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BIOMARKERS FOR PREDICTING MANDIBULAR OSTEORADIONECROSIS IN ORAL AND OROPHARYNGEAL CANCER PATIENTS

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ABSTRACT

Background: Mandibular osteoradionecrosis (ORN) is a severe complication following radiotherapy (RT) in patients with oral and oropharyngeal cancers. It is characterized by non-healing necrotic bone, ORN leads to significant morbidity, including pain, infection, and impaired oral function. Identifying biomarkers that can predict ORN risk is crucial for early intervention and personalized treatment, potentially reducing the severity and incidence of ORN.

Objective: This systematic review aims to evaluate the current evidence on biomarkers that predict the development of ORN in patients receiving radiotherapy for oral and oropharyngeal cancers. By identifying key molecular and genetic markers, the review seeks to highlight potential clinical applications in risk stratification and patient management.

Methodology: A systematic search was conducted in PubMed, EMBASE, and Cochrane databases, including studies published between 2000 and 2024. Studies that examined associations between biomarkers and ORN risk in head and neck cancer patients treated with radiotherapy were included. Data extraction focused on patient demographics, biomarker types, study outcomes, and incidence of ORN. The quality of studies was assessed using standardized tools such as the Newcastle-Ottawa Scale and Cochrane Risk of Bias tool.

Results: 72 studies met the inclusion criteria, identifying several key biomarkers associated with ORN risk. These include inflammatory cytokines (e.g., TNF-α, IL-6), matrix metalloproteinases (MMP-2, MMP-9), and hypoxia-inducible factors (HIF-1α). Elevated levels of these markers were significantly correlated with increased risk of ORN, reflecting their role in inflammation, tissue hypoxia, and impaired

bone healing. Genetic polymorphisms in bone remodeling and angiogenesis pathways, such as VEGF and BMP, were also linked to ORN susceptibility, though further validation is required.
Conclusion: This systematic review highlights the potential of biomarkers in predicting ORN risk in patients undergoing radiotherapy. The data underscore the need for larger studies to confirm these findings and integrate biomarkers into clinical practice.

Keywords: Mandibular osteoradionecrosis, biomarkers, oral cancer, oropharyngeal cancer, radiotherapy complications, inflammation, matrix metalloproteinase, hypoxia-inducible factors.

INTRODUCTION

Mandibular osteoradionecrosis (ORN) is a severe and potentially life-altering complication that arises after radiation therapy (RT), primarily in patients treated for head and neck cancers, including oral and oropharyngeal cancers. RT, although effective in targeting malignancies, damages the bone, blood vessels, and surrounding soft tissues, leading to hypoxia, hypovascularity, and hypocellularity. These conditions impair the bone's ability to heal, especially in the mandible, which is more susceptible due to its dense cortical structure and limited blood supply Patients with ORN experience chronic pain, persistent infections, and reduced oral function, which significantly diminishes their quality of life [5].
The incidence of ORN has been reported to vary widely, from 3% to 15%, depending on factors such as radiation dose, treatment modalities, and patient-specific characteristics[6]. Although advancements in RT techniques, such as intensity-modulated radiotherapy (IMRT), have reduced the incidence, ORN remains a significant clinical concern. For instance, higher radiation doses to the mandible, concurrent chemotherapy, smoking, and poor oral hygiene are known risk factors that contribute to the development of ORN [2].
Given the complex and multifactorial nature of ORN, it is crucial to identify patients at high risk before clinical symptoms manifest. This has driven the growing interest in biomarkers—measurable biological molecules that provide insight into pathological processes or treatment responses. In oncology and radiation therapy, biomarkers are increasingly used to predict treatment outcomes, guide therapeutic interventions, and monitor the development of complications such as ORN [9].
Inflammatory biomarkers, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), play a central role in the body's response to tissue injury and have been strongly associated with chronic inflammation following RT [6]. Additionally, matrix metalloproteinases (MMPs), which degrade the extracellular matrix, and hypoxia-inducible factors (HIFs), which regulate the cellular response to low oxygen levels, are key players in tissue remodeling and wound healing. These biomarkers not only reflect the body's response to radiation-induced injury but also indicate the likelihood of delayed bone healing and necrosis, which are hallmarks of ORN [4].
Moreover, genetic predispositions may influence a patient's susceptibility to ORN. Variations in genes involved in bone remodeling and angiogenesis, such as vascular endothelial growth factor (VEGF) and bone morphogenetic proteins (BMPs), have been associated with impaired healing and increased ORN risk [6]. Although these genetic markers hold promise, further large-scale studies are needed to validate their predictive utility. By understanding the role of these biomarkers, clinicians can identify high-risk patients early, allowing for timely interventions, such as modifications to RT protocols or adjunctive therapies, to reduce the risk and severity of ORN [2]. This systematic review aims to synthesize the current evidence on biomarkers associated with ORN risk in patients receiving RT for oral and oropharyngeal cancers. By identifying reliable molecular and genetic markers, this review highlights potential clinical applications for risk stratification and personalized treatment approaches that could improve patient outcomes.

Research Objectives

This review aims to assess the predictive role of biomarkers in mandibular osteoradionecrosis among patients undergoing RT for oral and oropharyngeal cancers. The goal is to identify reliable biomarkers that can be used to implement early interventions and modify treatment protocols to prevent ORN development.

METHODOLOGY

Study design and setting

This systematic review followed PRISMA guidelines. Databases searched included PubMed, EMBASE, and Cochrane, focusing on studies published between 2000 and 2024. Both prospective and retrospective cohort studies, as well as randomized controlled trials (RCTs), were included.

Inclusion and Exclusion Criteria

Studies that examined biomarkers predicting ORN in head and neck cancer patients treated with RT were included. While; preclinical studies, studies on cancers not involving the head and neck, and case reports with fewer than five patients were excluded.

Sample Size Collection

The review included studies with variable sample sizes. The largest study had over 500 patients, while smaller studies had around 50 participants.

WHO Sample Size Formula

The sample size was calculated using the WHO formula:
n=Z2P (1−P) d2n = ¥frac{Z^2 P (1 - P)} {d^2} n=d2Z2P (1−P)
Where:
Z = 1.96 for 95% confidence level
P = Prevalence of ORN (assumed to be 3.5%)
d = Desired precision (2%)

Parameters Used:
Confidence Level: 95%
Expected Prevalence of ORN: 3.5%
Precision: ±2%

Total Sample Size

The total sample size across all studies combined was approximately 1,200 patients.

Adjusted Sample Size

Adjusted sample size accounted for dropout rates, leading to a final sample of around 1,050 patients.

Data Collection

Data were extracted on biomarker types, patient characteristics, and ORN outcomes. Studies were evaluated using the Newcastle-Ottawa Scale for cohort studies and the Cochrane Risk of Bias tool for randomized trials.

Statistical Analysis

The statistical analysis for this systematic review and meta-analysis was conducted to synthesize the available evidence on the association between biomarkers and the risk of developing mandibular osteoradionecrosis (ORN) in patients undergoing radiotherapy for oral and oropharyngeal cancers.

Table 1: Univariate Analysis of Risk Factors for Osteoradionecrosis Occurrence

Risk Factor	Cases (%)	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Age < 60	20.6%	1.00 (Ref)	--	--
Age ≥ 60	14.8%	0.90	0.60 - 1.30	0.25
HIV Infection	75.0%	8.53	4.00 - 17.90	<0.01
Mandibular Surgery	25.0%	9.13	3.50 - 15.60	0.02
Smoking History	30.2%	1.75	1.10 - 2.40	0.05

Table 2: Multivariate Analysis of Risk Factors for Osteoradionecrosis Development

Risk Factor	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Mandibular Surgery	8.30	3.10 - 17.50	0.01
HIV Infection	18.60	6.50 - 39.40	<0.01
Radiation Dose ≥ 60Gy	1.80	0.80 - 3.50	0.12
Smoking History	1.75	0.95 - 2.80	0.05

Table 3: Incidence Rate of Osteoradionecrosis by Radiation Treatment Type

Radiation Technique	Incidence Rate (%)	95% Confidence Interval (CI)
Two-Dimensional Radiotherapy	5 - 20%	4 - 23%
Three-Dimensional Radiotherapy	2 - 12%	2 - 14%
Intensity-Modulated Radiotherapy	3 - 7%	2 - 8%
Overall Incidence	**18%**	--

Table 4: Cumulative Hazard of Osteoradionecrosis Occurrence Based on Mandibulotomy

Procedure	Hazard Ratio (HR)	95% Confidence Interval (CI)	p-value
Mandibulotomy	9.13	3.00 - 15.90	0.02
No Mandibulotomy	1.00 (Reference)	--	--

Table 5: Osteoradionecrosis Incidence by Radiation Dose

Radiation Dose	Incidence (%)	95% Confidence Interval (CI)
≥ 60Gy	19.3%	15.0 - 24.0%
< 60Gy (Reference)	--	--

RESULTS

In the systematic review, 72 studies met the inclusion criteria, each examining different biomarkers and their potential role in predicting mandibular osteoradionecrosis (ORN) in patients undergoing radiotherapy for oral and oropharyngeal cancers. The biomarkers included inflammatory cytokines (TNF-α, IL-6), matrix metalloproteinases (MMP-2, MMP-9), hypoxia-inducible factors (HIF-1α), and genetic polymorphisms related to angiogenesis and bone remodeling (e.g., VEGF, BMP). [10].

TNF-α and IL-6 were strong predictors of ORN, with pooled hazard ratios and odds ratios indicating a significant increase in ORN risk in patients with elevated levels of these inflammatory markers.

MMP-9 showed a strong association with ORN risk, indicating that matrix metalloproteinases play a critical role in tissue degradation following radiotherapy.

HIF-1α was significantly associated with hypoxia-related bone damage, emphasizing its importance as a biomarker for identifying patients at high risk for ORN.

Genetic markers like VEGF and BMP require further investigation, as their associations were less conclusive due to limited sample sizes and variability in study designs.

Overall, the results of the meta-analysis support the role of inflammatory, hypoxia-related, and genetic biomarkers in predicting ORN risk in patients receiving radiotherapy for oral and oropharyngeal cancers. These findings could have significant implications for early identification of at-risk patients and the implementation of personalized treatment strategies.

Ethical Approval

No ethical approval was required for this systematic review, as it involved a secondary analysis of published data.

DISCUSSION

Inflammatory biomarkers such as TNF-α and IL-6 play a significant role in the body's immune response

to injury, including radiation-induced damage. Elevated levels of TNF-α have been shown to exacerbate tissue inflammation, contributing to the development of ORN (Sroussi et al., 2017). Similarly, IL-6 is linked to chronic inflammation and impaired bone healing, increasing ORN risk (Treister et al., 2020). These findings underscore the importance of inflammation in ORN pathogenesis and highlight TNF-α and IL-6 as potential predictive markers for the condition.

Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are involved in the degradation of the extracellular matrix. Overexpression of these enzymes has been associated with delayed bone healing and higher ORN risk in patients undergoing radiotherapy (Tasoulas et al., 2019). MMP-9, in particular, has been linked to advanced stages of ORN, suggesting that measuring MMP levels could serve as an early indicator of poor tissue regeneration.

Hypoxia-inducible factors (HIFs), such as HIF-1α, are markers of hypoxia, a condition commonly induced by radiotherapy. Elevated levels of HIF-1α have been correlated with ischemic changes in the mandible, contributing to ORN progression (Wong et al., 2020). The role of hypoxia in ORN pathogenesis makes HIF-1α a valuable predictive biomarker.

Genetic Biomarkers

Genetic factors also play a significant role in determining a patient's susceptibility to ORN. Polymorphisms in genes related to angiogenesis and bone remodeling, such as VEGF and BMP, have been linked to increased ORN risk. VEGF is a key regulator of blood vessel formation, and its impaired expression can lead to reduced vascularization of irradiated tissues, contributing to ischemia and delayed healing [7]. BMPs, on the other hand, are involved in bone formation and repair. Mutations in BMP-related genes have been associated with an increased risk of ORN due to a diminished capacity for bone regeneration following radiation-induced damage [6].

These genetic biomarkers, while promising, require further investigation in larger cohorts to validate their predictive value. Nonetheless, they represent a critical area of research that could lead to personalized treatment approaches based on a patient's genetic profile.

The identification of reliable biomarkers for predicting ORN risk has significant clinical implications. Early detection of high-risk patients allows for the implementation of preventive measures, such as modifying radiation doses or adding adjunctive therapies like hyperbaric oxygen therapy, to improve outcomes. Personalized treatment plans based on a patient's biomarker profile could help reduce the incidence and severity of ORN, leading to improved quality of life for cancer survivors [5].

However, several challenges remain. One of the main limitations in current biomarker research is the heterogeneity of study designs and methodologies used to measure biomarker levels. Standardizing these protocols will be essential for comparing results across studies and validating the clinical utility of biomarkers. Additionally, many studies included in this review had small sample sizes, limiting the generalizability of their findings. Future research should focus on conducting larger, multicenter studies that can provide more robust evidence for the role of biomarkers in predicting ORN risk [2].

Further exploration of genetic biomarkers is also warranted, as they hold the potential to revolutionize the way ORN is predicted and managed. By integrating genomics, proteomics, and metabolomics, researchers may uncover additional molecular markers that provide a more comprehensive understanding of the mechanisms underlying ORN development. Ultimately, the goal is to translate these findings into clinical practice, allowing for the early identification of at-risk patients and the development of personalized, preventive treatment strategies.

Strengths and limitations: This comprehensive literature review identifies several biomarkers that show potential for clinical applications. By examining various studies, it highlights the significance of these biomarkers in diagnosing, monitoring, and predicting disease outcomes. The review also provides insights into how these biomarkers can be utilized effectively in clinical practice. While, the studies that were reviewed had a limited number of participants, which can affect the reliability and generalizability of the findings and different methods were used to measure biomarkers across the studies, making it difficult to compare results and draw consistent conclusions.

CONCLUSION

Biomarkers related to inflammation, hypoxia, and bone remodeling have a strong potential for predicting ORN risk in radiotherapy patients. Early identification of at-risk patients could lead to more personalized treatment strategies, reducing the incidence and severity of ORN. However, limitations in current research, including small sample sizes and heterogeneous methodologies, highlight the need for larger, standardized studies to confirm these findings and translate them into clinical practice.

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