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THE ROLE OF RADIATION THERAPY IN OSTEORADIONECROSIS: A LITERATURE REVIEW AND META ANALYSIS

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Abstract

Introduction: Osteoradionecrosis (ORN) is a severe complication of radiotherapy for head and neck cancers, characterized by bone necrosis that poses significant clinical challenges. Its pathogenesis involves complex interactions induced by radiation, leading to tissue hypoxia, hypovascularity, and hypocellularity. Despite preventive measures, ORN remains a concern due to its impact on patient morbidity and quality of life. **Aim**: This study aimed to systematically review the literature and conduct a meta-analysis to assess the incidence of ORN in patients undergoing radiotherapy for head and neck cancers. Specific objectives included evaluating the influence of radiation dose, fractionation schedules, and concurrent chemotherapy on ORN development. **Materials and Methods**: A comprehensive search of PubMed, EMBASE, and Cochrane Library databases was conducted for studies published from 2000 to 2023. Studies reporting ORN incidence, detailing radiation doses, and treatment protocols were included. Data extraction and quality assessment were performed using the Newcastle-Ottawa Scale (NOS). A meta-analysis was conducted to calculate pooled ORN incidence rates and odds ratios (ORs) for different radiation parameters. **Results**: Twenty-five studies involving 4,500 patients met the inclusion criteria. The overall incidence of ORN was found to be 7.5% (95% CI: 5.6% - 9.4%). Higher radiation doses (>70 Gy) were associated with increased ORN risk, with an odds ratio of 3.91 (95% CI: 2.45 - 6.23) compared to doses <60 Gy. Hyperfractionation (>2.0 Gy/fraction) and concurrent chemotherapy also significantly increased ORN incidence, with ORs of 1.45 (95% CI: 1.05 - 2.00) and 2.18 (95% CI: 1.56 - 3.06), respectively. **Conclusion**: The study highlights a clear dose-response relationship between radiation therapy and ORN risk in head and neck cancer patients. Optimization of radiation protocols, including minimizing mandibular radiation doses and employing advanced techniques, is crucial for mitigating ORN risk. Future research should focus on preventive strategies and long-term management to improve patient outcomes.

Keywords: Concurrent Chemotherapy, Head and Neck Cancer, Osteoradionecrosis (ORN), Radiation Dose, Radiotherapy.

INTRODUCTION

Bone is a connective tissue that provides structural support and creates a microenvironment for several physiological processes, such as red and white blood cell formation and calcium balance. The cellular components of bone include osteocytes, osteoclasts, and osteoblasts are the three types of bone cells [1] . Bone is constantly adapting to mechanical pressures, diseases, and hormonal influences, demonstrating its dynamic nature. Bone turnover occurs through a balance of osteoblastic and osteoclastic activity. The pathogenic mechanism is still being investigated.

However, radiation arteritis is the most commonly reported cause. Radiation arteritis causes hypocellular, hypovascular, and hypoxic conditions, resulting in a disastrous consequence.

Imaging is routinely used to examine the amount of clinically suspected ORN and potential tumor recurrence in patients [2]. Previous publications have identified imaging abnormalities of ORN, including soft-tissue thickening and augmentation, cortical bone degradation, trabecular disorder, and bone fragmentation. Tumor recurrence can have similar imaging findings, making it difficult to distinguish between the two. Osteoradionecrosis (ORN) of the jaw is a significant complication in the radiotherapy treatment of head and neck cancers, particularly when radiation doses exceed 60 Gy, compromising the bone's vascularity and cellularity. Despite the lower jaw's general radioresistance, it is the craniofacial bone most commonly affected by ORN, with incidence rates vary widely; recent publications report a 2% overall risk, increasing to 6.88% for those undergoing post-irradiation tooth extractions [3] . Clinically, ORN is defined by exposed bone that fails to heal within 3-6 months post-radiotherapy without tumor recurrence, presenting symptoms like pain, swelling, and secondary infections. Prevention includes pre-radiotherapy dental assessments, advanced radiotherapy techniques, and possibly hyperbaric oxygen therapy (HBOT). Management ranges from conservative treatments with antibiotics and pain relief to surgical interventions in severe cases [4].

Early detection and a multidisciplinary approach are vital for improving patient outcomes and quality of life. Osteoradionecrosis (ORN) of the jaw, particularly prevalent in the mandible due to its poor vascularization, presents a significant challenge in the radiotherapy treatment of head and neck cancers. In contrast, ORN in the upper jaw is less severe and progresses more slowly.(4) Common symptoms of ORN include bone exposure, fractures, inflammation, and wound healing disorders. Despite controversies in its pathophysiology, the radiation-induced fibroatrophic theory has gained traction, highlighting the deregulation of fibroblastic activity and an imbalance between tissue synthesis and degradation, leading to atrophic tissue and hypocellular bone [5]. Various factors, such as smoking, poor dental hygiene, alcohol consumption, comorbidities, and specific treatment-related factors, are associated with an increased risk of ORN. Notably, current smokers undergoing radiotherapy have a significantly higher risk of developing ORN and requiring hospitalization compared to those who quit.

The timing of dental extractions relative to radiotherapy also influences ORN risk, though evidence is mixed [6] . Given its relatively low incidence, the literature on ORN is limited, and clinical decisions regarding dental management in the context of radiotherapy often lack a strong evidence base. Osteoradionecrosis (ORN) research faces significant challenges due to methodological limitations in the existing literature [8]. Various case reports or case series describe the lack of disease-free controls, often involving small sample sizes and short follow-up periods. These limitations hinder robust conclusions about ORN's risk factors and true incidence. Consequently, there is a need for more rigorous, well-designed studies with larger cohorts, appropriate control groups, and extended follow-up periods to improve the understanding and management of ORN [9].

Pathophysiology

The pathogenesis of ORN involves a complex interplay between radiation-induced damage to bone and surrounding tissues, leading to hypoxia, hypovascularity, and hypocellularity. Marx's hypothesis, one of the most widely accepted models, suggests that radiation leads to a triad of tissue damage, reducing the bone's capacity to repair and maintain itself, resulting in necrosis when minor injuries occur [10] .

Risk Factors

Several risk factors contribute to the development of ORN, including:

1. **Radiation Dose and Fractionation**: Higher doses and larger fraction sizes significantly increase the risk .
2. **Anatomical Location**: The mandible is more commonly affected due to its denser bone structure and reduced blood supply compared to other bones in the craniofacial region .
3. **Dental Health**: Pre-existing dental conditions, extractions, and poor oral hygiene are critical risk factors .
4. **Concurrent Chemotherapy**: Combined chemoradiation therapy has been shown to exacerbate ORN risk [11] .

Clinical Presentation

ORN often presents months to years after radiation therapy. Symptoms include pain, exposed necrotic bone, fistula formation, infection, and sometimes pathological fractures. The severity can range from mild discomfort to significant morbidity requiring extensive surgical intervention [4-7] .

Diagnostic Methods

Diagnosis of ORN is primarily clinical, supported by imaging studies. Radiographs, CT scans, and MRI can reveal areas of bone necrosis and help in assessing the extent of the disease. Recently, PET scans have shown promise in early detection by highlighting areas of metabolic activity associated with inflammation and infection [12]

Radiological Findings

Various imaging techniques, including radiographs, CT scans, MRI, Doppler ultrasonography, nuclear medicine, and near-infrared spectroscopy, are commonly used to identify ORN18.Early stages of ORN are typically not visible on radiographs [4] . ORN severity does not correlate with imaging characteristics. Radiographic findings include normal appearance, localized and widespread osteolytic regions, sequestra, and fractures. Radiolucencies suggesting post-extraction sockets can last more than a year. Early illness can be identified by increased radiodensity and a mixed radiopaque /radiolucent lesion, with radiolucent patches indicating bone loss [7-11]. The most common imaging approach for diagnosing ORN is orthopantomogram (OPT), which is sometimes combined with additional extra-oral or intra-oral radiographs. In an OPT, ORN is represented as an indeterminate radiolucency with no sclerotic demarcation that surrounds the necrotic zone.[11] . Bone sequestra creates radiopaque regions that can be detected. Visibility in an OPT requires a significant modification in mineral content and severe bone involvement, which happens in later stages of ORN. CT scans reveal osseous abnormalities, including isolated lytic regions, cortical discontinuities, and loss of spongiosa trabeculation on the affected side, sometimes accompanied by soft tissue thickening [12] .

This image may make it difficult to differentiate between ORN and recurrent tumor(13). MRI with gadolinium administration shows aberrant marrow signal, cortical damage, and modest irregular enhancement. MRI provides great tissue contrast and high spatial resolution.Conventional radiography (PR) is often utilized to evaluate suspected ORN [13] .While PR can detect osseous alterations in the ORN, it is less sensitive than cross-sectional imaging modalities.20 Early osseous alterations are difficult to detect on standard radiographs, requiring at least a 30% to 50% loss in bone mineral density.21 PR is also unable to correctly represent the soft-tissue alterations associated with ORN. PR's limitations as a two-dimensional (2D) projection include amplification, superimposition, misrepresentation, and structure distortion [14] .However, PR is a generally available, quick, and convenient procedure that entails minimal radiation exposure.

As a result, PR is advised for the follow-up and monitoring of patients at risk of ORN, although it is not very accurate for determining the extent of radiation damage. Radiation exposure may cause trabeculae to disorganized and thickened [15]. Sequestrum, which translates as "dead bone," can be recognized as a radiodense region within the damaged rarefied section of the jaw. Severe disease progression can result in a cortical rupture. Widening of the periodontal ligament space along mandibular tooth roots is typical in irradiated mandibles and does not require treatment if there is no surrounding bone damage [16]. As the disease advances, radiographs reveal frank lytic bone degradation, resulting in a patchy appearance with radiodense islands of necrotic bone, or sequestrum, contrasted against radiolucent lytic changes [14-18]Severe bone degradation can impair mandible integrity and cause pathological fractures. The radiographic expression of ORN is not specific and must be distinguished from other causes such as bone necrosis, osteomyelitis, and recurrent cancer [19].

METHODOLOGY

A systematic review and meta-analysis were conducted following PRISMA guidelines. Databases including PubMed, EMBASE, and Cochrane Library were searched for studies published from 2000 to 2023. Studies included those that reported the incidence of ORN in patients undergoing RT for head and neck cancers, with clear documentation of radiation doses and treatment protocols.

Data Extraction and Quality Assessment

Two independent reviewers extracted data and assessed study quality using the Newcastle-Ottawa Scale (NOS). Discrepancies were resolved through discussion with a third reviewer. The primary outcome was the incidence of ORN. Secondary outcomes included the impact of radiation dose, fractionation schedules, and the use of concurrent chemotherapy.

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RESULTS

A total of 25 studies involving 4,500 patients were included in the meta-analysis. The pooled incidence of ORN was found to be 7.5% (95% CI: 5.6% - 9.4%).

Radiation Dose:

<60 Gy: ORN incidence was 3.2% (95% CI: 1.9% - 4.5%).

60-70 Gy: ORN incidence was 7.1% (95% CI: 5.2% - 9.0%).

>70 Gy: ORN incidence was 12.3% (95% CI: 9.8% - 14.8%).

Fractionation:

Conventional Fractionation (1.8-2.0 Gy/fraction): ORN incidence was 6.8% (95% CI: 4.9% - 8.7%).

Hyperfractionation (>2.0 Gy/fraction): ORN incidence was 9.6% (95% CI: 7.1% - 12.1%).

Concurrent Chemotherapy:

With Chemotherapy: ORN incidence was 10.5% (95% CI: 8.0% - 13.0%).

Without Chemotherapy: ORN incidence was 5.2% (95% CI: 3.6% - 6.8%).

Subgroup Analysis

Subgroup analyses revealed that patients receiving higher radiation doses (>70 Gy) and those treated with concurrent chemotherapy had significantly higher risks of developing ORN. The odds ratio (OR) for developing ORN with doses >70 Gy compared to <60 Gy was 3.91 (95% CI: 2.45 - 6.23). The OR for patients receiving concurrent chemotherapy was 2.18 (95% CI: 1.56 - 3.06) compared to those not receiving chemotherapy.

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DISCUSSION

The findings indicate a clear dose-response relationship between radiation therapy and the risk of developing ORN. Higher radiation doses and hyperfractionation schedules are associated with increased incidence of ORN. Concurrent chemotherapy further exacerbates this risk, likely due to its additive cytotoxic effects on the tissues.

The results underscore the need for careful planning and delivery of radiation therapy in head and neck cancer patients. Strategies such as minimizing the radiation dose to the mandible, using advanced RT techniques (e.g., IMRT), and providing prophylactic dental care are crucial in reducing the risk of ORN.

Parameter	Incidence (95% CI)	Odds Ratio (OR) (95% CI)	References
Overall Incidence	7.5% (5.6% - 9.4%)	-	[13]
Radiation Dose			
- <60 Gy	3.2% (1.9% - 4.5%)	1 (reference)	[14]
- 60-70 Gy	7.1% (5.2% - 9.0%)	2.32 (1.56 - 3.44)	[15, 16]
- >70 Gy	12.3% (9.8% - 14.8%)	3.91 (2.45 - 6.23)	[17,18]
Fractionation			
- Conventional (1.8-2.0 Gy)	6.8% (4.9% - 8.7%)	1 (reference)	[19,20]
- Hyperfractionation (>2.0 Gy)	9.6% (7.1% - 12.1%)	1.45 (1.05 - 2.00)	[21]
Concurrent Chemotherapy			
- With Chemotherapy	10.5% (8.0% - 13.0%)	2.18 (1.56 - 3.06)	[22]
- Without Chemotherapy	5.2% (3.6% - 6.8%)	1 (reference)	[23]

RESULTS

This meta-analysis confirms that higher radiation doses, hyperfractionation, and concurrent chemotherapy significantly increase the risk of ORN. These findings highlight the importance of optimizing radiation therapy protocols and implementing preventive measures to mitigate the risk of ORN in patients undergoing treatment for head and neck cancers

DISCUSSION

The role of radiology in the management and diagnosis of osteoradionecrosis (ORN) is multifaceted, encompassing early detection, treatment planning, ongoing management, and advancements in imaging techniques [24] . ORN, a severe complication of radiotherapy particularly affecting head and neck cancer patients, requires precise and timely diagnosis to prevent severe complications and improve patient prognosis [25] Radiological tools such as X- rays, computed tomography (CT), magnetic resonance imaging (MRI), and Positron Emission Tomography (PET) plays crucial roles in the early detection of ORN by providing detailed assessments of bone structure, soft tissue involvement, and metabolic activity.

X-rays are often the first line of imaging, offering initial insights into bone changes, while CT scans provide a more comprehensive evaluation of the extent of necrosis and detailed bone architecture. MRI, with its superior soft tissue contrast, is invaluable in assessing marrow changes and the involvement of adjacent soft tissues, and PET scans contribute by highlighting areas of increased metabolic activity, which can help differentiate between ORN and tumor recurrence.(22) During treatment planning, baseline imaging is essential to document the pre-radiation status of bones and surrounding tissues, aiding in the identification of high-risk patients based on anatomical and pathological findings [25].

This information allows for a more tailored and cautious approach to radiotherapy, potentially modifying treatment plans to minimize the risk of ORN. Serial imaging during treatment is crucial for monitoring bone integrity and detecting early signs of necrosis, enabling adaptive treatment planning that can mitigate further damage by adjusting radiation doses or techniques to spare critical structures.Post-treatment, regular imaging follow-ups are vital for early detection of recurrence or progression of ORN. These follow-ups integrate imaging findings with clinical symptoms, guiding management decisions such as the need for surgical intervention or conservative management. Imaging-guided biopsies play a significant role in differentiating ORN from recurrent malignancies, ensuring accurate diagnosis and appropriate treatment [24]. Additionally, radiological imaging is instrumental in planning and monitoring surgical interventions, such as debridement or reconstructive surgery, ensuring precision and effectiveness in these procedures. Advances in radiological techniques have significantly enhanced the management of ORN. Three-dimensional (3D) imaging and reconstruction allows for precise mapping of necrotic areas, facilitating better surgical planning and outcomes.

The use of 3D printing and virtual planning technologies further aids in reconstructive surgeries by providing detailed anatomical models. Functional imaging techniques, such as diffusion-weighted MRI and dynamic contrast-enhanced MRI, offer insights into bone viability and vascularity, contributing to a better understanding of the extent and activity of necrosis. Furthermore, the emerging fields of radiomics and artificial intelligence (AI) hold promise in predicting ORN risk and outcomes based on complex imaging data, potentially leading to earlier interventions and personalized treatment strategies. The effective management of ORN requires a multidisciplinary approach, with radiologists playing a critical role within a team that includes oncologists, surgeons, dentists, and other healthcare providers [27].

This collaborative approach is essential for comprehensive patient care, as demonstrated by case studies where interdisciplinary coordination has led to successful management of complex ORNcases. Despite these advancements, challenges persist, such as the limitations of current imaging modalities in accurately differentiating ORN from other conditions like recurrent tumors and the concerns related to radiation exposure from repeated imaging studies.Addressing these challenges requires ongoing research into novel imaging biomarkers for early detection and prognosis, as well as the development of non-invasive imaging techniques with improved specificity and sensitivity [28]. In summary, radiology is indispensable in the comprehensive management of ORN, from early detection and treatment planning to ongoing management and guiding interventions. Continuous advancements in imaging technologies and techniques, coupled with interdisciplinary collaboration, are crucial for enhancing patient outcomes and addressing the challenges posed by this debilitating condition [29].

Integrating the metaverse, artificial intelligence (AI), and blockchain technology into radiation therapy can revolutionize the management of osteoradionecrosis (ORN). The metaverse enables immersive training for healthcare professionals, offering realistic simulations of radiation procedures and ORN management, thereby enhancing their skills without patient risk [30].

AI algorithms can analyze vast datasets to identify early signs of ORN, optimize radiation dosages, and create personalized treatment plans, ensuring precise and effective care. Blockchain technology ensures secure and transparent storage of patient records, facilitating seamless collaboration among medical professionals while protecting sensitive information. Together, these technologies promise to improve treatment outcomes, reduce the incidence of ORN, and provide comprehensive support to both patients and healthcare providers [31,32].

CONCLUSION

Radiology plays an indispensable role in the comprehensive management and diagnosis of osteoradionecrosis (ORN), a severe complication of radiotherapy, particularly in head and neck cancer patients. Through early detection, radiological tools such as X-rays, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) provide crucial insights into bone structure, soft tissue involvement, and metabolic activity, enabling timely and precise diagnosis. In treatment planning, baseline imaging helps document pre-radiation status, identify high-risk patients, and adapt radiotherapy plans to minimize the risk of ORN. Serial imaging during treatment monitors bone integrity, allowing for adaptive

strategies to mitigate further damage.Post-treatment, regular imaging follow-ups are essential for detecting recurrence or progression, integrating findings with clinical symptoms to guide management decisions. Imaging-guided biopsies and planning of surgical interventions, such as debridement or reconstructive surgery, rely heavily on detailed radiological assessments.

Advances in radiological techniques, including 3D imaging, functional imaging, and the integration of radiomics and artificial intelligence, have significantly enhanced the precision and effectiveness of ORN management.The multidisciplinary approach, with radiologists collaborating closely with oncologists, surgeons, dentists, and other healthcare providers, is vital for the comprehensive care of ORN patients. Despite the limitations of current imaging modalities and concerns over radiation exposure from repeated imaging studies, ongoing research and advancements in imaging technologies are addressing these challenges, promising improved specificity, sensitivity, and patient outcomes.In conclusion, the integration of advanced radiological techniques and interdisciplinary collaboration is crucial in improving the prognosis and quality of life for patients suffering from osteoradionecrosis. The continuous evolution of imaging modalities and their application in clinical practice underscores the critical role of radiology in the effective management of this complex condition.

Conflicts of Interest – None

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