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Review Article

Do Irradiated Head and Neck Cancer Site or Prescribed Radiotherapy Dose Have Notable Impacts on the Development of Osteoradionecrosis of the Jaws? A Concise Review

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Abstract

Osteoradionecrosis of the jaws (ORNJ) represents a debilitating late complication of radiotherapy (RT) or concurrent chemo-RT, with a reported incidence ranging from 2% to 22%. Identifying risk factors and categorizing patients into distinct ORNJ risk groups is essential for prevention, early detection, and treatment. Frequently referred ORNJ risk factors include oral health status, periodontal condition, tumor characteristics (location, size, stage), neck node involvement (particularly levels IB-IIA), pre-RT mandibular surgery, tooth extractions conducted before or after RT, concurrent chemotherapy, implant placement before or after RT, and various RT parameters (modality, technique, total dose, per fraction dose). Additionally, significant considerations include mandibular dosimetric factors such as mandibular maximum point dose, mean dose, and Vx (volume receiving X Gy or more). However, despite the absence of robust scientific evidence, specific characteristics, namely the primary tumor location in the head and neck region and the prescribed tumor dose, are consistently regarded as risk factors for the development of ORNJ. Hence, the primary objective of this review is to provide an evidence-based overview of these frequently disputed risk factors' actual value as ORNJ risk factors, which may aid in distinguishing between genuine and pseudo-risk factors associated with ORNJ.

Keywords: Osteoradionecrosis; Radiotherapy; Primary Tumor Site; Prescription Tumor Dose; Risk

Abbreviations

RT: Radiotherapy; ORNJ: Osteoradionecrosis of the Jaws; HNC: Head and Neck Cancer; HPV: Human Papillomavirus; OCC: Oral Cavity Cancer; NPC: Nasopharyngeal Cancers; LA-HNC: Locally Advanced HNC; PTD: Prescribed Tumor Dose; OPC: Oropharyngeal Cancers; EBV: Epstein-Barr virus; HR: Hazard Ratio; PTV: Planning Target Volume; 2D-RT: Two-Dimensional RT; 3D-CRT: Three-Dimensional Conformal RT; PT: Proton Therapy; IMPT: Intensity-modulated PT; BED2: Biologically Effective Dose

Introduction

Head and neck cancers (HNCs) encompass a diverse range of tumors with distinct cellular origins, manifesting at various anatomical sites within the head and neck region. These sites include the nasopharynx, nasal cavity, paranasal sinuses, oral cavity, oropharynx, hypopharynx, larynx, cervical esophagus, parathyroid glands, thyroid gland, as well as the minor and major salivary glands. As a significant source of morbidity and mortality, HNCs account for approximately 6% of global cancer incidence and rank as the sixth most prevalent type of cancer [1]. Despite the implementation of highly effective smoking cessation programs, there has been a concerning increase in the overall incidence of HNCs, particularly in cases of human papillomavirus (HPV)-positive oropharyngeal cancers. This trend is closely correlated with the growing population aging rates and lifestyle choices shifts. Curative intent radiation therapy (RT) serves as the primary treatment modality

for nonmetastatic disease, a salvage maneuver for local and/or regional relapses, and an adjuvant to surgical intervention in the majority of cases of HNCs [2]. Furthermore, it can be integrated with sequential or concurrent chemotherapy, targeted therapies, and/or immunotherapies to provide a more effective treatment strategy depending on the disease stage [3]. RT also represents a viable palliative treatment option for managing various symptoms in advanced nonmetastatic and metastatic HNCs [4]. Additionally, despite the absence of level 1 evidence, emerging research findings suggest that integrating locoregional RT or chemo-RT into treatment regimens may enhance the survival rate of patients with recurrent or metastatic oral cavity (OCC) or nasopharyngeal cancers (NPC) [5-7].

Squamous cell carcinomas represent the predominant type of HNCs. For individuals with early-stage disease who are either medically unfit for surgical intervention or express reluctance towards it, RT stands as the exclusive curative treatment option. Moreover, in the absence of effective chemotherapeutic alternatives for the majority of patients, RT serves as the sole treatment for inoperable, locally advanced salivary gland carcinomas [8]. Patients with locally advanced HNC (LA-HNC) may benefit from receiving RT as an adjuvant treatment after surgery and as the foundation of organ-preserving treatment strategies when paired with concurrent chemotherapy [3].

The significant progress in RT technologies has led to improved tumor coverage, better preservation of surrounding tissues, and a notable decrease in early and late RT-induced toxicities [9]. Despite the notable technological advancements, a significant proportion of patients continue to suffer from severe late complications, mainly in the form of xerostomia, dysphagia, submucosal fibrosis, muscular stiffness and pain, restricted neck movements, carotid artery stenosis and blow-out, periodontitis, tooth decay, tooth loss, radiation-induced trismus, and osteoradionecrosis of the jaw (ORNJ) [10,11]. Such serious late complications can potentially compromise the functionality and quality of life of affected patients and threaten the overall success of their treatment and long-term survival chances directly or indirectly [12]. For instance, recent evidence indicates that the routine administration of antibiotics to combat periodontal or other oral pathogens may significantly reduce the survival rates of HNC patients undergoing treatment with RT, chemotherapy, and/or immunotherapy [13]. Similarly, weight loss resulting from treatment-related toxicity is a well-established indicator of poor prognosis in these patients [14]. Furthermore, radiation-induced trismus can even present a life-threatening situation for a patient during emergencies due to challenges in maintaining an open airway [15].

ORNJ is a disabling late complication of RT or concurrent chemo-RT, first documented by Regaud in 1922 [16]. Despite a century of medical progress, managing HNC patients still presents substantial challenges, as currently, we have no universally acknowledged preventive measures against ORNJ. Presently, ORNJ is defined as the failure of irradiated bone to heal within three months, devoid of any indication of a persistent, recurrent, or metastatic tumor [17,18]. The prevalence of ORNJ among patients with HNC varies widely, with the most frequently reported rates ranging from 2% to 22% [19]. The wide variability in ORNJ incidence rates can be attributed to several factors, including the specific definition criteria used, oral health status, periodontal status, specific tumor attributes such as location, size, and stage, involvement of neck nodes (particularly levels IB-IIA), pre-RT mandibular surgery, pre-RT or post-RT tooth extractions, concurrent administration of chemotherapy, pre-RT or post-RT implant placement, RT parameters including modality, technique, total dose, per fraction dose, as well as mandibular dosimetric parameters such as maximum point dose (Dmax), mean dose (Dmean), and Vx (volume receiving X Gy or more) [20-24]. However, as summarized in Table 1, the choice of RT modality, the specific RT planning and dose delivery technique utilized, and the RT dosage administered to the entire mandible, mandibular Vx, surgical site, or tooth extraction site are the most critical and reliable factors influencing the risk of ORNJ development, and therefore, its incidence rates [20-24].

Identifying risk factors and stratifying patients into distinctive ORNJ risk groups is crucial for prevention, early diagnosis, and treatment. However, despite the lack of solid scientific foundations, specific characteristics, including the primary tumor location in the head and neck region and the prescribed tumor dose (PTD), are continually considered risk factors for ORNJ development [20,26-28]. Therefore, the primary objective of this review is to offer a concise overview of these frequently disputed risk factors, particularly the primary tumor location and PTD, which may help distinguish between the genuine and pseudo-risk factors associated with ORNJ.

Table 1: Factors proposed to be linked to the development of osteoradionecrosis of the jaw and their relative strength.

Established and strong factors	Weak or questionable factors
Poor oral health	Tumor location
Periodontitis	Neoadjuvant chemotherapy
Tumor size	Adjuvant chemotherapy
Tumor stage	Prescribed tumor dose
Level IA-II lymph node involvement	Mandibular maximum point dose
Previous mandibular surgery	
Mandibular surgery type	
Pre-radiotherapy tooth extractions	
Post-radiotherapy tooth extractions	
Pre- or post-radiotherapy extracted tooth quantity	
Pre-radiotherapy implant placement	
Post-radiotherapy implant placement	
Pre- or post-radiotherapy implant quantity	
Concurrent chemotherapy	
Mandibular mean dose	
Mandibular median dose	
Mandibular Vx (% receiving ≥ X Gy)	
Planning target volume proportion intersecting with the mandible	
Tooth socket dose	
Implant placement site dose	
Mandibular surgical bed dose	
Radiotherapy modality	
Radiotherapy technique	
Radiotherapy plan quality	
Location of hot-spot doses	

Is the primary tumor site an actual risk factor for the development of osteoradionecrosis of the Jaws?

Compared to most of the other HNC sites, the oral cavity (OCC) and oropharyngeal cancers (OPC) are situated in close proximity to the upper and lower jaws. This specific localization predisposes them to the inadvertent administration of high doses of RT to the jaw regions, as high RT doses (66-74 Gy) are necessary for effective tumor control. Additionally, since these tumors often involve neck node levels IA-B and IIA, this fact further reduces the possibility of delivering lower doses to the mandible. Therefore, of all HNCs, OCC and OPC are the most frequently cited tumors that are marked to pose the highest risk for developing ORNJ after undergoing RT or concurrent chemo-RT. Moreover, based on the multivariate analysis results, which mostly lack dosimetric parameters, these tumor locations are often accentuated as having an increased risk of ORNJ independent of other factors [25-27]. However, this approach and its associated findings present challenges in light of specific biological and radiation dose and technique-related factors [20]. These factors can be outlined as follows: To our knowledge, no preclinical or clinical research data demonstrates an evidence-based genetic, physiological, or radiobiological (radiation hypersensitivity) basis for an increased risk of ORNJ in these particular tumors compared to other HNC types. There is also no substantiated proof indicating that OCCs or OPCs are associated with a specific genetic mutation or excessive production of an enzyme with osteolytic properties that elevate the risk of ORNJ in these tumors compared to other HNCs, such as nasopharyngeal or hypopharyngeal cancers. Furthermore, there is a lack of concrete data to allege that OCCs or OPCs produce a distinct chemokine, cytokine, or metabolite that could trigger or contribute to the development of ORNJ. From this standpoint, several researchers may logically suggest that certain tumor forms, such as HPV-positive OPCs, may create a persistent local and systemic inflammatory environment, thus increasing the vulnerability to ORNJ in afflicted individuals [29]. This statement

highlights the presumed significance of hyperinflammation in triggering processes associated with ORNJ, such as hypoxia and excessive fibrosis, which may also align with Epstein-Barr virus-positive (EBV-positive) NPCs. However, there is no unequivocal evidence to suggest that either HPV-positive or EBV-positive cancers of the oropharynx and nasopharynx provide a greater risk for ORNJ development compared to their HPV-negative or EBV-negative equivalents. Consequently, while there is an imperative for site-specific comparative fundamental and clinical research on these vital subjects, it is essential to underscore that there is no credible basic or clinical data to substantiate the assertion that OCCs and OPCs provide a greater risk of developing ORNJ compared to other HNC sites.

Although the OCC and OPC may appear as independent risk factors contributing to heightened rates of ORNJ in multivariate analyses across various studies [27,30,31], prompting researchers to posit these tumor sites as substantial risk factors, such an inference is methodologically unsound. This is because multivariate analysis can only assess the provided factors and their interactions rather than establish independent causality irrespective of the unaccounted but potentially significant confounders [32]. Multivariate analysis, distinct from univariate and bivariate analysis, is a comprehensive statistical method that examines more than two variables to discern potential associations among them. This method allows for meticulous data exploration by scrutinizing all conceivable independent variables and their interrelations. However, conducting multivariate analysis requires a substantial sample size due to the increased number of variables. This can be a limitation because the higher variable quantities increase the number of combinations that need to be tested. Therefore, having a larger group of patients to assess these combinations reliably is essential, as some groups may have considerably larger population sizes than others. Another critical limitation of multivariate analysis is the potential for generating confusing results. In some cases, multivariate testing may lead to ambiguous or conflicting outcomes that are challenging to interpret, especially if some dependent variables are missing. Therefore, the precise relationship between the primary tumor locations and the absolute risk of developing ORNJ cannot be fully elucidated through multivariate analysis in isolation, as a comprehensive analysis necessitates specific data, notably the received doses by the mandible per individual tumor site. Without such data, a thorough understanding of the relationships between primary tumor sites, contributing factors, and their genuine association with ORNJ risk will remain uncertain and open to debate despite demonstrating significant multivariate independence.

Regrettably, the dosimetric variables associated with the mandible, particularly the mandibular Dmean and Vx, are infrequently incorporated into multivariate analysis alongside PTLs despite their well-established mark on rates of ORNJ. The recent study by Watson and associates presented an unfortunate but illustrative exhibition of this approach [27]. Their extensive study sought to pinpoint risk factors associated with ORNJ and establish a new severity classification system for ORNJ in a cohort of 2,732 HNC patients. The study included consecutive HNC patients who underwent curative-intent IMRT (≥ 45Gy) treatment between 2011 and 2018. ORNJ cases were identified through prospective dental and clinical databases, and a multivariable logistic regression model was used to identify risk factors and categorize patients into high-risk and low-risk groups. Furthermore, a novel ORNJ classification system was developed to accurately represent the severity of ORNJ by modifying existing systems and incorporating expert input. The incidence rate of ORNJ was 8.0% (N = 219) among the patient population. Factors associated with a higher risk of ORNJ included having OCC or OPC, receiving IMRT at a dose of ≥ 60 Gy, current or former smoking status, and stage III-IV periodontal disease. The incidence of ORNJ in high-risk individuals was 12.7%, while it was 3.1% in low-risk patients ($P < 0.001$). The authors stated that current ORNJ methods tended to overclassify severe ORNJ incidents and could not identify cases of maxillary ORNJ. Compared to other methods, their categorization method, RadORN, was developed using the vertical extent of bone necrosis and the presence or absence of exposed bone or fistula. This approach successfully identified severe ORNJ occurrences in 5.7% of patients and has shown superior performance to other current systems. However, although the OCC and OPC were determined to be significant and independent risk factors for higher ORNJ rates, the authors of this study utilized PTD as a dosimetric parameter, eschewing the more dependable mandibular Dmean or Vx doses. It is important to note that while PTDs may remain indistinguishable across various types of HNCs, the doses to the mandible and the risk of ORNJ can vary significantly depending on how close the tumor or affected lymph nodes are to the mandible, even when the same PTDs are used. On the other hand, different PTDs may result in similar doses to the mandible and the same ORNJ risk. Hence, it is compulsory to balance or equalize the mandibular dosimetric characteristics between OCC/OPC and other HNC primaries to assess whether the primary tumor type poses a higher risk of ORNJ. For instance, a meticulously planned study can focus on patients with exclusive mandibular Dmean of > 60 Gy in both groups, who have been matched using propensity scores and compare the incidence rates of ORNJ between patients with OCC and patients with hypopharyngeal cancer.

Based on the provided information, it is evident that the dosimetric variables associated with the mandible, rather than the primary tumor location, are pivotal in determining the risk of ORNJ in HNC patients undergoing RT or concurrent chemo-RT, provided that all other contributing factors remain balanced across the primary tumors [20,24,33]. Clinical data substantiate this assertion, demonstrating comparable rates of ORNJ across different types of HNCs [35-37]. Yilmaz., *et al*. recently documented a 10.0% ORNJ incidence in LA-NPC patients undergoing definitive concurrent chemo-RT [34], which exceeds the 8.0% reported by de Almeida-Silva and colleagues for OCC patients [35] and the 9.6% for OPC patients as reported by Verdujin and colleagues [36]. Somay., *et al*. found that a mandibular Dmean ≥ 34.1 Gy (P = 0.007) and V57.5 Gy ≥ 34.7% (P = 0.017) are strong predictors of ORNJ in patients with LA- NPC undergoing IMRT concurrent with chemotherapy [37]. Similarly, Lang., *et al.* discovered that Dmean > 45 Gy (Hazard ratio (HR) = 2.4; 1.0-5.7), Dmax > 60 Gy (HR = 1.3; 1.1-2.8), and a planning target volume (PTV) proportion > 40% intersecting with the mandible (HR = 1.1; 1.0-1.1) were significantly associated with ORNJ in OCC patients [38]. These results underscore that the main predictor of ORNJ risk is not the tumor's location in the head and neck region but rather mandibular dosimetric variables such as Dmean and Vx.

In conclusion, existing scientific data fails to provide conclusive evidence suggesting that a specific initial tumor location in the head and neck region is more predictive than others in terms of elevated rates of ORNJ risk following RT or chemo-RT. The prevalent association of increased ORNJ risk with OCC and OPC likely stems mainly from their proximity to the mandible, resulting in elevated mandibular radiation doses. Furthermore, pre-RT surgery, commonly recommended for OCC patients, may indirectly heighten the likelihood of radiation-induced toxicities, including ORNJ development. It is imperative to emphasize that the heightened incidence of ORNJ in these cases may be attributable to surgical bone trauma, rendering individuals more susceptible to ORNJ rather than the anatomical location of the primary tumor. Thus, it is crucial to prioritize the mandibular dosimetric variables throughout the RT planning phase to reduce the mandibular Dmean and Vx values. This approach, accompanied by ongoing professional oral and dental care, is essential for mitigating the risk of ORNJ in HNC patients, irrespective of the tumor site. Otherwise, the classification of the OCC and OPC as the highest-risk tumor sites for ORNJ in the absence of reliable data may misleadingly imply that less stringent RT plans could be adopted for other HNC locations, thereby potentially increasing the incidence of ORNJ in patients receiving RT or concurrent chemo-RT for these tumors.

Is the prescribed tumor dose an actual risk factor for the development of osteoradionecrosis of the Jaws?

Optimizing RT efficacy while mitigating treatment-related toxicities requires a delicate balance in dose prescription. Both the dosage per fraction and the cumulative dose influence tumor and normal tissue response. Lower daily radiation doses are generally associated with a reduced likelihood of inducing toxicity. However, unfortunately, this susceptibility to relatively low daily doses is limited to specific tumor types, such as myeloma, leukemia, lymphoma, or seminoma. Therefore, a careful equilibrium must be achieved, where daily doses are minimized to spare normal tissue yet maintained at levels adequate to induce cancer cell death for HNCs and other relatively radioresistant tumors. A standard daily dose of 1.8 to 2.0 Gy is commonly used for many cancers, including HNCs. Conversely, total doses may vary significantly depending on the cancer type and treatment context (neoadjuvant, definitive, or adjuvant).

The PTD for HNC patients represents the comprehensive radiation dose administered to the PTV using any RT modality, technique, or dose-fractionation scheme regardless of the doses the organs considered at risk received. This volume encompasses the primary tumor, metastatic cervical lymphatics, and regions at intermediate and low risk for relapse, and it accounts for potential setup or organ motion errors. The PTD can vary widely, ranging from a single dose of 8 Gy to conventionally fractionated 70-74 Gy, depending on factors such as treatment intent (palliative versus curative), surgical margin status (negative versus close versus positive) in operated cases, and the sequence of therapy (neoadjuvant versus adjuvant versus definitive). Moreover, various hypofractionated RT regimens, such as 50 Gy in 20 fractions, 37.5 Gy in 15 fractions, 30 Gy in 10 fractions, or 30 Gy in 5 fractions, with a minimum of 3 days between treatments, or 44.4 Gy delivered in 12 fractions over three cycles, with each cycle separated by 2 to 3 weeks (QUAD SHOT) [39], are also available for use to shorten the overall irradiation duration in patients who are often older or have compromised Eastern Cooperative Oncology Group performance [40,41]. In curatively treated HNCs, contingent on the RT technique and treatment intent, the doses for low-, intermediate-, and high-risk PTVs typically range between 45-54 Gy, 54-59.4 Gy, and 66-74 Gy, respectively. In cases where simultaneous integrated boost IMRT is utilized, the per-fraction doses may vary between 1.6 to 2.25 Gy across different segments of the entire PTV. Regrettably, despite the precise definition of PTD, which does not serve as a metric for organs at risk, it is frequently cited as a significant contributing factor to elevated rates of ORNJ among HNC patients, albeit for unknown reasons.

The primary objective of any contemporary RT application is to ensure adequate coverage of the PTV while adhering to predetermined dose limits for organs at risk following universally accepted guideline recommendations [42]. However, it is critical to note that the PTD does not account for the doses absorbed by the entire mandible or a specific volume of the mandible to assign it as a significant ORNJ risk factor. Conversely, valuing PTD as a substantial risk factor for ORNJ development presents challenges in thoroughly evaluating the dose-dependent effects of radiation on the jaw [20]. Despite the scarcity of data, most ORNJ studies continually assert that PTD remains one of the most accurate predictors of ORNJ [27,31]. Consequently, these research outcomes prompt an investigation into whether PTD represents a genuine or a pseudo-risk factor for the emergence of ORNJ, which will be addressed in the subsequent paragraphs.

While PTD does not directly quantify the doses administered to the mandible, it can indirectly elevate the probability of ORNJ development based on the spatial relationship between the PTV and the mandible. The proximity of the PTV to the mandible or its involvement warrants attention to the potential ramifications of a high PTD resulting in escalated mandibular doses. Specifically, under the premise of a consistent RT modality, technique, and fractionated dosage, the mandibular doses will inevitably escalate proportionally to the PTD, leading to an upsurge in ORNJ risk. Additionally, the quality of the RT plan may result in elevated radiation doses in the mandible (hot spots), potentially exceeding the PTD by up to 15%, particularly in cases where the tumor has infiltrated the mandible, suggesting a direct link between higher PTD and escalated radiation exposure in the mandible. This correlation is particularly pertinent in instances of OCC and OPC primaries, where the primary tumor and affected lymph nodes (Levels IA-B and IIA) frequently abut or closely associate with the mandible [20,24,33]. To illustrate the situation, consider a scenario involving a retromolar trigone tumor, wherein contact is established without mandibular invasion. The treatment strategy calls for definitive concurrent chemo-RT without preceding surgical intervention attributable to the patient's concurrent comorbid conditions or expressed reluctance towards surgery. Similarly, an alternative course may entail surgical intervention for a patient deemed medically suitable, albeit yielding a postoperative pathological report disclosing grossly positive resection margins. In both instances, the designated therapeutic protocol mandates a PTD within the range of 66-74 Gy focused on the PTV. Moreover, both scenarios may result in the mandible being subjected to hot spot doses of up to 15%, resulting in some areas of the mandible being exposed to doses ranging from 76 to 85 Gy. These doses are unquestionably much higher than the 66-74 Gy PTD, posing an increased risk of ORNJ if the volume receiving > 50-60 Gy is substantial. On the other hand, lower PTDs delivered with less advanced RT techniques, such as two-dimensional RT (2D-RT) or three-dimensional conformal RT (3D-CRT), may also exert the same or even higher risk of ORNJ compared to more advanced RT techniques. This comparable or heightened risk is attributable to the limited organ-sparing capabilities of older techniques, in contrast to the superior radiation exposure mitigation offered by advanced modalities like IMRT or VMAT. It is important to note that the disparity in risk is particularly pronounced when comparing photon-based RT modalities with hadron therapies, such as proton therapy (PT), intensity-modulated PT (IMPT), or carbon ion therapy. Hadron therapies are distinguished by their ability to minimize critical organ doses through the physical dose distribution properties of the Bragg peak before reaching the mandible [43]. As a result, the PTD alone may not be a reliable metric for evaluating mandibular dosages and the resulting risk of ORNJ unless RT techniques, modalities, and plan qualities are considered.

As the predictive value of the PTD in determining the risk of ORNJ is limited, it is imperative to incorporate mandibular dosimetric parameters to ensure accurate prediction of ORNJ risk after RT or chemo-RT. These parameters commonly encompass the mandibular Dmax, Dmean, and Vx doses [38,44,45]. Despite their substantial predictive capability, these dosimetric attributes, easily obtainable from dose volume histograms (DVH), have frequently been overlooked in ORNJ research. The previously discussed dosimetric parameters hold significant importance in modern RT modalities such as IMRT, VMAT, PT, IMPT, and carbon ion therapy. These advanced techniques play a crucial role in shaping the dose distribution. They are instrumental in confining the high-dose region to the PTV while concurrently minimizing radiation exposure to critical anatomical structures, notably the mandible, achieving levels significantly lower than those attainable through traditional 2D-RT or 3D-CRT procedures. For example, when administering RT to manage locally advanced OCC or OPC, utilizing a total radiation dose of 70-74 Gy delivered in 35-37 fractions through conventional 2D-RT or 3D-CRT, the mandibular Dmean is anticipated to surpass 50-60 Gy in the majority of patients, a dosage range commonly associated with heightened risk of ORNJ. Additionally, a notable volume of the mandible may be subjected to doses exceeding 70-74 Gy if concentrated high-dose areas (hot-spots) partially encompass the mandible. This attribute bears significance across various contexts, irrespective of the extent of mandibular invasion, due to these modalities' limited or absent tissue-sparing capabilities. Nonetheless, these elevated mandibular Dmean values may be effectively lowered to 40 Gy or below through the employment of IMRT, VMAT, or IMPT, a dose level widely acknowledged as safe for ORNJ prevention. This remark is consistent with clinical research that assesses the dosimetric factors as risk parameters for ORNJ. In their

study, Tsai., *et al*. identified the mandibular V50 and V60 as reliable predictors of ORNJ rates [46]. De Felice and colleagues identified a Dmean > 60 Gy as a significant determinant of ORNJ risk [47]. Most recently, Topkan and colleagues reported that a mandibular Dmean of ≥ 36.2 Gy (P = 0.003) and V59 Gy ≥ 32% (P = 0.007) were substantially associated with an increased ORNJ risk in LA-NPC patients who were undergoing definitive concurrent chemo-RT [48]. Despite such tangible evidence from previous studies supporting the relevance of doses received by the mandible, Watson and colleagues recently documented that an IMRT-based PTD dosage of > 60 Gy substantially increased the incidence of ORNJ in their investigation [27]. However, this increase was reported without adequate consideration of mandibular dosage or dose-volume metrics, making the conclusions of Watson and colleagues dubious, given the established significance of mandibular dose metrics on ORNJ rates.

Another notable limitation of utilizing PTD as an ORNJ risk factor is its failure to account for the treatment protocol's fractionation scheme: conventional fractionation versus hyperfractionation versus hypofractionation. It is imperative to recognize that these distinct schemes may result in significantly varied radiobiological effects on the exposed tissues, with hypofractionated schemes demonstrating higher toxicity than the others. Traditional RT practice typically involves the administration of fractions of 1.8 - 2.0 Gy per session as a standard practice aimed at treating tumors while minimizing damage to healthy tissues. Technological advancements have enabled the delivery of precise RT and the utilization of higher doses per treatment session (usually ≥ 3 Gy), a practice known as hypofractionated RT. Whether used in isolation or conjunction with chemotherapy, this fractionation scheme capitalizes on diverse biological effects. Hypofractionated RT offers the potential advantage of reducing treatment duration and costs and alleviating the burden of frequent and prolonged RT sessions. However, it is essential to acknowledge that hypofractionated RT regimens generally pose increased toxicity compared to conventional RT schemes due to the employment of higher doses per fraction. Unfortunately, the physical PTD may underestimate the radiobiological PTD when using these dose fractionation schemes. To illustrate the situation, let's consider two treatment plans for the same patient with OCC. In the first scenario, the patient receives a total dose of 70.2 Gy delivered in 39 fractions (1.8 Gy per fraction). In the second scenario, the patient is given a total dose of 69 Gy over 30 fractions, each delivering a modestly hypofractionated 2.3 Gy. When applying the Biologically Effective Dose (BED2) formula, while the conventional fractionated scheme specifies a PTD of 70.2 Gy, yielding a BED2 of 133.4 Gy, the mildly hypofractionated 69 Gy PTD results in a BED2 value of 148.4 Gy. Consequently, despite the apparent similarity in reported PTDs, the radiobiological calculations indicate that the hypofractionated 69 Gy regimen is approximately 11% more biologically toxic than its conventionally fractionated 70.2 Gy counterpart. Unfortunately, when considering PTD as an ORNJ risk factor, the risk will be reported as identical for both fractionation schemes depending on the numerical similarity of the PTDs, notwithstanding the indisputably heightened radiobiological risk associated with the hypofractionated scheme. Consequently, the numeric assessment of PTD may inadequately project the ORNJ risk in HNC patients undergoing diverse RT fractionation schemes. Thus, the dosimetric parameters of the mandible, rather than the PTD, should be considered the primary determinant of the ORNJ risk. This is because the dose received by the mandible, not the doses received by the PTV, determines the ORNJ risk.

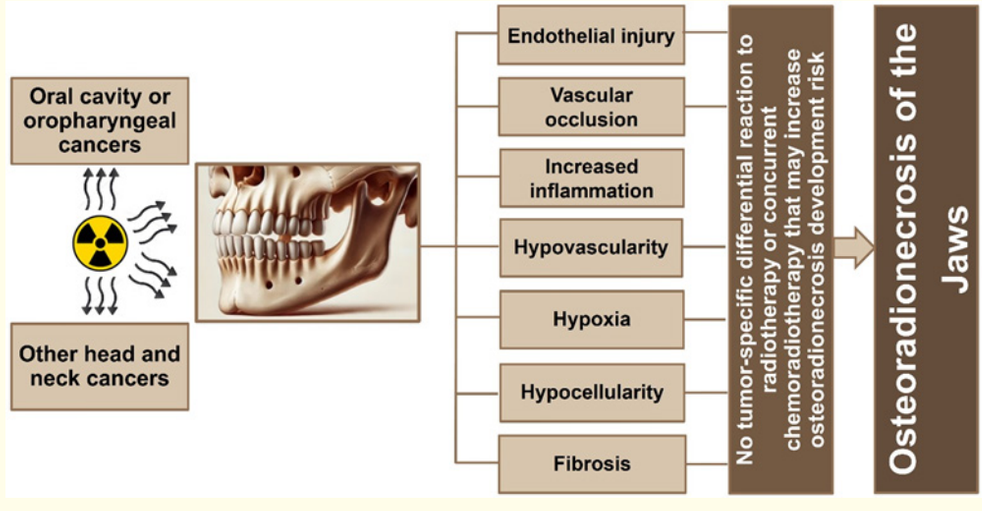

Figure 1: Pathophysiological mechanisms playing a significant role in osteoradionecrosis of jaw development originating from irradiation of various head and neck cancers.

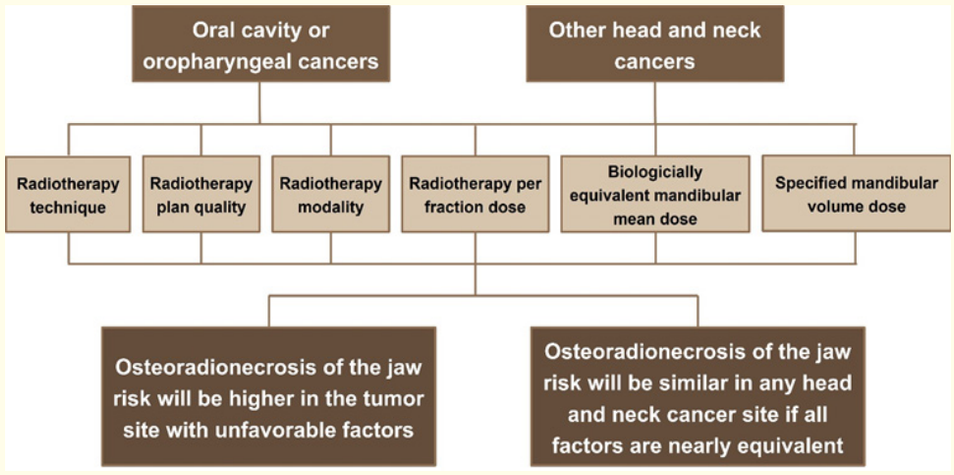

Figure 2: Comparison of osteoradionecrosis of the jaw risk between oral cavity/oropharynx and other head and neck cancers, based on radiotherapy-related factors.

Conclusion

Numerous studies have posited that OCC and OPC are the primary tumor sites associated with increased rates of ORNJ compared to other HNC primaries. However, these arguments lack empirical support and may merely mirror the elevated radiation doses inherently received by the mandible owing to its proximity to these anatomical locations. Similarly, the PTD has been repeatedly posited as a strong determinant of ORNJ risk in HNC patients treated with RT or concurrent chemo-RT. Nevertheless, if the mandibular Dmean, Vx, BED_2, dose per fractionation, and dose distribution within the mandible remain constant, the biological effects and, consequently, the risk of ORNJ will be the same regardless of the planned PTD. Hence, without substantial supporting data, it is crucial to utilize mandibular dose metrics instead of the primary tumor site or PTD as the determinants of ONRJ risk in HNC patients. This approach could facilitate more reliable comparisons between studies and the timely implementation of personalized preventive measures against ORNJ development and its negative influences on the patient's quality of life [49].

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Not Applicable.

Conflict of Interest

Declare if any financial interest or any conflict of interest exists.

Authors' Contributions

All authors contributed significantly and equally; and all authors approved the final form of the manuscript.

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