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REVIEW ARTICLE

A comprehensive approach to metastasis in the oral and maxillofacial region: a narrative review

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Abstract:

According to the latest *Head and Neck Tumor Classification* by the World Health Organization (WHO, 2022), metastases to the oral and maxillofacial region (OMFR) are rare, accounting for less than 1% of all neoplasms reported in this area. These lesions are more prevalent in adults between the sixth and seventh decades of life, with a survival rate of less than one year in 90% of cases, reflecting their high morbidity and mortality. Due to the absence of pathognomonic clinical, radiographic, and histopathological features, metastases in the OMFR present a significant diagnostic challenge. Immunohistochemical studies are essential for identifying the primary tumor in cases of unknown origin. This narrative review aims to describe the main clinical, radiographic, histopathological, and immunohistochemical characteristics of metastatic tumors in the OMFR, emphasizing the need for a comprehensive and multidisciplinary diagnostic approach to ensure accurate identification and timely management.

Keywords: Metastases; Oral and maxillofacial region; Head and neck neoplasms; Immunohistochemistry; Diagnosis.

INTRODUCTION

Metastases to the oral and maxillofacial region (OMFR) are uncommon, comprising less than 1% of all malignant neoplasms in this anatomical area[1,2]. Approximately 31% of metastatic cases in the OMFR are discovered incidentally[2]. The condition predominantly affects adults, particularly those in their sixth and seventh decades of life[1-5]. The posterior region of the mandible is the most frequently involved site[1-5], followed by soft tissues such as the attached gingiva and tongue[4].

Adenocarcinoma is the most common histopathological subtype of oral and maxillofacial metastases, often originating from primary tumors in the breast, lung, prostate, kidney, liver, colon, and thyroid[1-5]. The treatment of metastasis is typically palliative, and the prognosis is poor[2]. However, the state of prognosis depends on several factors related to the type of primary tumor, number and location of metastases, and individual therapy response. About 90% of patients have a survival rate of less than one year — highlighting the aggressive, destructive, and debilitating nature of these lesions[1-5].

While early detection and treatment of metastatic tumors represent the ideal clinical scenario, diagnosis remains a significant challenge due to the lack of specific clinical, radiographic, and histopathological features. A comprehensive and multidisciplinary approach is therefore crucial, particularly when the primary tumor is unknown[6,7]. This narrative review aims to present the current literature on the clinical, radiographic, histopathological, and immunohistochemical features of metastases in the OMFR, emphasizing the complexity of diagnosis and providing insights into their pathogenesis and therapeutic considerations.

Statement of Clinical Significance
Metastasis to the oral and maxillofacial region (OMFR) is a rare condition, known for its high morbidity and mortality rates. The aim of this review is to describe the clinical, radiographic, histopathological, and immunohistochemical characteristics of these metastases. Additionally, etiopathogenesis and therapeutic options are discussed.

METHODS

A comprehensive literature search was conducted in the PubMed/MEDLINE, Scopus/Elsevier,

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and EMBASE/Elsevier databases to identify scientific articles on bone metastases in the maxillofacial region published in English between 2013 and 2024. The aim of this review was to gather information on the clinical, radiographic, histopathological, molecular pathology, immunohistochemical, and etiopathogenic characteristics of maxillofacial bone metastases. The following search equation was used: (jawbones OR jaw [MeSH] OR maxilla [MeSH] OR mandible OR "maxillofacial region") AND ("oral metastasis" OR "head and neck metastasis" OR "skull metastasis" OR "bone metastasis"). Only descriptive studies and case reports of bone metastases in the head and neck region, craniofacial complex, or maxillofacial area were considered, regardless of age, ethnicity, or race, provided they included a complete description of clinical, histopathological, radiographic, molecular pathology, immunohistochemical, and etiopathogenic features. Additionally, a review of the reference lists ("snowball strategy") of the selected studies was carried out.

Literature review

Etiopathogenesis and metastatic latency

Metastasis is one of the most extensively studied processes in cancer biology, with various theories proposed over the years to explain its mechanisms. In 1889, Paget introduced the *"seed and soil"* theory, suggesting that metastasis is not a random event but a highly selective process in which tumor cells exhibit tropism for specific organs[8]. In contrast, in 1928, James Ewing proposed the mechanistic theory, arguing that the metastatic pattern is primarily determined by the hemodynamic relationship between the primary tumor and potential target organs[8]. By the 1970s, Bross et al.[9] introduced the cellular cascade model of metastatic dissemination (Figure 1A)[8], followed by Nowell and Fidler[10], who emphasized the clonal expansion and selection of tumor cells as key drivers of metastasis[8]. In 2001, Weissman et al.[11] highlighted the role of cancer stem cells in promoting metastatic spread[8]. Subsequently, in 2002, Bernard and Weinberg proposed the *"double propensity model"*, challenging the traditional clonal evolution theory by suggesting that metastatic potential may be established early in tumorigenesis[8]. In 2003, Hunter et al.[12] explored the influence of genetic mutations on metastatic susceptibility[8], while in 2005, Thiery[13] and Yang and Weinberg[14] redefined the field by introducing the concept of epithelial-mesenchymal transition (EMT) as a key mechanism underlying metastatic dissemination — an idea that remains widely accepted today[8].

Epithelial-mesenchymal transition (EMT) is a cellular process in which epithelial cells undergo transdifferentiation and acquire mesenchymal characteristics, primarily due to the increased expression of N-cadherin and decreased expression of E-cadherin[8,15,16]. This transition boosts the invasive potential of tumor cells by enhancing their plasticity, mobility, resistance to stress, and ability to proliferate[8,15,16]. However, metastatic cells that have spread can switch between epithelial and mesenchymal states, a process linked to resistance against cancer treatments[8]. The reactivation of the cell cycle at metastatic sites is promoted by mesenchymal-epithelial transition (MET), while the mesenchymal phenotype aids in successful colonization of tissues (Figure 1A)[15,16].

The process of metastatic latency is a phase of cellular inactivity during which disseminated tumor cells modify their metabolism to adapt to the metastatic microenvironment[8]. For example, in metastatic breast cancer, this process is influenced by a balance between ERK1/2 phosphorylation, which drives cell proliferation, and p38 activation, which favors the maintenance of the quiescent state[8]. Metastatic latency allows cells to adopt characteristics like stromal cells ("mimicry") and modify their metabolism ("Warburg Effect")[17]. This process can last for months or even years, making metastasis a silent phenomenon in many cases[17].

Metastatic dissemination in the oral and maxillofacial region: bone and soft tissues

Bone is an organ with a unique extracellular matrix, rich in growth factors, proteoglycans, glycoproteins, cytokines, type I collagen, and minerals such as phosphates and calcium[17,18]. Tumor cell homing to the bone involves the hematopoietic bone marrow, where the balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation is altered, leading to the formation of osteolytic and osteoblastic metastatic tumors, respectively[17-20].

Under normal conditions, RANKL expression by osteoblasts is essential for the differentiation and activation of pre-osteoclasts to osteoclasts (Figure 1B)[17-20]. However, tumor cells exploit this process to overstimulate RANKL levels through the expression of RANK, IL-11, IL-6, and parathyroid hormone-related peptide (PTHrP), which directly decreases the osteoprotective action of OPG, a decoy receptor against RANKL secreted by osteoblastic cells (Figure 1C)[5,7,16]. Thus, the genesis

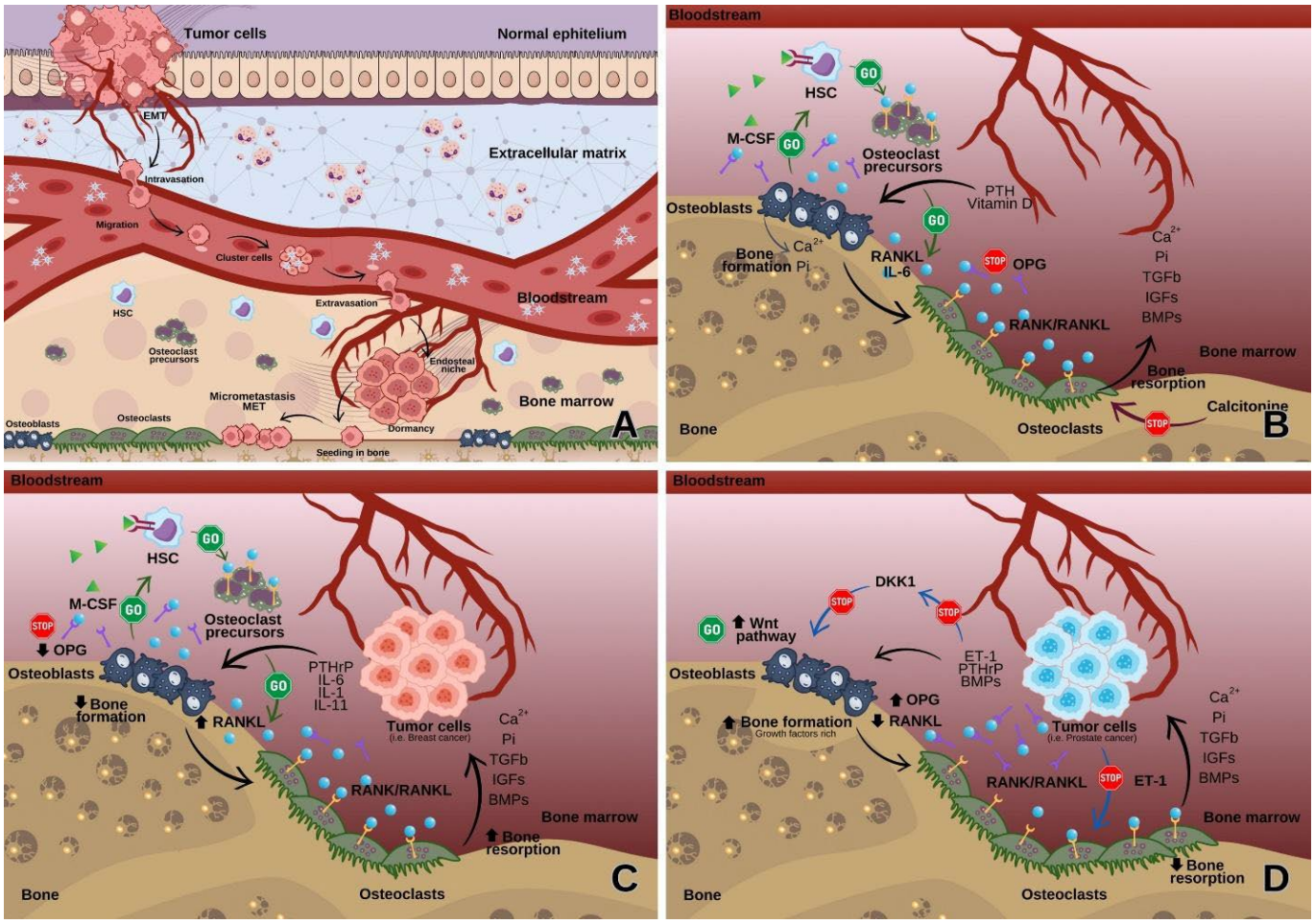

Figure 1. Model of metastatic bone dissemination and pathogenesis of osteolytic and osteoblastic bone metastases. **(A)** The cascade of metastatic dissemination is summarized as follows: EMT (epithelial-mesenchymal transition), basement membrane breakdown and local invasion of the extracellular matrix, entry into the systemic circulation (intravasation), cell migration to the target site, either as single cells or cell clusters, vascular adhesion and extravasation of the endothelial barrier, implantation in the metastatic niche, metastatic latency, MET (mesenchymal-epithelial transition), micrometastasis, and successful tissue colonization. **(B)** Normal bone metabolism. **(C)** Alteration of the OPG/RANK/RANKL pathway crucial to the pathogenesis of osteolytic metastasis ("vicious cycle"). **(D)** ET-1 plays a crucial role in antagonizing DKK-1 and modulating osteoclastic activity, one of the pathways involved in the pathogenesis of osteoblastic metastasis[32].

Abbreviations: HSC: Hematopoietic Stem Cell, M-CSF: Macrophage Colony-Stimulating Factor, PTH: Parathyroid Hormone, PTHrP: Parathyroid Hormone-Related Peptide, ET-1: Endothelin 1, BMPs: Bone Morphogenetic Proteins, IGF: Insulin-Like Growth Factors, TGF β: Transforming Growth Factor Beta, OPG: Osteoprotegerin.

Courtesy: Dr. Juan Pablo Rodríguez-Mora.

of osteolytic metastasis occurs due to the alteration of cellular activity and the aberration of the OPG/RANK/RANKL signaling pathway[17-20]. Factors like IGF-1, TGF-β, and Ca^{2+} released during the resorption process stimulate tumor cell growth within the bone, creating a "vicious cycle" that results in bone destruction (osteolytic metastasis) (Figure 1C)[17-20]. On the other hand, osteoblastic metastasis is characterized by bone-forming lesions, as seen in metastatic prostate cancer[17]. Factors such as PTHrP, PSA, uPA, FGFs, PDGF, VEGF, TGF-β, PAP (prostate acid phosphatase), substance P, Sema3A, and IGF-I have been directly or indirectly linked to the modulation of osteoclastic activity and differentiation[17]. For example, endothelin 1 (ET-1) blocks the action mechanism of DKK-1, facilitating osteoblastic differentiation and the formation of bone rich in growth factors (Figure 1D)[17].

Metastasis to oral soft tissues, such as the attached gingiva, tongue, tonsils, palate, lips, buccal mucosa, and floor of the mouth, is not fully elucidated[21,22].

However, some authors relate metastatic invasion of the oral mucosa to chronic proinflammatory conditions of the oral cavity and the intricate capillary network that nourishes inflamed tissues, such as in gingivitis and periodontitis[23-26].

Routes of metastatic dissemination to the oral and maxillofacial region

In 1940, Oscar V. Batson established a connection between the vertebral venous plexus without valves and metastatic dissemination to the head and neck areas[27]. The Batson plexus represents an alternative anatomical route to hematogenous cardiopulmonary dissemination, associated with primary tumor spread to the oral and maxillofacial region[27,28]. This vertebral venous system, functioning as an independent plexus, communicates directly with the pelvic veins, the proximal femur, the humerus, and the head and neck region[27,28]. As a result, any increase in intra-abdominal, intrathoracic, or stretching pressure can induce reflux into the vertebral plexuses, independent of cardiopulmonary circulation[27,28].

On the other hand, the lymphatic route constitutes an alternative to hematogenous dissemination[29,30], being the primary route used by metastatic carcinomas of the thyroid in the head and neck region[30]. The lymphatic dissemination process begins with the invasion of lymph nodes at levels III and IV in the neck, extending to level II nodes, and then spreading to different zones and subsites in the head and neck[30].

Clinical and radiographic features of the metastatic tumors in oral and maxillofacial region

Chronic pain is the most common symptom in most cases of mandibular metastasis (70%)[2], as tumor cells and osteoclasts create an acidogenic environment that leads to overproduction of bradykinins, endothelins, prostaglandins, proteases, and tyrosine kinase activators such as nerve growth factor (NGF)[17]. Perineural invasion of the vascular nerve bundle by the spreading tumor mass results in alterations in the sensory activity of peripheral nerves, which can lead to paresthesia in the lower lip and chin, known as the "numb chin syndrome"[2,5-7,31,32]. Other signs and symptoms include dental mobility, dental pain, bleeding, soft tissue alterations, presence of masses or indurated inflammation, facial asymmetry, trismus, exophthalmos, tooth loss, cervical lymphadenopathy, failure of alveolar healing post-extraction, and joint symptoms, although these are not always specific to metastasis[2,5-7,31,32].

The radiographic pattern of bone metastases varies depending on the type of primary tumor[33]. For example, metastatic prostate carcinoma is usually predominantly osteoblastic (75%)[33], while osteolytic metastases are more common in renal, lung, and breast carcinomas, although the latter may occasionally present a mixed pattern (15%) (Figure 2)[33]. Approximately 90% of mandibular metastases are osteolytic[2], located within the bone marrow, either focal or extensive, with poorly defined margins, invasion of adjacent structures, occasional fracture lines, and limited periosteal reaction[33]. These metastases are most found in the posterior body of the mandible, the angle, and the mandibular ramus, and may or may not be related to teeth, in addition to causing root resorption, severe mandibular osteolysis, or dental displacement[2]. These radiographic characteristics can complicate the differential diagnosis, as they resemble other maxillofacial bone pathologies such as cysts, odontogenic tumors, or bone infectious processes.

Magnetic resonance imaging (MRI) is useful for detecting subtle changes in marrow patterns and the degree of soft tissue infiltration[33]. Osteolytic metastases are best visualized in the T2 -weighted compared to T1 -weighted, where the lesion appears hyperintense relative to normal bone marrow, and in some cases surrounded by a bright halo that limits the lesion[33] (Figure 2). In contrast, osteoblastic metastases appear as hypointense lesions in both T1 -weighted and T2 -weighted due to their low signal uptake[33]. On the other hand, positron emission tomography (PET) is particularly useful for evaluating the extent and severity of metastasis[33]. However, it is not a specific exam as it may lead to false positives[33].

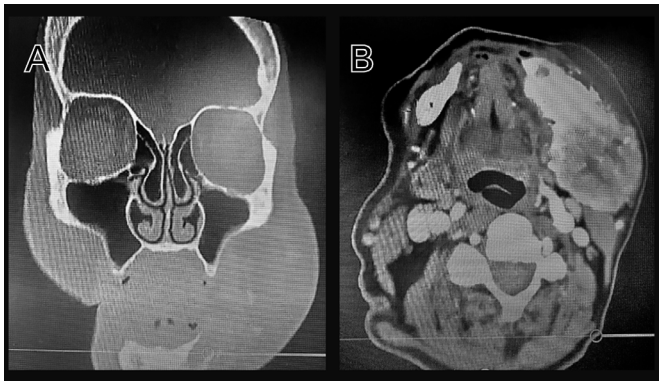

Figure 2. Radiographic features of metastatic tumors. **(A, B)**. Computed Tomography imaging demonstrated a mandibular lesion consistent with metastatic breast carcinoma, with a reported evolution of approximately one year.
Courtesy: Dr. Claudia Patricia Peña Vega.

Histopathological and immunohistochemistry features

Adenocarcinoma is the most common origin of metastasis in OMFR[7]. Metastatic tumors tend to retain phenotypic features like those of the primary tumor, with varying degrees of progression and differentiation[34]. In bone metastatic tumors, pathological alterations can occur in the bone pattern, known as carcinoma *"osteodysplasia"*, when tumor cells arranged in nests, cords, or trabeculae, establish three classic patterns of bone destruction: osteolysis (uniform rarefaction, lacunar osteolysis, and fragmentation), osteosclerosis (layered, sprouting, or net-like pattern), and a mixed pattern[35].

Histopathologically, three main patterns are distinguished based on the characteristics of the cellular population forming the tumor. One of these patterns corresponds to small cell neoplasms, consisting of basaloid, small, round cells, which poses a challenge for pathologists as they can be confused with small, round, blue cell bone sarcomas, such as Ewing's sarcoma[34]. However, these tumors are typically of endocrine and neuroendocrine origin, such as small cell carcinoma, carcinoma of the aerodigestive tract, breast carcinoma (Figure 3), and metastatic melanoma[34]. Another pattern corresponds to large, undifferentiated polygonal cells, which lack phenotypic characteristics of their primary tumor and are often accompanied by a pseudovascular component[34]. As a result, the differential diagnosis for these tumors is broad, with potential primary origins including renal, lung, skin, and breast cancers[34]. Finally, metastatic carcinomas of pleomorphic and malignant spindle cells share a similar cytoskeletal architecture with primary fibrogenic bone tumors, such as fibrosarcoma[34]. This histopathological pattern is characteristic of sarcomatoid renal cell carcinoma and pulmonary carcinoma metastases[34].

Cytokeratin 7 and 20 are the most used immunohistochemical markers for diagnosing metastatic tumors[7,22,36] (Figure 4). Cytokeratin 20 (CK20) is a highly specific marker for diagnosing metastatic tumors[36]. For example, CK20 is not normally expressed in bone marrow or blood, so its positivity in these sites, as well as in serous membranes and brain tissue, suggests the possibility of metastatic spread to these areas[36]. CK20 positivity is characteristic of metastatic carcinomas of colorectal origin (gastrointestinal mucosa), ductal (non-special) breast carcinoma (Figure 5), urothelial carcinoma, and Merkel cell carcinoma[22,36]. On the other hand, cytokeratin 7 (CK7) is a marker with limited reactivity[36], making the CK20/CK7 pattern one

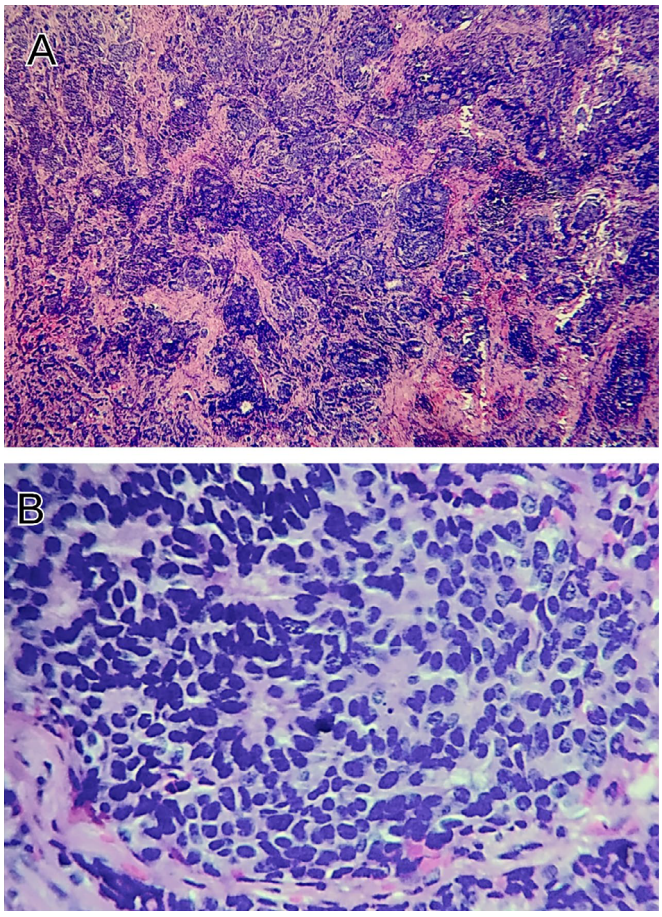

Figure 3. Histopathological features of metastatic tumors. **(A, B)**. Ductal breast metastatic carcinoma. Multiple small, round basaloid cells grouped in nest (rosettes-like pattern), trabeculae and cords that form a destructive bone pattern like vanished bone. A. H&E (10X), B. H&E (40X).
Courtesy: Dr. Claudia Patricia Peña Vega.

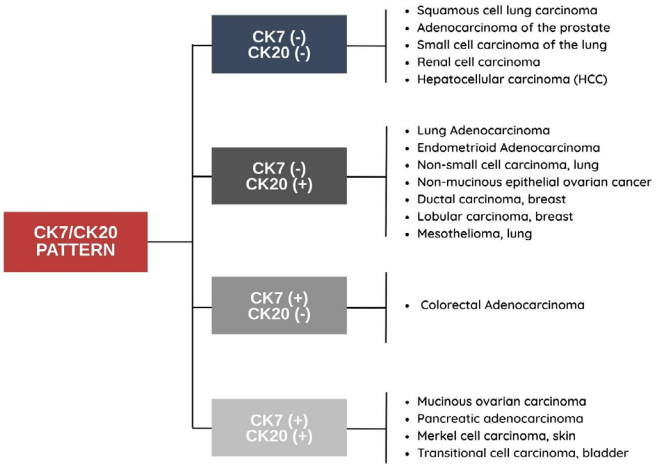

Figure 4. Possible primary origins based on the CK20/CK7 profile.
Courtesy: Dr. Juan Pablo Rodríguez-Mora.

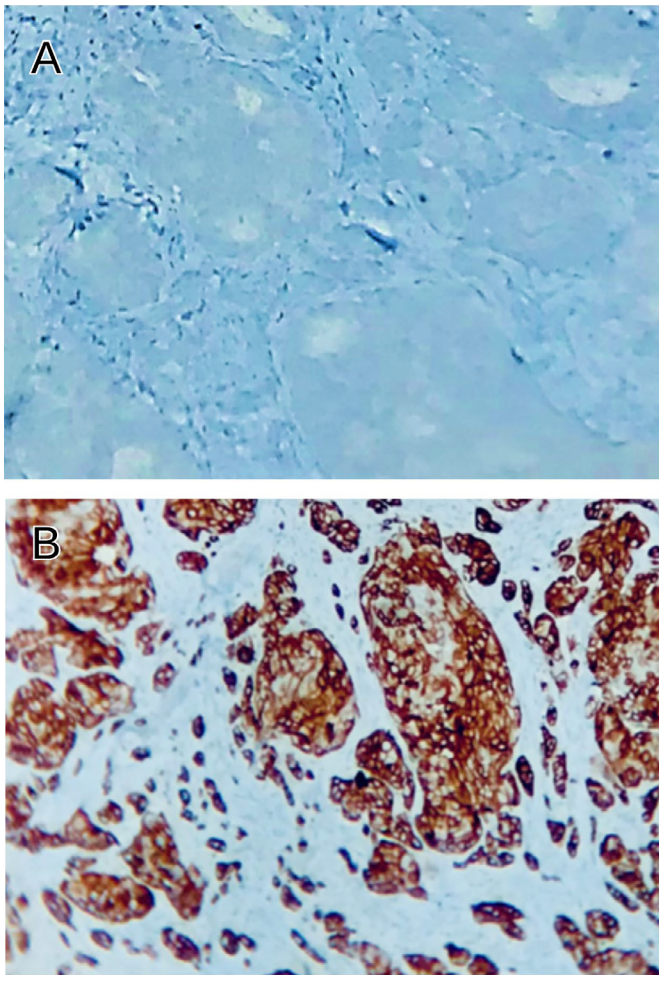

Figure 5. CK20/CK7 profile of ductal breast metastatic carcinoma. **(A)** CK20 (-) and B. CK7 (+) are the most-common pattern of metastasis of breast cancer. **(A, B)**. (40X).
Courtesy: Dr. Claudia Patricia Peña Vega.

of the most frequent, straightforward, and practical for immunohistochemical characterization of various metastatic tumor types[7,22,36]. Immunohistochemistry can be very useful in many cases, but it is not necessary for all cases, especially when the clinic course of the neoplasm suggests metastatic dissemination or the conventional histopathological analysis of the tumor with hematoxylin and eosin is suggestive of metastatic primary origin. On the other hand, it is estimated that between 3% and 5% of all cancer types are classified as "CUP confirmed" (Cancers of Unknown Primary), referring to tumors whose primary origin cannot be confirmed through clinical-radiographic characterization or conventional histopathological analysis[7]. Therefore, the primary origin of these tumors should be traced using molecular tracers as immunohistochemical panels to determinate the tumor's molecular profile[7].

Prognosis and treatment

Metastases have a survival rate of less than one year and a mortality rate of 90%[2]. Treatment depends on the localization of the tumor, the degree of metastatic spread, and the primary tumor[37]. Therefore, the ideal treatment for metastatic tumors should be safe, effective, and better tolerated to maintain functionality and the patient's quality of life[32,37].

Radiotherapy, cryoablation, chemotherapy, and radiofrequency ablation are considered conservative treatments and key approaches in palliative care[4,32,38]. Surgical intervention is an ideal approach for pain control and reducing morbidity, and it can create favorable conditions for radiotherapy[19,20]. However, it is important to consider the principle of personalized treatment for each individual case, as not all patients are candidates for surgical intervention[20]. Currently, combination therapy is commonly used to achieve pain relief and reduce morbidity associated with skeletal-related events (SREs), such as chronic pain, hypercalcemia, bone fragility, pathologic fractures, and disability[20].

Kirschnick et al. found that chemotherapy alone is the most used approach for the treatment of metastatic tumors in the oral and maxillofacial region (40%)[4]. They also observed that the survival rate decreased from 64.8% at 6-month follow-up to 13.2% at 43 months, even independently of patient age, although they mention this finding should be interpreted with caution[4]. On the other hand, Li et al. reported five cases of different oral and maxillofacial tumors in which cryoablation provided better preservation of organ function and recovery in elderly patients with poor general health status, making cryoablation a well-tolerated option for managing tumor size and controlling pain in the oral and maxillofacial region[39]. Similarly, a systematic review conducted by Khanmohammadi et al. found that cryoablation is a useful treatment in the palliative management of bone metastases[40]. The authors highlighted a significant reduction in pain between 1 day and 6 months after the cryoablation procedure in all the studies analyzed[40].

Finally, the use of monoclonal antibodies such as denosumab — a therapeutic agent against RANKL that prevents its binding to RANK — and bisphosphonates such as zoledronic acid, are beneficial because they inhibit osteoclastic activity, limit bone destruction, and reduce tumor progression within the bone[17,19]. These agents improve quality of life by reducing pain, fracture risk, and hypercalcemia (SREs)[17,19,20]. With a better understanding of the etiopathogenesis of bone metastases, new and improved treatments are continuously being

explored, including targeted therapies, hormone therapy, immunomodulation, and others, creating an optimistic outlook for both patients and medical teams[20].

CONCLUSION

Due to its rarity and the variability in clinical and radiographic findings, the diagnosis of metastases in the OMFR is complex, requiring a comprehensive diagnostic approach and multidisciplinary management. Early identification and treatment are crucial to reduce associated morbidity and improve quality of life, despite its unfavorable prognosis. This study highlights the importance of immunohistochemistry as a key diagnostic tool, regarded as the "gold standard" for determining the primary tumor origin, particularly when it is unknown.

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AUTHORS' CONTRIBUTIONS

JPRM: conceptualization, data curation, investigation, methodology, writing – original draft, writing – review & editing. CPPV: conceptualization, data curation, investigation, methodology, writing – original draft, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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Ethics approval: The study was approved by the Research Ethics Committee of the School of Dentistry at the Universidad Nacional de Colombia [B.CIEFO-230-2023] and was conducted in accordance with the Helsinki's Declaration and Resolution 8430 of 1993 by the Ministry of Health and Social Protection of the Republic of Colombia.

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