck region is distinctly uncommon, representing only 1–9% of all reported cases. Within the craniofacial skeleton, the mandible is the most frequently affected site, followed by the maxilla, skull, zygoma, nasal cavity, paranasal sinuses, and temporal bone. Because of its rarity at these locations and its tendency to mimic inflammatory, odontogenic, and other malignant conditions, diagnosis is frequently delayed, thereby adversely affecting treatment outcomes[17-20].

Clinically, patients present with rapidly enlarging painful swelling, facial asymmetry, tooth mobility, paraesthesia, loosening of teeth, trismus, and occasionally ulceration of the overlying mucosa. Constitutional symptoms such as fever, malaise, weight loss, and elevated inflammatory markers may also occur, occasionally leading to an initial misdiagnosis of odontogenic infection or osteomyelitis. Radiographically, lesions often appear as poorly defined osteolytic defects with cortical destruction, aggressive periosteal reaction, and soft tissue extension. However, these imaging findings are not pathognomonic and frequently overlap with those of osteomyelitis, lymphoma, rhabdomyosarcoma, Langerhans cell histiocytosis, osteosarcoma, and metastatic neuroblastoma. Consequently, accurate diagnosis requires integration of clinical, radiological, histopathological, immunohistochemical, and molecular findings[21-24].

Histopathologically, ES is characterized by diffuse sheets of uniform small round blue cells possessing scant clear cytoplasm rich in glycogen, round nuclei with finely dispersed chromatin, and inconspicuous nucleoli. Mitotic activity varies according to tumor grade, while extensive necrosis may be present in advanced lesions. Although diffuse membranous expression of CD99 (MIC2) remains one of the most sensitive immunohistochemical markers, it lacks specificity because several other malignant small round cell tumors demonstrate similar expression patterns. Additional markers, including NKX2.2, FLI1, and ERG, have improved diagnostic confidence; however, definitive diagnosis increasingly relies upon molecular confirmation using fluorescence in situ hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), or next-generation sequencing (NGS) to identify characteristic EWSR1 gene rearrangements[25-28].

The molecular landscape of Ewing sarcoma has been extensively investigated over the past two decades. Approximately 85% of tumors harbor the classical t(11;22)(q24;q12) translocation resulting in the EWSR1–FLI1 fusion gene, whereas another 5–10% contain alternative EWSR1–ERG fusions. Rare variants involving ETV1, ETV4, FEV, or FUS have also been identified. These fusion proteins induce widespread epigenetic remodeling and transcriptional reprogramming, thereby promoting uncontrolled cellular proliferation while inhibiting normal mesenchymal differentiation. The recognition of these molecular alterations has not only refined diagnostic accuracy but has also stimulated the development of novel targeted therapeutic strategies directed against downstream signaling pathways, epigenetic regulators, and transcriptional machinery[29-32].

The therapeutic management of ES has undergone remarkable evolution over the last four decades. Before the introduction of systemic chemotherapy, survival rates rarely exceeded 10%. Contemporary multimodal treatment protocols incorporating neoadjuvant multi-agent chemotherapy followed by

complete surgical excision whenever feasible and adjuvant radiotherapy have increased the 5-year overall survival of patients with localized disease to approximately 70–80%. Current international treatment regimens generally employ combinations of vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VDC/IE), reflecting decades of collaborative clinical trials conducted by the Children's Oncology Group (COG), Euro Ewing Consortium, and other international sarcoma groups. Nevertheless, patients presenting with metastatic disease, recurrent tumors, or poor histological response to chemotherapy continue to experience poor long-term survival, highlighting the need for more effective systemic therapies[33-36].

Recent advances in precision oncology have substantially expanded the therapeutic landscape of Ewing sarcoma. Investigational strategies targeting insulin-like growth factor-1 receptor (IGF-1R), poly(ADP-ribose) polymerase (PARP), cyclin-dependent kinases, epigenetic modifiers, and immune checkpoint pathways have demonstrated encouraging preclinical and early clinical results. Furthermore, the integration of comprehensive genomic profiling and next-generation sequencing has facilitated a more precise classification of undifferentiated round cell sarcomas, distinguishing classical Ewing sarcoma from recently recognized entities such as CIC-rearranged sarcoma, BCOR-rearranged sarcoma, and other EWSR1-non-ETS fusion sarcomas, each exhibiting distinct biological behavior, prognosis, and therapeutic responsiveness[37-40].

Given the rarity of oral and maxillofacial involvement and the rapid expansion of knowledge regarding molecular pathology, diagnostic techniques, and targeted therapies, an updated evidence-based review is warranted. The purpose of this review is to comprehensively summarize the current understanding of the epidemiology, molecular genetics, pathogenesis, clinicopathological features, imaging characteristics, histopathology, immunophenotype, molecular diagnosis, differential diagnosis, multidisciplinary management, prognostic factors, and emerging therapeutic strategies for Ewing sarcoma, with special emphasis on lesions affecting the oral and maxillofacial region.

2. Epidemiology

Ewing sarcoma (ES) is a rare, highly aggressive malignant neoplasm belonging to the Ewing sarcoma family of tumors (ESFT). Although uncommon in the general population, it represents the **second most frequent primary malignant bone tumor in children and adolescents**, following osteosarcoma. The annual incidence of ES is estimated to be approximately **2–3 cases per million population**, with nearly **200–250 new cases diagnosed annually in the United States** and approximately **900–1,000 cases reported each year across Europe**[11,41,42]. Owing to its rarity, ES is classified as an orphan malignancy, and most epidemiological data are derived from collaborative multicenter registries and population-based cancer databases.

Age is one of the most significant epidemiological determinants of ES. The disease predominantly affects **children, adolescents, and young adults**, with approximately **80% of patients diagnosed before the age of 20 years** and a median age at diagnosis ranging from **14 to 16 years**[13,43].The incidence rises sharply during puberty, coinciding with periods of rapid skeletal growth, suggesting that physiological bone remodeling and increased cellular proliferation may contribute to disease susceptibility. Occurrence before the age of 5 years or after the age of 30 years is relatively uncommon and should prompt careful clinicopathological evaluation to exclude other small round cell malignancies or Ewing-like sarcomas[15,44].

A slight **male predominance** has consistently been reported, with a male-to-female ratio ranging from **1.2:1 to 1.5:1**[13,45]. Although the precise biological basis for this sex difference remains uncertain, hormonal influences, differences in skeletal growth velocity, and genetic susceptibility have been proposed as contributing factors. Importantly, survival outcomes do not appear to differ significantly between sexes when treatment protocols and disease stage are comparable.[46]

One of the most distinctive epidemiological features of ES is its marked **ethnic variation**. The tumor occurs predominantly among individuals of **European ancestry**, whereas it is considerably less common in African, East Asian, and Indigenous populations[11,47]. Population-based studies have demonstrated an incidence nearly **nine-fold higher in Caucasian populations compared with individuals of African ancestry**, while rates among East Asian populations remain substantially lower. These findings suggest that inherited genetic factors, rather than environmental exposures alone, play an important role in disease susceptibility. Genome-wide association studies have identified several susceptibility loci, including variants near **EGR2, TARDBP, and BMF**, that may partially explain these racial differences[48,49].

Approximately **80–85% of Ewing sarcomas arise within bone**, whereas **15–20% originate in soft tissues**, where they are classified as **extraskeletal Ewing sarcoma (EES)**[18,50]. Skeletal lesions most commonly involve the **pelvis, femur, tibia, humerus, ribs, vertebrae, and scapula**, reflecting the predilection of ES for the axial skeleton and the diaphyseal regions of long bones. Extraskeletal tumors occur in the deep soft tissues of the trunk,

paravertebral region, thoracic wall, retroperitoneum, and lower extremities. Although skeletal and extraskeletal tumors share nearly identical molecular abnormalities and histopathological characteristics, subtle differences in clinical presentation, age distribution, and local treatment strategies have been reported[50,51].

The **head and neck region** accounts for only **1–9% of all Ewing sarcoma cases**, making craniofacial involvement distinctly uncommon[17,52]. Within this region, the **mandible is the most frequently affected bone**, followed by the maxilla, skull, nasal cavity, paranasal sinuses, zygomatic bone, and temporal bone[17,20,53]. Mandibular lesions occur predominantly in the posterior body and ramus, although anterior involvement has also been described. Because these tumors frequently present with pain, swelling, loosening of teeth, facial asymmetry, or paraesthesia, they are often initially mistaken for odontogenic infections, periodontal disease, or osteomyelitis, leading to diagnostic delays[21,54].

Metastatic disease is present at the time of diagnosis in approximately **20–25% of patients**, representing one of the strongest adverse prognostic factors[34]. The lungs constitute the most frequent site of distant metastasis, followed by bone, bone marrow, and, less commonly, lymph nodes or other visceral organs. Patients presenting with isolated pulmonary metastases generally demonstrate a more favorable prognosis than those with combined pulmonary and skeletal dissemination[35,55]. Advances in systemic chemotherapy and multimodal treatment have significantly improved the prognosis of patients with localized disease, with current 5-year overall survival rates approaching **70–80%**. However, the survival of patients with metastatic or recurrent ES remains poor, typically ranging between **20% and 40%**, underscoring the need for improved therapeutic strategies[33,37].

From an oral and maxillofacial perspective, the rarity of jaw involvement has limited the availability of large prospective studies, and most published evidence consists of retrospective analyses, institutional case series, and individual case reports. Nevertheless, accumulating evidence indicates that patients with craniofacial ES generally present with **smaller primary tumors, earlier symptom recognition, and lower metastatic rates** than those with pelvic or axial lesions, factors that may contribute to comparatively favorable survival outcomes when treated using contemporary multidisciplinary protocols[17,52,56].

Table 1. Epidemiological characteristics of Ewing sarcoma

Parameter	Findings
Annual incidence	2–3 cases per million population
Peak age	10–20 years
Median age	14–16 years
Male:Female ratio	1.2–1.5:1
Skeletal tumors	80–85%
Extraskeletal tumors	15–20%
Head and neck involvement	1–9%
Most common craniofacial site	Mandible
Metastasis at diagnosis	20–25%
Common metastatic sites	Lung, bone, bone marrow
Localized disease survival	~70–80% (5-year OS)
Metastatic disease survival	~20–40% (5-year OS)

3. Etiology, Molecular Genetics, and Pathogenesis

3.1 Etiology

The precise etiology of Ewing sarcoma (ES) remains incompletely understood despite significant advances in molecular oncology. Unlike many epithelial malignancies, ES has not been linked to established environmental carcinogens such as tobacco, alcohol, ionizing radiation, occupational chemical exposure, or viral oncogenesis. Instead, the disease is primarily driven by **somatic chromosomal translocations** that occur during early mesenchymal cell development, leading to the formation of oncogenic fusion genes. These genomic rearrangements are considered the initiating molecular events in tumorigenesis and are present in nearly all cases of classical ES[57-59].

Current evidence indicates that ES arises from **sporadic genetic events** rather than inherited germline mutations. Most patients have no significant family history of sarcoma or other hereditary cancer syndromes, and familial clustering is exceedingly rare. Large epidemiological studies have failed to demonstrate a consistent association between ES and inherited cancer predisposition syndromes such as **Li-Fraumeni syndrome**, **familial adenomatous polyposis**, **neurofibromatosis type 1**, or **hereditary retinoblastoma**, which are more commonly

associated with other sarcoma subtypes. Consequently, ES is generally regarded as a **non-hereditary malignancy** resulting from acquired somatic genetic alterations[60,61].

The hallmark genetic event in ES is the reciprocal chromosomal translocation involving the **EWSR1** gene located on chromosome **22q12** and a member of the **ETS family** of transcription factors. The most common rearrangement, **t(11;22)(q24;q12)**, generates the **EWSR1–FLI1** fusion gene, which is identified in approximately **85% of patients**. Alternative translocations involving **ERG**, **ETV1**, **ETV4**, or **FEV** account for most of the remaining cases. These chromosomal rearrangements arise during the patient's lifetime and are confined to tumor cells, distinguishing them from inherited germline mutations[58,62].

Although no definitive environmental risk factors have been identified, several hypotheses have been proposed regarding potential contributors to the development of ES. Earlier investigations explored possible associations with prenatal exposures, parental occupation, agricultural chemicals, pesticides, birth weight, and childhood infections; however, none of these factors has demonstrated a reproducible causal relationship across large population-based studies. Similarly, exposure to therapeutic radiation has not been recognized as a significant etiological factor in the majority of ES cases, unlike radiation-induced osteosarcoma or soft tissue sarcomas[63,64].

Recent genomic studies have suggested that inherited **genetic susceptibility** may influence an individual's likelihood of developing ES, despite the absence of a hereditary inheritance pattern. Genome-wide association studies (GWAS) have identified susceptibility loci near genes such as **EGR2**, **TARDBP**, and **BMF**, as well as polymorphisms affecting GGAA microsatellite sequences that serve as binding sites for the EWSR1–FLI1 fusion protein. These inherited genetic variants appear to increase the probability of acquiring oncogenic translocations rather than directly causing malignant transformation. Such findings may partially explain the marked racial differences observed in ES incidence, with significantly higher rates among individuals of European ancestry compared with African and East Asian populations[48,65,66].

The cellular origin of ES has remained a subject of investigation for several decades. Initially, the tumor was believed to arise from primitive neuroectodermal cells because of its neural immunophenotype and occasional expression of neuronal markers. However, accumulating experimental evidence now supports the hypothesis that ES originates from **primitive mesenchymal stem or progenitor cells** capable of undergoing malignant transformation following acquisition of the characteristic **EWSR1–ETS fusion gene**. Functional studies have demonstrated that expression of EWSR1–FLI1 in mesenchymal stem cells induces transcriptional reprogramming, inhibits normal differentiation, and promotes acquisition of the molecular and phenotypic characteristics observed in human ES[67-69].

Another notable feature of ES is its **remarkably low mutational burden** compared with many adult solid tumors. Whole-genome and whole-exome sequencing studies have consistently shown that ES contains relatively few recurrent somatic mutations beyond the defining fusion oncogene. This finding suggests that the **EWSR1–ETS fusion protein itself functions as the primary oncogenic driver**, capable of initiating tumorigenesis through widespread transcriptional and epigenetic dysregulation without requiring extensive accumulation of additional genetic alterations. Secondary mutations involving genes such as **STAG2**, **TP53**, and **CDKN2A** may occur during tumor progression and have been associated with more aggressive disease and poorer prognosis, but they are not considered initiating events[32,70,71].

Collectively, current evidence supports the concept that ES is a molecularly driven malignancy initiated by sporadic chromosomal translocations in susceptible mesenchymal precursor cells. While environmental and hereditary influences appear to play only minor roles, inherited genetic polymorphisms may modify individual susceptibility to acquiring these translocations. Continued advances in genomic sequencing and molecular biology are expected to further elucidate the mechanisms responsible for fusion gene formation and identify novel biomarkers that may facilitate early diagnosis, risk stratification, and targeted therapeutic intervention.

3.2 Molecular Genetics

Ewing sarcoma (ES) is defined by recurrent chromosomal translocations involving the **EWSR1** gene on chromosome **22q12**, resulting in fusion with members of the ETS family of transcription factors. These fusion genes are the molecular hallmark of ES and are detected in more than 95% of cases, making them indispensable for diagnosis and disease classification[72-74].

The most common rearrangement is the reciprocal translocation **t(11;22)(q24;q12)**, which generates the **EWSR1–FLI1** fusion gene and is identified in approximately **85%** of patients. The resulting fusion protein combines the N-terminal transactivation domain of EWSR1 with the DNA-binding domain of FLI1, producing an aberrant transcription factor that drives oncogenesis by altering the expression of numerous genes involved in proliferation, differentiation, apoptosis, and cell survival[57,72].

Approximately **5–10%** of tumors harbor the **EWSR1–ERG** fusion resulting from **t(21;22)(q22;q12)**. Less

frequently, EWSR1 may fuse with other ETS family members, including **ETV1, ETV4,** and **FEV**. Rare tumors involving **FUS** instead of **EWSR1** have also been described. Although these variants share similar histological features, their biological behavior and clinical significance remain under investigation[62,75].

The **2020 WHO Classification of Soft Tissue and Bone Tumours** recognizes ES as a distinct molecular entity and differentiates it from other undifferentiated round cell sarcomas, including **CIC-rearranged sarcoma**, **BCOR-rearranged sarcoma**, and sarcomas with **EWSR1-non-ETS** fusions. This distinction is clinically important because these tumors differ in prognosis, molecular profile, and therapeutic response[15,76].

Molecular confirmation has become an essential component of diagnosis, particularly in tumors with atypical morphology or unusual anatomical locations. **Fluorescence in situ hybridization (FISH)** is widely used to detect **EWSR1** gene rearrangements, while **reverse transcription-polymerase chain reaction (RT-PCR)** identifies specific fusion transcripts such as **EWSR1–FLI1** and **EWSR1–ERG**. More recently, **next-generation sequencing (NGS)** and **RNA sequencing** have enabled comprehensive detection of known and novel fusion genes with high sensitivity and specificity, especially in diagnostically challenging cases[27,77,78].

In addition to fusion genes, secondary genomic alterations contribute to disease progression. Mutations or deletions involving **STAG2**, **TP53**, and **CDKN2A** are among the most frequently reported secondary events and are associated with increased genomic instability, treatment resistance, and poor prognosis. However, unlike many other malignancies, ES exhibits a relatively low overall mutational burden, emphasizing the dominant oncogenic role of the fusion protein itself[70,71].

The identification of these molecular abnormalities has significantly improved diagnostic accuracy and has facilitated the development of targeted therapeutic strategies aimed at disrupting fusion protein function, epigenetic regulation, and downstream signaling pathways. Consequently, molecular profiling has become an integral component of modern ES diagnosis and represents a promising avenue for precision oncology.

Table 2. Common fusion genes identified in Ewing sarcoma

Fusion Gene	Chromosomal Translocation	Frequency (%)
EWSR1–FLI1	t(11;22)(q24;q12)	~85
EWSR1–ERG	t(21;22)(q22;q12)	5–10
EWSR1–ETV1	Variant	<1
EWSR1–ETV4	Variant	<1
EWSR1–FEV	Variant	<1
FUS–ERG / FUS–FEV	Rare variants	Rare

3.3 Pathogenesis

The pathogenesis of Ewing sarcoma (ES) is primarily driven by the **EWSR1–ETS fusion protein**, most commonly **EWSR1–FLI1**, which functions as an aberrant transcription factor. Unlike conventional oncogenes that activate a single signaling pathway, EWSR1–FLI1 induces widespread transcriptional and epigenetic reprogramming, resulting in uncontrolled cellular proliferation, impaired differentiation, resistance to apoptosis, and enhanced metastatic potential[79-81].

Current evidence suggests that ES originates from **primitive mesenchymal stem or progenitor cells**. Expression of the EWSR1–FLI1 fusion protein in these cells alters their transcriptional program, suppresses normal osteogenic differentiation, and promotes acquisition of an undifferentiated malignant phenotype[68,82].

A characteristic feature of EWSR1–FLI1 is its ability to bind **GGAA microsatellite sequences** within the genome, converting these repetitive DNA elements into active enhancers. This mechanism leads to abnormal activation of multiple oncogenic genes, including **NKX2.2, NR0B1, EZH2,** and **GLI1**, while simultaneously repressing genes involved in cellular differentiation and tumor suppression[83,84].

Several intracellular signaling pathways are dysregulated during ES development. Activation of the **insulin-like growth factor (IGF-1/IGF-1R) pathway** promotes tumor cell proliferation and survival through downstream **PI3K/AKT/mTOR** and **RAS/MAPK** signaling cascades. Increased expression of vascular endothelial growth factor (VEGF) further stimulates angiogenesis, facilitating tumor growth and metastatic spread[85,86].

Epigenetic alterations also play a crucial role in ES pathogenesis. The EWSR1–FLI1 fusion protein interacts with chromatin-remodeling complexes and histone-modifying enzymes, leading to extensive changes in chromatin accessibility and gene expression. Overexpression of **EZH2**, a catalytic component of the Polycomb Repressive Complex 2 (PRC2), contributes to maintenance of the undifferentiated state and has emerged as a potential

therapeutic target[87,88].

Although the fusion oncogene is sufficient to initiate tumorigenesis, secondary genetic alterations influence disease progression. Loss-of-function mutations involving **STAG2**, **TP53**, and **CDKN2A** have been associated with increased genomic instability, chemotherapy resistance, metastatic disease, and inferior survival outcomes. These alterations are considered late events that contribute to tumor aggressiveness rather than primary drivers of malignant transformation[70,71].

Metastasis remains the principal cause of mortality in ES. Tumor dissemination is facilitated by enhanced cellular motility, extracellular matrix degradation, epithelial-to-mesenchymal transition-like processes, and interactions with the tumor microenvironment. The lungs, bone, and bone marrow are the most common sites of metastasis. Emerging evidence also suggests that immune evasion, mediated through an immunosuppressive tumor microenvironment and low immune cell infiltration, contributes to disease progression and limits the effectiveness of current immunotherapeutic strategies[89,90].

A comprehensive understanding of the molecular mechanisms underlying ES has not only improved diagnostic precision but has also facilitated the development of targeted therapies directed against **IGF-1R, PARP, CDK4/6, EZH2**, and other signaling pathways. Although most of these approaches remain under clinical investigation, they represent promising strategies for improving outcomes in patients with recurrent or metastatic disease[6,37,91].

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4. Clinical Presentation

The clinical presentation of Ewing sarcoma (ES) varies according to the anatomical site, tumor size, and presence of metastatic disease. Patients typically present with **progressive localized pain and swelling**, which may mimic inflammatory or odontogenic conditions in the maxillofacial region. Constitutional symptoms such as fever, fatigue, weight loss, and elevated inflammatory markers are observed in a minority of patients and are usually associated with advanced disease[92-94].

In the oral and maxillofacial region, the **mandible is more commonly affected than the maxilla**, particularly the posterior body and ramus. Patients frequently complain of facial swelling, pain, tooth mobility, delayed tooth eruption, paraesthesia of the lower lip (Vincent's symptom), trismus, and malocclusion. Soft tissue extension may produce facial asymmetry, while cortical perforation can result in intraoral swelling or ulceration. Because these manifestations resemble odontogenic infections, osteomyelitis, or benign jaw lesions, delayed diagnosis is common[17,95].

Approximately **20–25% of patients** present with metastatic disease at diagnosis, most commonly involving the lungs, bone, or bone marrow. Pulmonary metastasis remains the most frequent distant site and is associated with a better prognosis than combined skeletal metastases[35,96].

Table 3. Common clinical manifestations of Ewing sarcoma of the jaws

Clinical feature	Frequency
Pain	Very common
Progressive swelling	Very common
Facial asymmetry	Common
Tooth mobility	Common
Paraesthesia	Common
Trismus	Occasional
Mucosal ulceration	Occasional
Fever/weight loss	Less common
Pathological fracture	Rare

5. Diagnostic Evaluation

Diagnosis of ES requires a multidisciplinary approach integrating **clinical examination, imaging, histopathology, immunohistochemistry, and molecular testing**. Initial evaluation includes plain radiographs followed by **contrast-enhanced MRI**, which is the preferred modality for assessing intraosseous extension, cortical destruction, neurovascular involvement, and soft tissue spread. **CT** is useful for evaluating cortical bone destruction and detecting pulmonary metastases, whereas **18F-FDG PET/CT** is increasingly employed for staging, treatment response assessment, and surveillance[97-99].

Histological confirmation through **core needle or incisional biopsy** is mandatory before initiating treatment. Molecular confirmation using **FISH, RT-PCR, or NGS** is recommended, particularly in tumors with atypical morphology[91,100].

6. Histopathology and Immunohistochemistry

Microscopically, ES consists of **uniform small round**

blue cells arranged in diffuse sheets separated by delicate fibrous septa. The tumor cells possess round nuclei with finely dispersed chromatin, inconspicuous nucleoli, and scant glycogen-rich cytoplasm that demonstrates **periodic acid–Schiff (PAS) positivity**. Mitotic activity and necrosis vary according to tumor grade[101].

Immunohistochemically, **CD99** demonstrates strong diffuse membranous positivity and remains the most sensitive marker. Additional markers including **NKX2.2**, **FLI1**, and **ERG** improve diagnostic specificity. Molecular confirmation is essential because CD99 positivity is not unique to ES and may occur in other small round cell tumors[27,102].

Table 4. Characteristic immunohistochemical markers

Marker	Expression
CD99	Diffuse membranous positive
NKX2.2	Positive
FLI1	Positive
ERG	Variable
Cytokeratin	Usually negative/focal
Desmin	Negative
Myogenin	Negative
LCA (CD45)	Negative

7. Differential Diagnosis

The diagnosis of Ewing sarcoma (ES) can be challenging because of its overlapping clinical, radiological, and histopathological features with several malignant small round cell tumors. A definitive diagnosis requires correlation of histopathology, immunohistochemistry, and molecular studies. Diffuse membranous **CD99** expression is highly sensitive but lacks specificity; therefore, molecular confirmation of **EWSR1-ETS** gene rearrangements is recommended, particularly in diagnostically challenging cases[27,76,102].

The principal differential diagnoses include **lymphoblastic lymphoma**, which is positive for **CD45** and lymphoid markers; **alveolar rhabdomyosarcoma**, characterized by **desmin, myogenin, and MyoD1 positivity**; **small-cell osteosarcoma**, which demonstrates osteoid production; **mesenchymal chondrosarcoma**, showing islands of hyaline cartilage; **neuroblastoma**, expressing **synaptophysin and chromogranin**; and **CIC- or BCOR-rearranged sarcomas**, which are molecularly distinct from classical ES and exhibit different clinical behavior. Accurate differentiation is essential because treatment protocols and prognosis differ considerably among these entities[76,103-105].

Table 5. Differential diagnosis of Ewing sarcoma

Lesion	Key distinguishing features
Lymphoblastic lymphoma	CD45+, TdT+, lymphoid markers
Alveolar rhabdomyosarcoma	Desmin+, Myogenin+, MyoD1+
Small-cell osteosarcoma	Malignant osteoid formation
Mesenchymal chondrosarcoma	Biphasic pattern with cartilage
Neuroblastoma	Synaptophysin+, Chromogranin+
CIC-rearranged sarcoma	CIC rearrangement, WT1 positive
BCOR-rearranged sarcoma	BCOR immunopositivity and gene alteration

8. Treatment

Management of ES requires a **multidisciplinary approach** involving medical oncologists, orthopedic or maxillofacial surgeons, radiation oncologists, radiologists, and pathologists. Contemporary treatment consists of **systemic chemotherapy combined with local control by surgery and/or radiotherapy**[6,91].

Neoadjuvant chemotherapy is administered to eradicate micrometastatic disease and reduce tumor volume before definitive local treatment. The current standard regimen comprises alternating cycles of **vincristine, doxorubicin, cyclophosphamide (VDC)** and **ifosfamide plus etoposide (IE)**. Patients demonstrating a good histological response generally have improved survival outcomes[33,91].

Complete surgical excision with histologically negative margins remains the preferred method of local control whenever anatomically feasible. In the maxillofacial region, treatment should aim to achieve oncological clearance while preserving function and aesthetics. Radiotherapy is indicated for unresectable tumors, positive surgical margins, or poor response to chemotherapy, and may also be used as definitive local treatment in selected cases[35,99].

Patients with metastatic or recurrent disease require

individualized treatment, including salvage chemotherapy, metastatectomy in selected patients, stereotactic radiotherapy, and enrollment in clinical trials investigating targeted therapies and immunotherapy. Despite advances in multimodal therapy, metastatic ES continues to have a poor prognosis[6,37].

Table 6. Current treatment strategy for Ewing sarcoma

Treatment modality	Indication
Neoadjuvant chemotherapy	All patients
Surgical resection	Preferred local control when feasible
Radiotherapy	Unresectable disease, positive margins, poor responders
Adjuvant chemotherapy	Following surgery/radiotherapy
Targeted therapy/Clinical trials	Recurrent or metastatic disease

9. Prognosis

Prognosis depends primarily on **disease stage at presentation**, **tumor size**, **primary site**, **response to neoadjuvant chemotherapy**, and **presence of metastatic disease**. Patients with localized ES treated using modern multimodal protocols achieve **5-year overall survival rates of approximately 70–80%**, whereas survival for metastatic disease remains below **30–40%**[33,107].

Poor prognostic factors include metastatic disease at diagnosis, pelvic primary tumors, large tumor volume, poor histological response to chemotherapy (<90% tumor necrosis), positive surgical margins, and secondary mutations involving **TP53** or **STAG2**. Long-term follow-up is essential because survivors remain at risk of local recurrence, distant metastasis, treatment-related cardiotoxicity, infertility, and secondary malignancies[34,71].

10. Recent Advances and Future Perspectives

Rapid advances in molecular oncology have led to the development of novel therapeutic approaches targeting the biological mechanisms underlying ES. Agents directed against **IGF-1R**, **PARP**, **CDK4/6**, and **EZH2** have demonstrated encouraging preclinical and early clinical results. Although none has yet replaced conventional chemotherapy, these therapies may improve outcomes in patients with recurrent or refractory disease[90,108].

Emerging technologies such as **next-generation sequencing (NGS)**, **liquid biopsy**, circulating tumor DNA (ctDNA) analysis, and molecular risk stratification are expected to facilitate earlier diagnosis, treatment monitoring, and personalized therapeutic strategies. In addition, artificial intelligence-assisted digital pathology and radiomics may enhance diagnostic accuracy and prognostic prediction in the future. Continued international collaborative trials are essential to validate these innovations and improve survival in this rare malignancy.

11. Conclusion

Ewing sarcoma is a rare but highly aggressive malignant small round cell sarcoma characterized by **EWSR1-ETS fusion genes**, most commonly **EWSR1-FLI1**. Although involvement of the oral and maxillofacial region is uncommon, early recognition is essential because its clinical presentation often mimics odontogenic infections and other benign conditions. Accurate diagnosis requires integration of clinical findings, advanced imaging, histopathology, immunohistochemistry, and molecular testing. Contemporary multimodal treatment combining chemotherapy, surgery, and radiotherapy has substantially improved survival for localized disease; however, metastatic and recurrent tumors continue to pose significant therapeutic challenges. Ongoing advances in molecular diagnostics, precision oncology, targeted therapies, and immunotherapy hold promise for improving outcomes and establishing more individualized treatment strategies in the future.

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