Osteonecrosis of the jaw in patients with metastatic renal carcinoma: systematic review and meta-analysis

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Abstract

Osteonecrosis of the jaws (ONJ) is a drug-related complication characterized by the presence of necrotic bone or fistula in the maxillofacial region for over eight weeks in patients treated with anti-resorptive and/or anti-angiogenic drugs without head and neck radiation therapy. Initially documented in cancer patients treated with bisphosphonates in 2003, the definition of ONJ has expanded to include cases associated with other drugs such as denosumab and bone-modifying agents, leading to the broader term Medication-Related Osteonecrosis of the Jaw (MRONJ). Due to their anti-osteoclastic and antiangiogenic effects, these drugs are used to treat bone metastases, multiple myeloma, and osteoporosis. Although effective in reducing cancer-related skeletal events, their use can lead to ONJ, causing pain and infections.

This study focuses on renal cell carcinoma (RCC), which often presents with bone metastases, increasing the risk of skeletal events. The systematic literature review evaluated the incidence of MRONJ in patients with metastatic RCC treated with bisphosphonates and other drugs. Retrospective studies were analyzed to identify risk factors for ONJ, including drug type, administration, treatment duration, and local or systemic conditions. Out of 130 initial articles, six retrospective studies were included in the review, highlighting an overall incidence of ONJ of 1.3% in patients with metastatic RCC. These findings underscore the importance of carefully monitoring patients undergoing BMA treatment to prevent and effectively manage ONJ.

Keywords: Osteonecrosis of the Jaw (ONJ); Medication-Related Osteonecrosis of the Jaw (MRONJ); Bisphosphonates

Introduction

Osteonecrosis of the jaws (ONJ) is a "drug-related adverse reaction, characterized by the presence of necrotic bone or intra/extra oral fistula, in the maxillofacial district, for more than eight weeks in patients treated with anti-resorptive drugs and/or anti-angiogenic, who have never undergone head and neck radiotherapy" (1).
Marx et al. highlighted the exposure of necrotic bone in the oral cavity for the first time in 2003 (2) in cancer patients treated with bisphosphonates; since then, numerous reports of this event have been documented in case reports, case series and retrospective studies, leading to the identification of classification systems for the pathology and consequent proposals for changes in therapies following scientific discoveries (3-6).
For this reason, the initial definition was formulated as BRONJ (Bisphosphonate-Related Osteonecrosis of the Jaws) by the American Association of Oral and Maxillofacial Surgery (AAOMS), defined as: "the presence of exposed necrotic bone

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in the oral cavity for more than eight weeks in patients treated with bisphosphonates and never subjected to head and neck radiotherapy" (3).
Since 2008, however, reports began to appear of osteonecrosis with characteristics similar to BRONJ but in patients treated with other categories of drugs such as denosumab (a monoclonal antibody that acts through immune complexes with the RANK-L receptor) and bone-modifying agents (BMA); for this reason, the more inclusive concept of BRONJ was introduced in the literature[7], that is, Drug-Related Osteonecrosis of the Jaw or, according to the AAOMS in 2014, Medication-Related Osteonecrosis of the Jaw (BRONJ), to define all osteonecrotic processes associated with the use of drugs, regardless of their mechanism of action (4-9).
The scope of these drugs includes the treatment of bone metastases, multiple myeloma, and osteoporosis (10-11), thanks to their anti-osteoclastic and antiangiogenic effects, aiming to interrupt bone remodeling and turnover through the inhibitory effect of osteoclasts, or the inhibition of vascular endothelial growth factor (VEGF) production, angiogenesis, and proliferation endothelial (12-16).
In recent years, in particular, these drugs have proven effective in reducing the incidence of skeletal-related events (SREs) in cancer patients, resulting from the presence of bone metastases from various solid tumors such as breast, prostate, and renal cancer.
The study focused on renal cell carcinoma (RCC), which is an essential area of oncology due to its prevalence and increasing incidence in recent years. This type of tumor originates from the renal tubules and includes several subtypes, such as clear cell carcinoma (RCC), which is the most common and represents about 80% of RCC cases (17-19).
Renal cell carcinoma (RCC) can present significant challenges, mainly when associated with bone metastases, both at the time of diagnosis and subsequently, despite curative interventions such as nephrectomy. Bone metastases in RCC significantly increase the risk of skeletal-related events (SREs), which include hypercalcemia, pathological fractures, and spinal cord compression, often requiring interventions such as radiation therapy or bone surgery for pain management and prevention of complications (20).
The use of drugs that inhibit bone remodeling has significantly improved the management of bone metastases. This has led to increased overall survival of patients and significantly improved their quality of life by reducing pain and the need for surgical or radiotherapeutic interventions.
Despite the benefits, these drugs are not free from side effects. One of the most severe adverse events associated with them is osteonecrosis of the jaws (ONJ) (21-22). ONJ can cause significant complications, including pain, difficulty chewing, and secondary infections. Its management can be complex, requiring both medical and dental intervention.
Before 2003, cases of ONJ in patients with metastatic RCC were relatively rare. However, this changed in the following years. Between 2003 and 2008, reports of ONJ cases in this population began to increase. This can be related to several factors, such as:

1. Increased use of anti-angiogenic therapies: Anti-angiogenic drugs, such as sunitinib or sorafenib, have become common in the treatment of metastatic RCC.
2. Combination drug use: Many patients receive combination therapies that include bisphosphonates and anti-angiogenics. The combination of these drugs increases the risk of developing ONJ.
3. Longer patient survival: Thanks to advances in metastatic renal cell carcinoma treatment, patients are living longer. This increased survival exposes patients to prolonged risk of side effects such as ONJ (23-26).

For these reasons, metastatic renal cell carcinoma represents a significant clinical challenge, not only for the treatment of the tumor itself but also for the management of complications associated with drug treatments.

Materials and methods

A systematic literature review was conducted by searching PubMed (http://www.ncbi.nlm.nih.gov/sites/pubmed) and Scopus (http://www.scopus.com).
The search string used consisted of the following terms, used alone or in combination via the boolean operators AND and OR, in this sequence: "Osteonecrosis of the Jaw" - OR - "Osteonecrosis of the jaw associated with bisphosphonates" - AND - "Kidney Neoplasms" - OR - "Renal Cell Carcinoma" - OR - "Metastatic renal cell carcinoma" - OR - "Bone metastasis" - AND - "Bisphosphonates," Denosumab" - OR - "Sunitinib."
Only randomized controlled trials, case-control studies, and retrospective studies were considered for evaluation. These studies had as their primary or secondary objective the assessment of the incidence of MRONJ associated with bisphosphonates and other drugs, as well as the incidence of side effects related to bone modifying agents (BMAs), including osteonecrosis, in patients with metastatic renal cell carcinoma (RCC) undergoing treatment to reduce or prevent bone metastases and skeletal-related events (SREs).

The inclusion criteria for this review are outlined in the following PICO model:

- **P (Population):** Patients with metastatic renal cell carcinoma (mRCC), treated for bone metastases, osteometabolic diseases, and/or reduction of SREs, without limitations on age, gender, or ethnicity.
- **I (Intervention):** Treatment with bone-modifying agents, such as bisphosphonates (zoledronic acid, pamidronate, alendronate, etc.), denosumab and/or targeted molecular therapies (drugs with predominant anti-angiogenic action, Tyrosine Kinase inhibitors, mTOR inhibitors).
- **C (Comparison):** Patients with mRCC who received treatments with bone-modifying agents and/or targeted therapies who subsequently did not develop osteonecrosis.
- **O (Outcome):** Incidence of osteonecrosis of the jaws (ONJ), identification of risk factors for ONJ (such as tooth extraction, combination of therapies), evaluation of the site and symptoms of ONJ.

No language restrictions were imposed, and the publication period is from 2000 to 2023.
Case series, case reports, editorials, and articles studying the incidence of MRONJ in solid tumors other than RCC were excluded from the selection.

Results

One hundred thirty articles were evaluated and retrieved through searches in the PUBMED (25 articles) and SCOPUS (105 articles) databases. Of these, 98 were excluded after a preliminary review of titles and abstracts, as they were not relevant to the topic of our systematic review. Further exclusions included 1 case series, 6 case reports, and 1 editorial. Among the 24 articles initially considered eligible, 2 were excluded due to a lack of necessary university credentials for access. After a full-text review of the remaining 22 articles, 17 were excluded as they needed to meet the defined inclusion criteria. In the end, 6 articles were selected for the systematic review, including 3 multicenter retrospective studies and 3 retrospective studies, all published between 2012 and 2021.The research flowchart is shown in the figure 1.

Characteristics of the studies

The included studies are shown in Table 1.
Yasuyuki Sakai et al (26) study analyzed a total of 218 patients, 168 with prostate cancer and 50 with kidney cancer, both with bone metastases and treated with a bone-modifying agent between January 2012 and February 2019. Of the 50 RCCm patients, 32 received Denosumab, 18 received Zoledronado as BMA, and 44 patients were additionally administered molecular-targeted drugs (sunitinib, axitinib, pazopanib, temsirolimus, everolimus or sorafenib). The study reported an MRONJ incidence of 26% with 13 of 50 patients diagnosed with osteonecrosis during the follow-up period. The multivariate analysis also indicated that kidney cancer, tooth extraction before BMA intake and BMI≥25 kg/m2 are significant predictive factors for MRONJ.
The study by Torben Smidt-Hansen et al (27) examined a total of 46 with metastatic renal cell carcinoma treated with zoledronic acid in combination withsunitinib, sorafenib, bevacizumab, temsirolimus, everolimus, pazopanib or interleukin-2-based immunotherapy from 1 January 2007 to 31 July 2010. They were subsequently divided into 3 groups (cohort A/B/C) based on the reason for administration and whether they had undergone an oral-maxillofacial examination (OM) before treatment. In the first group, 21 patients (Cohort A) were treated to prevent SRE; in the second group (Cohort B) 16 patients were treated to reduce hypercalcemia; in the third group, 9 patients (Cohort C) were treated to prevent SREs, preceded by an oral-maxillofacial examination. At the end of the study, 6 patients in cohort A developed ONJ (only those who received the combination of sunitinib

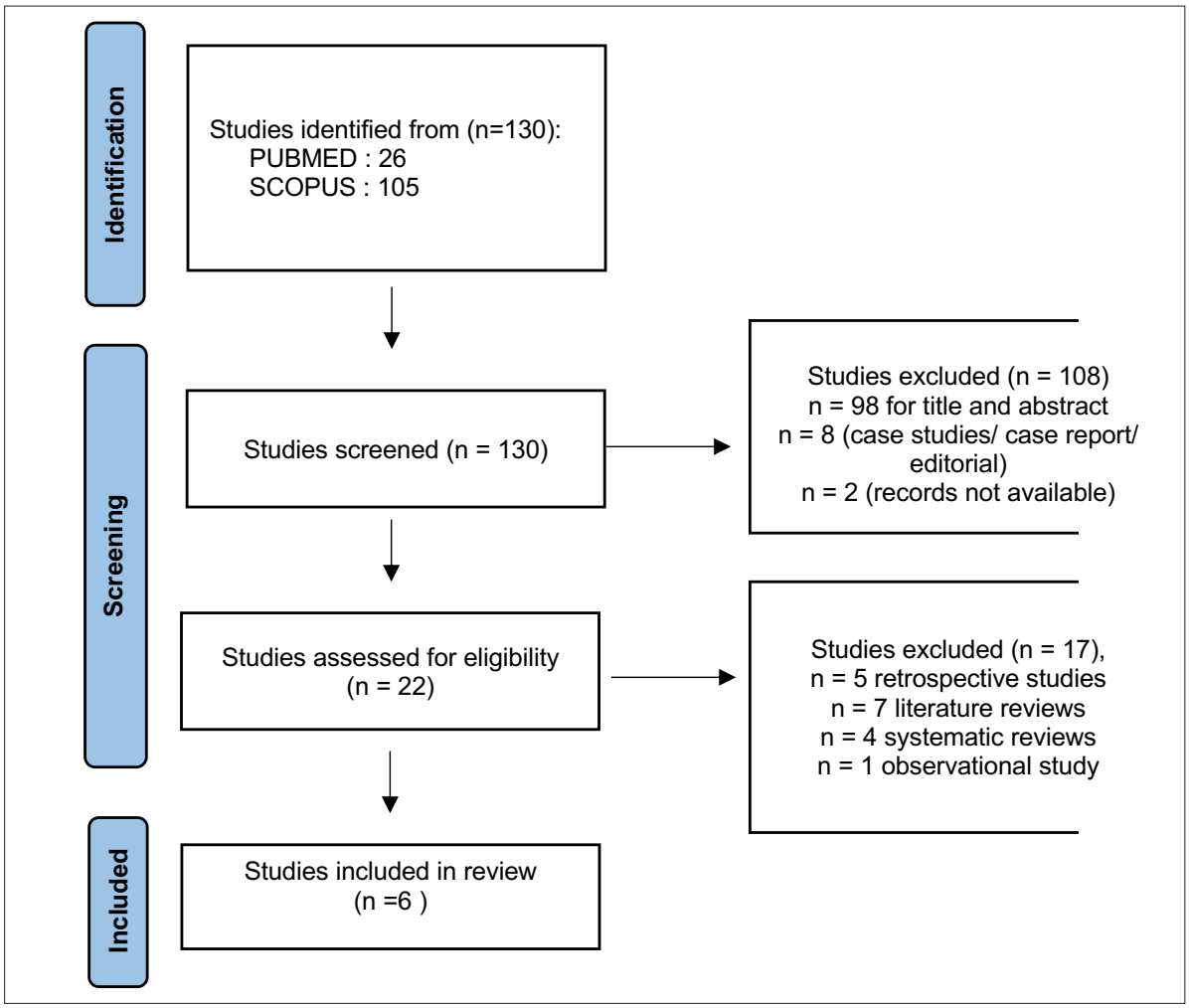

Figure 1. Identification of studies via databases and registers

Table 1.

ARTICLE	AUTHOR	YEAR OF PUBLICATION	STUDY DESIGN	OBJECTIVE OF THE STUDY
Antiresorptive agent-related osteonecrosis of the jaw (ARONJ) in urological malignancies: a multi-center retrospective study	Yasuyuki Sakai et al	2021	Multicenter retrospective study	To evaluate the incidence and risk factors for antiresorptive agent-related osteonecrosis of the jaw (ARONJ) in patients with prostate and renal cancer.
Combination of zoledronic acid and targeted therapy is active but may induce osteonecrosis of the jaw in patients with metastatic renal cell carcinoma	Torben Smidt-Hansen et al	2013	Retrospective study	To study the efficacy and safety of zoledronic acid (ZA) combined with targeted therapy (TT) in patients with mRCC.
Concomitant oral tyrosine kinase inhibitors and bisphosphonates in advanced renal cell carcinoma with bone metastases	B Beuselinck et al	2012	Retrospective study	To evaluate the impact of concomitant bisphosphonates on PFS in first-line treatment with the Tyrosine Kinase Inhibitors (TKIs) sunitinib and sorafenib and to quantify the incidence of ONJ
Denosumab Toxicity When Combined With Anti-angiogenic Therapies on Patients With Metastatic Renal Cell Carcinoma: A GETUG Study	Aline Guillot et al	2018	Multicenter retrospective study	To evaluate the incidence of toxicity (presence of ONJ and hypocalcemia) in patients with mRCC treated with Denosumab therapy and anti-angiogenic therapies (sunitib)
Prognostic significance of bone metastases and bisphosphonate therapy in patients with renal cell carcinoma	Rana R McKay et al	2014	Retrospective study	The primary outcome is to evaluate the overall survival (OS) and progression-free survival (PFS) of patients with BM compared to those without BM. The secondary outcome is to evaluate the OS and PFS of bone marrow patients treated with BT compared to those who did not receive BT.
A retrospective study evaluating frequency and risk factors of osteonecrosis of the jaw in 576 cancer patients receiving intravenous bisphosphonates	Thumbigere-Math	2012	Retrospective study	To evaluate the frequency, risk factors, and clinical presentation of bisphosphonate (BP)-related osteonecrosis of the jaw (BRONJ)

and ZA), no ONJ was observed in cohort B, in cohort C 1 patient developed ONJ. Overall, an MRONJI incidence of 17% was evaluated.

The study by B. Beuselinck et al (28) included 76 patients with mRCC with bone metastases from November 2005 to May 2012, 27 treated only with TKI and 49 with TKI and bisphosphonates, to evaluate the impact of concomitant bisphosphonates on progression-free survival (PFS) in first-line treatment with TKIs sunitinib and sorafenib and to quantify the incidence of ONJ. The incidence of ONJ was evaluated for 52 patients, with an MRONJ incidence of 10% (5 out of 52 patients).

Aline Guillot et al (29) study examined the toxicity profile (mainly osteonecrosis of the jaw) in patients with metastatic renal cell carcinoma treated with denosumab and an antiangiogenic combination (sunitinib), including a total of 41 patients (average age 62 years), 7 already diagnosed with ONJ and 34 without ONJ. Of the 30 patients receiving concomitant TKI and denosumab, 7 (23%) developed ONJ with an incidence of 17%, while no osteonecrosis was diagnosed in patients not exposed to this combination. The mean duration of exposure to denosumab before the onset of ONJ was 19.9 months.

The study by Rana R McKay et al. (30) examined 2749 patients treated for mRCC between January 2003 and November 2011 to evaluate the impact of bone metastases (BM) and bisphosphonate therapy (BT) on outcomes in mRCC. Of these, 285 (10.4%) received bisphosphonates (zoledronic acid: n =233; pamidronate: n =57; unspecified: n =1), with three patients receiving more than one agent sequentially. No patients received denosumab. ONJ was diagnosed in 7 patients, all treated with suntinib, resulting in an incidence of 0.25%.

Vivek Thumbigere-Math et al. (31) study evaluated the frequency, risk factors, and clinical presentation of bisphosphonate-related osteonecrosis of the jaw (BRONJ) by conducting a retrospective analysis of 576 cancer patients treated with intravenous pamidronate and zoledronate between January 2003 and December 2007 at the University of Minnesota Masonic Cancer Center and Park Nicollet Institute. Of these patients, 52 had renal cell carcinoma, and 1 had ONJ, with an estimated occurrence of 1.9%. MRONJ was noted more frequently in the mandible (76%) than in the maxilla (24%), and the most commonly affected site was the posterior mandible. While some patients (59%) developed MRONJ after dentoalveolar treatment, others (41%) developed it without an apparent precipitating event. Pain was the typical presenting symptom in most patients, while some showed evidence of erythema and infection with or without purulence.

Discussion

Osteonecrosis of the jaw (ONJ) represents a significant complication for metastatic cancer patients treated with bone-modifying agents (BMAs), such as bisphosphonates and denosumab. This condition can significantly impact the patient's quality of life. BMAs are essential in managing bone metastases and osteometabolic diseases, such as hormone therapy-induced osteoporosis. However, the use of these drugs is associated with an increased risk of developing ONJ, especially with long-term treatments or in patients with specific pre-existing oral health problems.

The risk factors for ONJ are divided into:

1. **Drug-related Factors**:
   - *Type of Drug*: Some bisphosphonates (such as zoledronate, alendronate) and denosumab are more closely associated with ONJ.
   - *Method of Administration*: ONJ is more frequent with intravenous administration, typical for the treatment of skeletal lesions, compared to oral administration.
   - *Duration and Dose*: The risk increases with duration of treatment and cumulative dose.
2. **Systemic and Local Factors**.
   - *Concomitant Diseases*: The presence of dental or periodontal disease, advanced age of the patient, and other comorbid conditions may increase the risk of ONJ.
   - *Trauma or Oral Surgery*: Procedures such as tooth extractions can expose bone tissue, increasing the risk of ONJ.

The anti-angiogenic action and reduction in bone turnover are predominant effects of BMAs, particularly on the jaw bones. This can be attributed to several reasons that explain their direct involvement, including (32-42):

- A physiologically higher bone turnover in the jaws compared to the rest of the skeleton
- Terminal vascularization of the mandible
- The presence of a thin mucoperiosteal covering to protect the underlying bone tissue, which is easily subject to trauma
- A peculiar oral cavity microflora/biofilm
- The dento-alveolar interface, which predisposes, in the case of dental-periodontal disease (e.g. peri-apical lesions and abscesses, periodontopathy) or oral-dental surgery, to the exposure of the underlying bone tissue

The BMAs in question are, in particular, bisphosphonates (including zoledronate, pamidronate, alendronate, ibandronate, neridronate, risedronate, administered orally or intravenously), Denosumab (monoclonal antibody that acts by forming immune complexes with RANK- L), all drugs with a predominantly anti-angiogenic action (bevacizumab and alilibercept), Tyrosine Kinase inhibitors (sunitinib, sorafenib, cabozantinib, regorafenib, axitinib), and m-TOR inhibitors (temsirolimus, everolimus), prescribed alone or in combination.

In cancer patients, administration can take place monthly intravenously in the presence of skeletal lesions[1.34], or orally for the prevention and therapy of osteometabolic diseases (ie, osteoporosis induced by hormone therapy).

In the case of patients with renal cancer, approximately one third of them will develop bone metastases, with serious consequences on survival and therapeutic management due to SREs (skeletal-related events).

In recent years, it was believed that patients with metastatic renal cell carcinoma (mRCC) were less prone to ONJ compared to other solid tumors, due to their limited survival and short-term duration of NBP treatment. Since the introduction of targeted therapies, the life expectancy of patients with metastatic RCC has nearly tripled across all prognostic risk groups, leading to longer exposure to BMA treatments and increased risk of ONJ (44-45)

In this systematic review, we conducted comprehensive searches in the PubMed and Scopus databases, retrieving a total of 130 articles. The search was

performed using a combination of specific terms related to osteonecrosis of the jaw, renal neoplasms, bone metastases and drugs such as bisphosphonates, denosumab and sunitinib. After an initial screening based on the titles and abstracts, 98 articles were excluded as irrelevant, 8 more were discarded as case series/case reports, while for 2 articles it was not possible to obtain full access.
A complete review of the texts of 22 articles led to the exclusion of an additional 17, resulting in a final selection of 6 articles for the review, all published between 2012 and 2021
These articles are retrospective studies focused on evaluating the incidence and risk factors associated with the use of bone-modifying agents (BMAs) in patients with metastatic renal cell carcinoma (RCCm). In these studies, patients were retrospectively enrolled, and their clinical data were compared with those of a control sample over a specific period.

1. **Yasuyuki Sakai et al.**- In the study conducted from January 2012 to February 2019, 50 patients with RCCm were included, with 13 of theme developing osteonecrosis during the follow-up.
2. **Torben Smidt-Hansen et al.** This study, conducted between January 2007 and July 2010, analyzed 46 patients with RCCm, identifying 7 cases of osteonecrosis of the jaw (ONJ).
3. **B. Beuselinick et al.** Between November 2005 and May 2012, the study included 52 patients, with 5 of them diagnosed with ONJ at the end of follow-up.
4. **Aline Guillot et al.** From January 2013 to November 2016, 41 patients were evaluated, and 7 of these developed ONJ.
5. **Rana R McKay et al.** - In a large sample of 2749 patients observed from January 2003 to November 2011, 7 patients showed signs of osteonecrosis.
6. **Vivek Thumbigere-Math et al.** The study examined 576 medical records from January 2003 to December 2007, identifying 52 patients with mRCC and 1 case of ONJ at the end of follow-up.

These studies provide us with a comprehensive overview of the incidence of ONJ in patients treated with BMAs for RCCm, highlighting the importance of risk assessment and monitoring in therapeutic regimens for bone metastases (Table 2).
An incidence 1.3% of ONJ is evident in patients with RCCm, which, although relatively low, raises significant clinical concerns given the severity of this complication. This incidence, derived from the analysis of 2990 patients, is consistent with literature data, which indicate variations in the ONJ incidence depending on the patient groups and specific treatments.

The most notable finding is the significantly higher incidence of ONJ in patients receiving a combination of BMA with molecularly targeted drugs. The incidence of ONJ ranges from 11.1% to 17% in this group, suggesting a negative synergy between these agents that increases the risk of severe bone complications. This phenomenon could be due to the cumulative effect on bone dynamics, where BMAs alter bone remodeling while molecularly targeted drugs could further compromise vascularization and tissue healing (46-47). In this review, the combined use of Denosumab with molecularly targeted drugs in half of ONJ cases (50%) stands out as an important risk factor. Denosumab, being a monoclonal antibody that inhibits RANKL, is known for its effects on bone and may contribute to ONJ, especially when used in combination with other agents that affect vascularization or bone turnover.
Similarly, bisphosphonates, which are used to prevent bone mass loss, show a similar risk when administered together with targeted therapies (47%). The fact that 2.5% of ONJ cases are associated with the use of bisphosphonates alone demonstrates that these agents also contribute to the development of ONJ by themselves, but the risk increases significantly with combined therapy.
The predominant role of Tyrosine Kinase inhibitors, particularly Sunitinib, which represents 35% of

Table 2.

Article	Drugs used	Total N patients per study	f RCCm patients with MRON	Incidence of MRONJ (%)
Yasuyuki Sakai et al	Denosumab/Zoledronic acid + molecularly targeted drugs	218 (50 with RCCm)	13	26
Torben Smidt-Hansen et al	Zoledronic acid + sunitinib/ sorafenib / bevacizumab / temsirolimus / evetolimus / pazopanib, interleuikin-2	46	7	17
B Beuselinck et al	Zoledronic acid, TKI (sunitinib, sorafenib)	76 with RCCm (52 evaluable for ONJ)	5	10
Aline Guillot et al	Denosumab + TKI (Tyrosine Kinase Inhibitors)	41 with mRCC	7	17
Rana R McKay et al	Bisphosphonates + Sunitinib, Sorafenib, Axitinib, Temsirolimus, Temsirolimus + interferon-UN and IFN-UN	2749	7	0.25
Thumbigere-Math et al	Pamidronate, Zoledronate	576 (52 with RCCm)	1	1.9

administrations among patients with ONJ, further emphasizes the importance of monitoring the bone side effects of these treatments. These drugs are designed to inhibit various tyrosine kinases involved in tumor growth and angiogenesis, but they may also negatively affect the bone microenvironment and healing.
Zoledronic acid, being the most used bisphosphonate (47%), further demonstrates the implication of bisphosphonates in ONJ, especially considering its potency and specific mechanism of action in inhibiting bone resorption.
In the context of developing osteonecrosis of the jaws (ONJ), it is believed that a combination of environmental and genetic risk factors plays a critical role. Among the various environmental factors, dental trauma is recognized as the main trigger for ONJ. According to a study by Woo et al.[38], 60% of cases emerged following tooth extractions. Marx et al[34]. observed that in 37.8% of cases, ONJ was caused by tooth extractions, while periodontitis was present in 28.6% of cases, and 25.2% occurred spontaneously.
The study by Vittorio Fusco et al (48). retrospectively examined the onset of ONJ in patients with renal cell carcinoma (RCC) treated with bisphosphonates (NBPs) and targeted agents. Among the 44 patients analyzed, 49 ONJ sites were identified. The mandible was the most frequent site of ONJ, affecting 52% of cases, followed by the maxilla with 36%. In 5 cases, both maxillae were affected. Additionally, the analysis revealed that 23% of cases had no evident oral triggers. Dental or periodontal infection was the most common trigger (34%), followed by tooth extractions (30%). Other causes included pressure ulcers caused by illfitting prostheses (9%) and other oral surgical interventions (4.5%).
These data highlight the importance of carefully considering dental procedures in at-risk patients, promoting thorough pre-procedural evaluations and constant monitoring to prevent the onset of ONJ, especially in those undergoing treatments that affect bone metabolism.
The increasing incidence of osteonecrosis of the jaw (ONJ) among metastatic renal cell carcinoma (RCC) patients treated with anti-angiogenic therapies and antiresorptive drugs raises important questions about the management and prevention of this complication. Antiresorptive drugs, such as bisphosphonates (NBPs) and denosumab, are widely used to prevent bone events in patients with bone metastases, but they may also contribute to the risk of ONJ, especially when used in combination with molecularly targeted drugs.
For this reason, thorough oral screening is crucial to identify any pre-existing conditions that may predispose to the risk of ONJ. This should include:

- **Complete dental examination:** to identify and treat tooth decay, infections, periodontal diseases, or any other oral pathology before starting drug therapy.
- **Periodic evaluation:** regular monitoring of oral health during treatment to early detect signs of ONJ.
- **Interdisciplinary collaboration:** involvement of oncologists, nephrologists, dentists and, if necessary, radiologists for integrated patient management.

Adopting preventive protocols is essential to reduce the risk of developing ONJ in patients with RCC. These protocols may include:

- **Patient education:** inform patients about the signs and symptoms of ONJ and the importance of maintaining good oral hygiene.
- **Reduction of procedural risk:** avoiding, if possible, invasive dental interventions during treatment. If necessary, these should be performed with extreme caution and under antibiotic coverage.
- **Pharmacological monitoring:** assessing the duration of treatment with antiresorptive drugs and the possibility of therapeutic interruptions, based on current guidelines and the patient's clinical condition.

Conclusion

The recent study on osteonecrosis of the jaws (ONJ) in metastatic renal cell carcinoma (RCC) patients treated with bisphosphonates and targeted agents raises a crucial and potentially underestimated issue in the oral health management in this specific population. The systematic review conducted suggests that the incidence of ONJ may be higher than currently recognized, highlighting a significant need for further prospective research.
It is particularly relevant to call upon the medical and dental communities for more accurate and systematic monitoring of oral health before and during the use of targeted therapies in combination with bone-modifying agents. Early identification of ONJ signs and appropriate management by dentists can make a difference in the patient's treatment path and quality of life.
This study emphasizes the importance of an interdisciplinary approach in the care of oncology patients, where prevention and active surveillance play a fundamental role in mitigating severe complications. It is hoped that this awareness will lead to improved strategies that positively influence both the outcome of oncological treatment and the prevention of associated oral complications.

References

1. Campisi, G., Bedogni, Alberto., Fusco, V., Italian Society of Maxillofacial Surgery. & Society of Pathology and Oral Medicine. Clinical-Therapeutic Recommendations on Drug-Related Osteonecrosis of the Jaw Bones (ONJ) and Its Prevention. (New Digital Press, 2020).
2. Marx, RE Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic (1). Journal of Oral and Maxillofacial Surgery 61, (2003).
3. Ruggiero, SLet al.American association of oral and maxillofacial surgeons position paper on medica-tion-related osteonecrosis of the jaw - 2014 update. Journal of Oral and Maxillofacial Surgery vol. 72 Preprint at https://doi.org/10.1016/j.joms.2014.04.031 (2014).
4. Bedogni, A., Fusco, V., Agrillo, A. & Campisi, G. Learning from experience. Proposal of a refined definition and staging system for bisphosphonate-related osteonecrosis of the jaw (BRONJ). Oral Diseases vol. 18 Preprint at https://doi.org/10.1111/j.1601-0825.2012.01903.x (2012).
5. G., C.et al.Epidemiology, manifestation clinicals, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents. Future Oncology 10, (2014).
6. Ruggiero, SLet al.American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws-2009 Update. Journal of Oral and Maxillofacial Surgery 67, (2009).
7. Bagan, JVet al.Osteonecrosis of the jaws in intravenous bisphosphonate use: Proposal for a modifica-tion of the clinical classification. Oral Oncology vol. 45 Preprint at https://doi.org/10.1016/j.oraloncology.2008.05.011 (2009).

8. Mignogna, MD, Sadile, G. & Leuci, S. Drug-related osteonecrosis of the jaws: 'Exposure, or not exposure: That is the question'. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology vol. 113 Preprint at https://doi.org/10.1016/j.oooo.2012.01.004 (2012).
9. Marchetti E., Mummolo S., Mancini L., Quinzi V., Pontieri E., Marzo G., Campanella V. Decontamina-tion in the dental office: a comparative assessment of a new active principle (2021) Dental Cadmos, 89 (3), pp. 200 - 206
10. Sacco, R.et al.A systematic review of metastatic cancer presenting in osteonecrosis of the jaws (MC-ONJ) in patients undergoing antiresorptive and/or antiangiogenic therapy for skeletal-related adverse events. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology vol. 131 Preprint at https://doi.org/10.1016/j.oooo.2021.01.001 (2021).
11. Ribbon, E. et al. Bisphosphonate-associated osteonecrosis of the jaw in patients with multiple myeloma and breast cancer. Acta Haematol 117, (2007).
12. Ferretti, G.et al.Zoledronic-acid-induced circulating level modifications of angiogenic factors, metalloproteinases and proinflammatory cytokines in metastatic breast cancer patients. Oncology 69, (2005).
13. Lo Giudice, G.et al.Is the Mandibular Condyle Involved in Medication-Related Osteonecrosis of the Jaw? Audit of a Single Tertiary Referral Center and Literature Review. Open Dent J 15, (2022).
14. Bambini, F., De Stefano, C.A., Giannetti, L., Memè, L., Pellecchia, M. Influence of biphosphonates on the integration process of endos seousimplants evaluated using single photon emission computerize tomography (spect) I Valutazione scintigrafica con metodica SPECT dell'ef-fetto dei bifosfonati sul processo di osseointegrazione implantare Minerva Stomatologica, 2003, 52(6), pp. 331–338
15. Bambini, F., Greci, L., Memè, L., ... Procaccini, M., Lo Muzio, L. Raloxifene covalently bonded to titanium implants by interfacing with (3-aminopropyl)-triethoxysilane af-fects osteoblast-like cell gene expression International Journal of Immunopathology and Pharmacology, 2006, 19(4), pp. 905–914
16. Lo Muzio, L., Santarelli, A., Orsini, G., ... Putignano, A., Bambini, F. MG63 and MC3T3-E1 osteoblastic cell lines response to raloxifene European Journal of Inflammation, 2013, 11(3), pp. 797–804
17. Padala, S.A. et al. Epidemiology of renal cell carcinoma. World J Oncol 11, (2020).
18. Guida, A., Escudier, B. & Albiges, L. Treating patients with renal cell carcinoma and bone metastases. Expert Review of Anticancer Therapy vol. 18 Preprint at https://doi.org/10.1080/14737140.2018.1520097 (2018).
19. Woodward, E.et al.Skeletal complications and survival in renal cancer patients with bone metastases. Bone 48, (2011).
20. D'Amario M., De Angelis F., Vadini M., Marchili N., Mummolo S., D'Arcangelo C. Influence of a repeated preheating procedure on mechanical properties of three resin compo-sites(2015) Operative Dentistry, 40 (2), pp. 181 - 189,
21. Bambini, F., Giannetti, L., Memè, L., Pellecchia, M., Selvaggio, R. Comparative analysis of direct and indirect implant impression techniques: An in vitro study Minerva Stomatologica, 2005, 54(6), pp. 395–402
22. Omae, K. et al. Comparative efficacy and safety of bone-modifying agents for the treatment of bone metastases in patients with advanced renal cell carcinoma: a systematic review and meta-analysis. Oncotarget 8, (2017).
23. Fusco, V.et al.Osteonecrosis of the Jaw in Patients with Metastatic Renal Cell Cancer Treated with Bisphosphonates and Targeted Agents: Results of an Italian Multicenter Study and Review of the Lit-erature. Clinical Genitourinary Cancer vol. 13 Preprint at https://doi.org/10.1016/j.clgc.2014.12.002 (2015).
24. Mummolo S., Nota A., De Felice M.E., Marcattili D., Tecco S., Marzo G. Periodontal status of buccally and palatally impacted maxillary canines after surgical orthodontic treatment with open technique (2018) Journal of Oral Science, 60 (4), pp. 552 – 556.
25. Bambini, F., Memè, L., Pellecchia, M., Sabatucci, A., Selvaggio, R. Comparative analysis of deformation of two implant/abutment connection systems during implant inser-tion. An in vitro study. Minerva Stomatologica, 2005, 54(3), pp. 129–138
26. Sakai, Y.et al.Antiresorptive agent-related osteonecrosis of the jaw (ARONJ) in urological malignan-cies: a multi-center retrospective study. J Bone Miner Metab 39, (2021).
27. Smidt-Hansen, T.,Folkmar, T.B., Fode, K., Agerbaek, M. & Donskov, F. Combination of zoledronic acid and targeted therapy is active but may induce osteonecrosis of the jaw in patients with metastatic renal cell carcinoma. Journal of Oral and Maxillofacial Surgery 71, (2013).
28. Beuselinck, B. et al. Concomitant oral tyrosine kinase inhibitors and bisphosphonates in advanced renal cell carcinoma with bone metastases. Br J Cancer 107, (2012).
29. Guillot, A.et al.Denosumab Toxicity When Combined With Anti-angiogenic Therapies on Patients With Metastatic Renal Cell Carcinoma: A GETUG Study. Clin Genitourin Cancer 17, (2019).
30. McKay, R.Ret al.Prognostic significance of bone metastases and bisphosphonate therapy in patients with renal cell carcinoma. Eur Urol 66, (2014).
31. Thumbigere-Math, V. et al. A retrospective study evaluating frequency and risk factors of jaw osteonecrosis in 576 cancer patients receiving intravenous bisphosphonates. American Journal of Clin-ical Oncology: Cancer Clinical Trials 35, (2012).
32. Marx, RE Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic (1). Journal of Oral and Maxillofacial Surgery 61, 1115–1117 (2003).
33. Buser, D., Urban, I., Monje, A., Kunrath, MF & Dahlin, C. Guided bone regeneration in implant dentistry: Basic principle, progress over 35 years, and recent research activities. Periodontol 2000 93, 9–25 (2023).
34. Mummolo S., Nota A., Marchetti E., Capuano S., Tecco S., Marzo G., Campanella V. Histologic and histomorphometric analysis of maxillary sinus augmentation with differentbiomateri-als. A pilot split-mouth human study2018) ORAL and Implantology, 11 (4), pp. 249 – 256.
35. Bambini, F., Santarelli, A., Putignano, A., ... Emanuelli, M., Lo Muzio, L. Use of supercharged cover screw as static magnetic field generator for bone healing, 1st part: In vitro enhancement of osteoblast-like cell differentiation Journal of Biological Regulators and Homeostatic Agents, 2017, 31(1), pp. 215–220
36. Bagan, JVet al.Avascular jaw osteonecrosis in association with cancer chemotherapy: series of 10 cases. J Oral Pathol Med 34, 120–123 (2005).
37. Eckert, A.Wet al.Bisphosphonate-related jaw necrosis--severe complication in maxillofacial surgery. Cancer Treat Rev 33, 58–63 (2007).
38. Mummolo S., Severino M., Campanella V., Barlattani A., Jr., Quinzi V., Marchetti E. Periodontal disease in subjects suffering from coronary heart disease(2019) Journal of Biological Regulators and Homeostatic Agents, 33 (3), pp. 73 – 82.
39. MarcBaltensperger. Osteomyelitis of the Jaws. (2009).
40. Migliorati, C. A., Epstein, J. B., Abt, E. & Berenson, J. R. Osteonecrosis of the jaw and bisphosphonates in cancer: a narrative review. Nat Rev Endocrinol 7, 34–42 (2011).
41. Heng, D.Y.Cet al.Prognostic factors for overall survival in patients with metastatic renal cell carcino-ma treated with vascular endothelial growth factor-targeted agents: Results from a large, multicen-ter study. Journal of Clinical Oncology 27, 5794–5799 (2009).
42. vanCann, T. et al. Incidence of medication-related osteonecrosis of the jaw in patients treated with both bone resorption inhibitors and vascular endothelial growth factor receptor tyrosine kinase inhibi-tors. Supportive Care in Cancer 26, 869–878 (2018).
43. Christodoulou, C.et al.Combination of bisphosphonates and antiangiogenic factors induces osteone-crosis of the jaw more frequently than bisphosphonates alone. Oncology 76, 209–211 (2009).

44. Woo, S. Bin,Hellstein, J.W. & Kalmar, J.R. Narrative (corrected) review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 144, 753–761 (2006).
45. Marx, R.E.,Sawatari, Y., Fortin, M. & Broumand, V. Bisphosphonate-induced exposed bone (osteone-crosis/ osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillo-fac Surg 63, 1567–1575 (2005).
46. Bambini, F., Pellecchia, M., Meme, L., ... Procaccini, M., Lo Muzio, L. Anti-inflammatory cytokines in peri-implant soft tissues: A preliminary study on humans using cDNA microarray technology European Journal of Inflammation, 2007, 5(3), pp. 121–127
47. Campanella V., Mummolo S., Grazzini F., Barlattani A., Jr., Di Girolamo M. The effectiveness of endodontic sealers and endodontic medicaments on the elimination of Entero-coccus faecalis: An in vitro study (2019) Journal of Biological Regulators and Homeostatic Agents, 33 (3), pp. 97 - 102
48. Fusco, V.et al.Osteonecrosis of the Jaw in Patients with Metastatic Renal Cell Cancer Treated with Bisphosphonates and Targeted Agents: Results of an Italian Multicenter Study and Review of the Lit-erature. Clinical Genitourinary Cancer vol. 13 287–294 Preprint at https://doi.org/10.1016/j.clgc.2014.12.002 (2015).