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Review

Osteoradionecrosis Risk Factors in Patients Undergoing Maxil-lofacial Radiotherapy – a Systematic Review

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Abstract: The objective of this systematic review was to identify and evaluate risk factors for osteoradi-onecrosis (ORN) among oncologic patients undergoing radiotherapy in the maxillofacial area; Methods: A search in Medline, Scopus and Embase databases was performed for relevant stud-ies, adhering to the Cochrane Collaboration Guidelines. The research was conducted using the MeSH terms: osteoradionecrosis, risk factors, radiotherapy, and head and neck cancer, with the last update in June 2024; Results: In the systematic review of 13 studies, out of 12977 patients, 1083(8%) developed osteoradionecrosis, while the remaining 11,894 (92%) did not. Among the 934 current smokers reported in five of these studies, 102 (11%) developed osteoradionecrosis, whereas 832 (89%) did not.; Conclusions: This systematic review highlights the multifactorial na-ture of ORN risks in patients undergoing radiotherapy for maxillofacial cancers. Significant risk factors identified include higher radiation doses, male gender, smoking habits, and dental pro-cedures performed either before or after radiotherapy. These insights underscore the urgent need for targeted preventive measures and customized management strategies to reduce the in-cidence of ORN in this vulnerable patient group (protocol registered at PROSPERO https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024570900)z.

Keywords: osteoradionecrosis; risk factors; radiotherapy complications head and neck cancer

1. Introduction

Head and neck cancer is one of the most common types of cancer, with an incidence of over half a million diagnosed cases annually. Oral, pharyngeal, and laryngeal squamous cell carcinoma accounts for almost 90% of cases. Surgical resection, radiotherapy, or both have been used over the past decades to treat this type of cancer [1, 2]. Currently, nearly 75% of patients with head and neck cancer will benefit from radiotherapy, either as primary therapy or as adjuvant therapy after surgical resection of the tumor [3-5]. Radiotherapy (RT), a method that uses ionizing radiation, exerts a therapeutic effect by selectively damaging the genetic material of sensitive malignant cells, either directly or by producing free radicals, leading to cell death. This method is frequently used to treat head and neck cancers.

The same mechanism also causes normal cells, especially those that multiply rapidly or, conversely, those with a lower regeneration rate, to be damaged by RT [6]. In the oral cavity, such types of cells can be found in the basal cell layer, underlying soft tissues, teeth, periosteum, bone, glands, vessels, and nerves, leading to acute or

late radiation toxicity. The symptoms include xerostomia and dysgeusia due to salivary gland damage, mucositis due to epithelial tissue damage, pathological changes in the oral cavity microbiome, radiation caries, limited mouth opening due to changes in collagen structure, and ORN due to reduced bone healing capacity [7-11].

ORN is one of the chronic complications that arise following radiotherapy. Radiotherapy leads to a reduction in tissue vascularization and oxygenation, resulting in aseptic and avascular bone necrosis, which can lead to infections, tooth loss, and even pathological fractures of the mandible [12]. The incidence of mandibular ORN among patients diagnosed with head and neck cancers varies between 4% to 13% in developing mandibular osteoradionecrosis [13] The use of more advanced radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), has been associated with a lower incidence of mandibular osteoradionecrosis [14-15]. Osteoradionecrosis is more frequently encountered in the mandible, and rarely in the maxilla. These differences are related to the lower vascularization of the mandible compared to the maxilla, as well as the fact that the mandible bears greater pressure and load compared to the maxilla [16].

Risk factors for the development of ORN include local, systemic, and genetic factors. Local factors include tumor size, xerostomia, neglected dental condition, poor oral hygiene, and associated local traumas such as tooth extraction/surgery before or after radiotherapy. Systemic factors include immune system dysfunction, malnutrition, peripheral vascular diseases, excessive smoking, and excessive alcohol consumption [17-19].

The purpose of this study is to identify and evaluate research published after 2010 concerning the risk factors for ORN. The objectives are to determine the incidence of ORN reported in these studies and to assess the risk of ORN based on factors such as tumor location, radiation dose, tobacco use, and dental extractions performed before or after radiotherapy.

2. Materials and Methods

2.1. Identification of studies

We conducted a comprehensive search of the Medline, Scopus, and Embase databases up to June 2024, following the Cochrane Collaboration Guidelines [20]. The search terms used included "osteoradionecrosis," "risk factors," "radiotherapy complications," and "head and neck cancer" (protocol registered at PROSPERO https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42024570900)

The inclusion criteria were, as follows: articles offering full access to content, observational studies (e.g., cohort, case-control, cross-sectional), clinical trials (randomized and non-randomized), studies examining risk factors for osteoradionecrosis, and studies involving human subjects with a minimum of 20 participants aged 18 and older. Relevant studies included those focusing on maxillofacial cancers and radiotherapy treatments alone or combined with other treatments like chemotherapy or surgery.

The exclusion criteria related to articles without full access, studies on animals, non-English publications, studies with fewer than 20 subjects, those not focusing on radiotherapy as part of the treatment regimen, and studies lacking sufficient methodological detail.

2.2. Selection of studies

The titles and abstracts of all articles retrieved by the electronic search were reviewed. The full text was obtained for articles that reported outcomes of radiotherapy for head and neck cancer, or for those with insufficient data in the title and abstract to make a clear decision.

These articles were then evaluated and those that met the inclusion criteria were accepted for further evaluation. Articles that met the inclusion criteria were assessed using predefined eligibility criteria for inclusion in the final review. Studies rejected

at the eligibility assessment stage were recorded and the reasons for exclusion were noted.

Cohort studies, case-control studies, cross-sectional studies and randomized clinical trials with a minimum sample size of 20 patients per experimental group were considered. A minimum of 20 patients is required to have at least one case of ORN, based on the incidence rate of 4.74% reported by Withers et al [21]. A smaller sample size could result in the absence of ORN, making it impossible to compare the difference in the risk of developing ORN between the different treatment groups. In addition, articles were required to report ORN. Other restrictions included English language, publication date after 2010, and studies on human subjects.

Participants: Eligible groups were adult patients who underwent radiotherapy in the head and neck region.

Intervention: All radiotherapy regimens conducted as curative or adjuvant therapy in the management of head and neck cancer, in combination with surgical interventions, were included.

Outcome Measurement: The primary event monitored was the occurrence of ORN following irradiation of the head and neck region. ORN can be reported as present (yes/no) or as the presence of bone toxicity according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer Late Radiation Morbidity Scoring Schema (RTOG/EORTC) [22], criteria proposed by Galzmann and Graetz [23], or the National Cancer Institute Common Toxicity Criteria (CTCAE) [24].

2.3. Evaluation of Eligibility

To assess the eligibility of studies for inclusion in this systematic review, we employed the ROBINS-I (Risk of Bias in Non-randomized Studies of Interventions) tool. This approach was chosen to ensure a comprehensive and systematic evaluation of potential biases within the studies considered. Each study was meticulously screened based on predetermined criteria derived from ROBINS-I, focusing on the coherence of interventions, outcomes measured, and comparability of groups. Only studies that met these criteria and demonstrated a low to moderate risk of bias, as determined by the ROBINS-I framework, were included for further analysis. This rigorous assessment method supports the reliability and validity of our review findings by minimizing the impact of confounding variables and bias.

Articles meeting the following criteria were accepted for final review: Reported actual cases of bone toxicity/osteonecrosis/ORN; Original data (no secondary analyses); Mean or median follow-up of surviving patients of at least 3 years.

The studies were read in full and then assessed for eligibility based on the eligibility criteria mentioned in the previous section. Based on these criteria, 13 studies were identified for inclusion in the final review. Figure 1 summarizes the search, selection, and review algorithm for the studies.

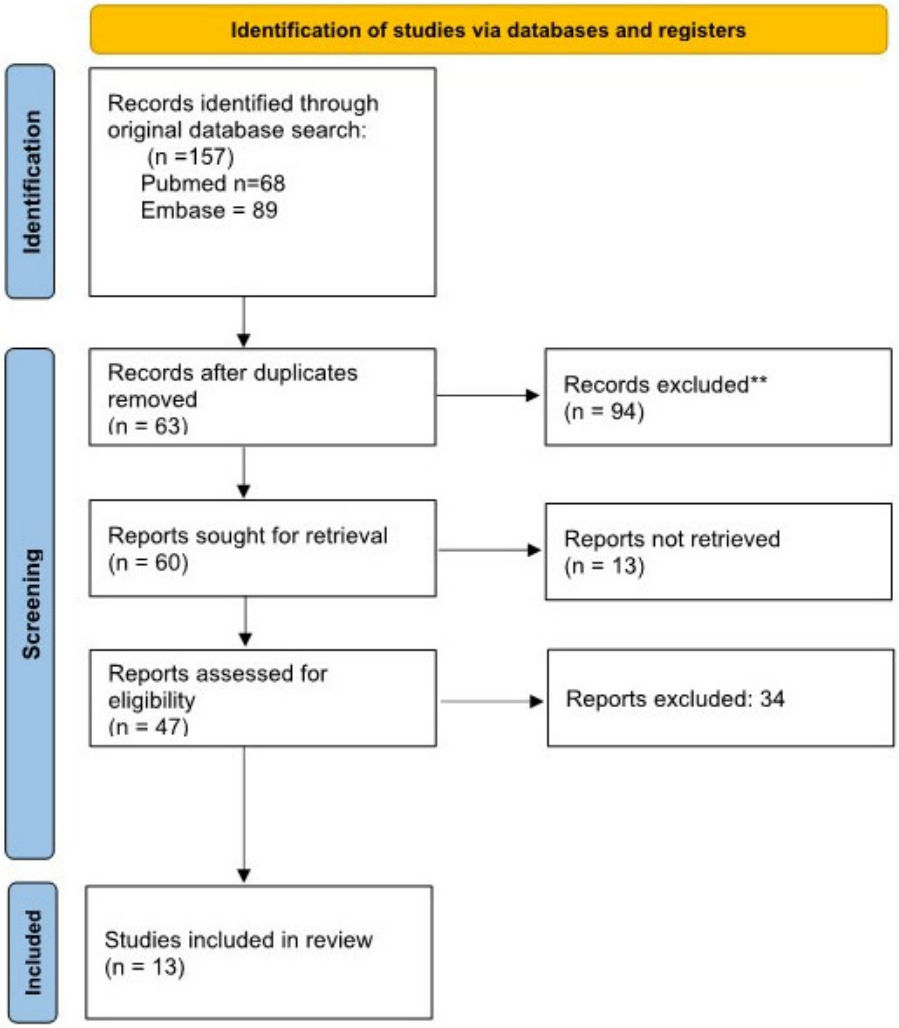

Figure 1. – Algorithm for Search and Selection of Studies – PRISMA flowchart.

2.4. Data Collection

Data for this study were systematically collected using Microsoft Excel (version 16.50), with rigorous checks to ensure completeness and accuracy during the extraction process.

The data extracted for each study included: (1) Authors and year of publication; (2)Type of study: (3) Total number of patients undergoing radiotherapy; (4) Gender distribution of subjects; (5) Pathology necessitating radiotherapy; (6) Types of radiotherapy administered; (7) Median or mean follow-up duration in months; (8) Maximum radiation dose received, measured in Grays (Gy); (9) Total cases of ORN; (10) Criteria utilized for defining ORN; (11) Proportion of current smokers; (12) Proportion of smokers who developed ORN; (13) Details on dental extractions performed before radiotherapy (Yes/No); (14) Number of patients who underwent dental extractions before radiotherapy; (15) Time elapsed from dental extraction to the start of radiotherapy; (16) Number of ORN cases following pre-radiotherapy dental extractions; (17) Information on dental extractions performed post-radiotherapy (Yes/No); (18) Number of patients undergoing post-radiotherapy dental extractions; (19) Number of ORN cases following post-radiotherapy dental extractions.

The most recent update to the database was conducted in June 2024. Table I presents a synthesis of data concerning the pathology types and treatments administered to the studies' participants.

The risk of bias for each study was assessed using the Cochrane Risk of Bias tool for cohort studies. This evaluation involved answering eight critical questions about each study's design and execution, with responses options of "Yes," "Probably yes," "Probably no," and "Unclear." These questions assessed the selection of cohorts, reliability of exposure and outcome assessments, adequacy of follow-up, and comparability of interventions across groups.

3. Results

3.1. Results of Individual studies

In Table I and Table 2, few of the variables extracted for each of the 13 articles included in this systematic review are described, such as - study details: authors, year of publication, study type, total number of patients undergoing radiotherapy, , pathology for which radiotherapy was performed, type of radiotherapy administered, maximum radiation dose, number of ORN cases, criteria used for defining ORN, median follow-up.Few data were reported on pre-radiotherapy teeth extractions (8 of 13 studies), number of patients who underwent pre-radiotherapy tooth extraction (5 studies), number of days between tooth extraction and the start of radiotherapy (5 studies), number of patients who developed ORN after pre-radiotherapy tooth extraction (4 studies), postradiotherapy extractions (4 studies), number of patients who underwent postradiotherapy tooth extraction (3 studies), number of patients who developed ORN postradiotherapy tooth extraction (3 studies).

Table 1. The included studies for systematic review.

No.	Authors & year of publication	Study Type	Pathology	Criteria Used for Defining ORN
1	Moring et al. 2017 [25]	Retrospective	Cancer of the oral cavity	CTCAE* and Notani
2	Niewald et al. 2013 [26]	Retrospective cohort	Squamous cell carcinoma of the oral cavity	RTOG*/EORTC*
3	Sashara et al. 2014 [27]	Retrospective	Maxillary/sinus carcinoma	CTCAE*
4	Raguse et al. 2016 [28]	Retrospective	Head and neck cancer	Not reported
5	Studer et al. 2016 [29]	Retrospective	Cancer of the oral cavity, oropharynx, and salivary	Galzmann și Graetz Modified
6	Kuhnt et al. 2016 [30]	Retrospective	Head and neck cancer	RTOG*/EORTC*
7	Owosho et al. 2017 [31]	Case-control	Cancer of the oral cavity, oropharynx	Galzmann și Graetz Modified
8	Baker et al. 2019 [32]	Retrospective	Squamous cell carcinoma of the oropharynx	CTCAE*
9	Liao et al. 2020 [33]	Retrospective	Head and neck cancer	-
10	Kubota et al. 2021 [34]	Retrospective	Squamous cell carcinoma of the head and neck	CTCAE*
11	Verduijn et al. 2023 [35]	Retrospective	Squamous cell carcinoma of the oropharynx	CTCAE
12	Kovarik et al.2024 [36]	Retrospective	Head and neck cancer	CTCAE
13	Kovarik et al. 2023 [37]	Retrospective	Head and neck cancer	Aarup-Kristensen

3.2. Combined study results

Out of a total of 12,977 patients included in the 13 studies in the systematic review, 1,083 subjects developed osteoradionecrosis, representing a percentage of approximately 8%. The remaining 11,894 patients did not develop osteoradionecrosis, representing 92% of the cohort. (table 2).

Table 2 – Summary of the patients included in the study and median follow-up

Author/ ref. no.	Total no. of patients	Total cases of ORN (n, %)	ORN Grades Reported	Median follow-up (months)	Type of Radiotherapy	Total Radiation Dose (Gy)	Details
Moring et al. 2017 [25]	227	46 (20%)	44 (92.7 %) - Grade ≥ 2	49	IMRT*	60	Mean Dose to Mandible (Dmean): 37.1 Gy
Niewald et al. 2013 [26]	90	11 (12%)	Al 11 cases grad II ORN	42	CRT* and HRT*	Conventional fractionated RT: 70 Gy Hyper-fractionated RT: 82.8 Gy	Conventional: 70 Gy, Hyper: 82.8 Gy
Sashara et al. 2014 [27]	63	26 (41%)	All 11 cases were grade ≥ 1	79	C-ion RT*	67.6	V50 for maxillary/sinus carcinoma
Raguse et al. 2016 [28]	149	38 (25%)	6 (16%)- Grade I 14 (37%) – Grade II 10 (26%) - GradeIII 8 (21%) – Grade IV	41	IMRT* and Conventional RT*	73	Details not specified
Studer et al. 2016 [29]	531	36 (7%)	2 (5%) Grade 1 5 (14%) Grade 2 21(58%) Grade 4 (11%) Grade 3 4 (11%) Grade 4	38	IMRT	70	69.6-70 Gy typical dose range
Kuhnt et al. 2016 [30]	776	51 (7%)	Not specified	36	IMRT, 3D-CRT*	65	70.6 Gy for postoperative, 77.6 Gy for definitive
Owosho et al. 2017 [31]	1023	44 (4%)	8 (18%) Grade 0 6 (14%) Grade 1 22 (50%) Grade 2 8 (18%) Grade 3	52.5	IMRT	70	70 Gy typically used
Baker et al. 2019 [32]	195	11 (6%)	5 (45%) Grade 4 1 (9%) Grade 5	52	IMRT* then SBRT*	62.5	Total dose: 62.5 Gy
Liao et al. 2020 [33]	5062	52 (10%)	Not specified	48	IMRT* and VMAT*	Not reported	Dose specifics not provided
Kubota et al. 2021 [34]	616	46 (7%)	All cases grade ≥ 2 ORN	40	IMRT* and 3D-CRT*	69.96	Prescribed dose: 69.96 Gy
Verduijn et al. 2023 [35]	334	32 (10%)	All cases grade ≥ 2 ORN	55	HF-SRBT, IMRT	80 Gy (HF-SRBT) 30-40 Gy (IMRT)	80 Gy in HF-SRBT, 30-40 Gy in IMRT
Kovarik et al.2024 [36]	1608	141 (9%)	Not specified	36	IMRT	61.5	Prescribed dose: 61.5 Gy
Kovarik et al. 2023 [37]	2303	185 (8%)	Not specified	59 (for maxillary follow up 65 (temporal follow-up0)	IMRT	66.5 Gy	Max dose: 66.5 Gy, focused on extra-mandibular ORN

*ORN – osteoradionecrosis; *CRT- chemoradiotherapy *HRT-hormone therapy *C-ion RT-carbon ion radiotherapy *IMRT- Intensity modulated radiotherapy; *RT-conventional radiotherapy; *SBRT- stereotactic body radiotherapy *VMAT-Volumetric Modulated Arc Therapy *RTOG- Radiation Therapy Oncology Group *EORTC- European Organization for Research and Treatment of Cancer; *CTCAE- National Cancer Institute Common Toxicity; [1] - Moring et al.'s analysis included only patients with oral cavity subsite cancers, which clarifies why a subset of these cases involved maxillary ORN.; [2] - Patients were treated with carbon ion radiotherapy, which involves different dosimetry and biological considerations compared to photon-based therapies.; [3] - The 'maximum radiation dose received' refers to the median dose at the origin of ORN as determined by dose mapping.

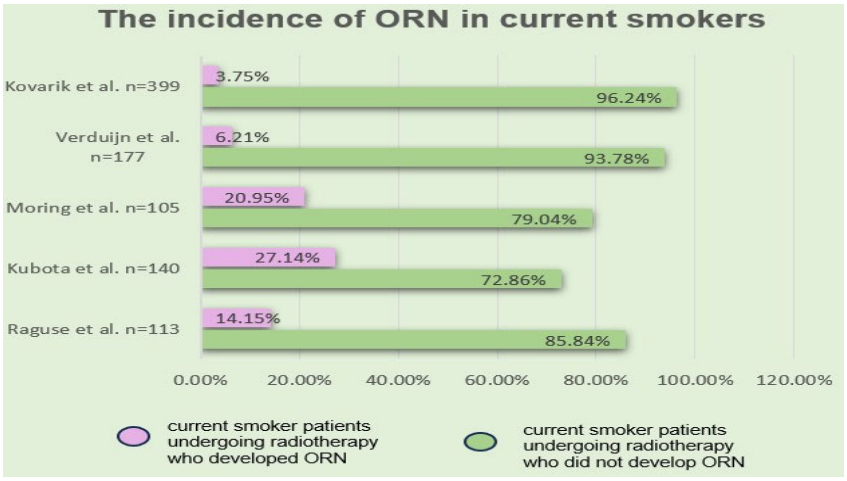

Figure 2 - The incidence of ORN in current smoker patients reported in 5 of the studies included in the systematic review.

Out of the 13 studies reviewed, 7 provided the number of current smokers among the 1059 patients (figure 3). Five studies reported the incidence of ORN, with 102 smokers and 200 non-smokers affected. Among 934 current smoker patients in these 5 studies, 102 developed ORN, representing 10.92%. Among 2000 non-smokers in the same studies, 200 developed ORN, representing 10%.

The gender distribution of subjects included in the studies shows a relatively higher incidence of this pathology among male patients.

The follow-up duration reported was between 36 and 55 months with an overall median follow-up of 47.37 months. The maximum radiation dose is described for each study included in the systematic review (ranging from 40 Gy to 82,8Gy) with a mean value of 67.10 Gy (± 10.08 standard deviation) (table 2)

3.3. Risk of Bias Estimation

The ROBINS-I plot (figure 3) visually summarizes the risk of bias across several domains for 13 studies (numbered 1 to 13) evaluated using the ROBINS-I tool. The overall risk of bias is predominantly low for the majority of studies, suggesting that the results of these studies are relatively reliable. Studies 2, 6, and 13

show a moderate overall risk of bias.

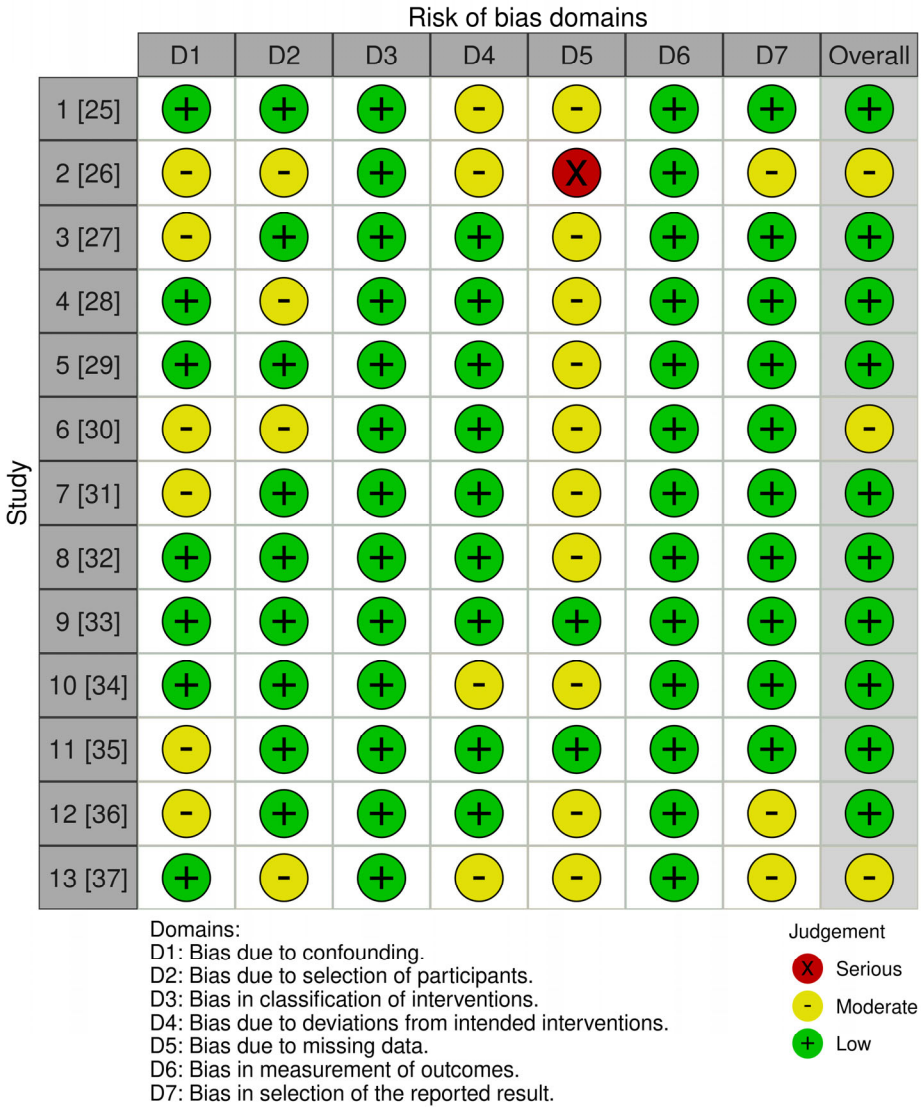

Figure 3 – Risk of bias assessement

4. Discussion

While ORN is a significant and debilitating complication of radiotherapy (RT), it is important to recognize that it is one of several potential severe side effects. Conditions such as carotid blow-out syndrome, though less common, represent even more critical threats and underscore the complex risk profile associated with radiotherapy treatments. Although ORN was first described in 1922, its definition, pathogenesis mechanism, incidence, risk factors, clinical staging, and associated treatment protocols require further investigation [38].

In this regard, the current systematic review has achieved its primary objective of identifying risk factors for ORN in patients treated with radiotherapy for head and neck cancers. Although calculating a cumulative effect of these risk factors was challenging, the significant results reported by the authors were based on individual studies and the indicators used in each study.

4.1. The incidence of ORN

Table 2 provides a detailed compilation of radiation dose regimens and associated ORN outcomes in thirteen major trials focusing on the treatment of head and

neck cancer. Reflecting a wide range of treatment approaches, the table shows a wide range of total radiation doses, from 60 Gy in IMRT protocols to 82.8 Gy in hyperfractionated regimens. In particular, the incidence of ORN varies widely, ranging from 4.3% to 41.1%, highlighting the critical impact of radiation dose and modality on ORN risk. For example, studies using carbon ion radiotherapy (C-ion RT) at 67.6 Gy reported a notably high ORN incidence of 41.1%, highlighting the potent biological effects of high-LET radiation such as carbon ions, especially in sensitive structures such as the maxilla and sinuses. Conversely, more conventional IMRT treatments at doses around 70 Gy tended to have lower ORN rates, suggesting that modern conformal techniques can mitigate some of the risks associated with higher doses. The data also highlights the importance of dose specifications and treatment details in understanding ORN risk; for example, the use of high-dose regimens focused on extra-mandibular regions resulted in significant ORN events, as shown by Kovarik et al. (2023) with an ORN rate of 8% at 66.5 Gy. This comprehensive review facilitates a nuanced understanding of how different radiotherapy regimens influence ORN development and provides invaluable insight into optimizing treatment strategies to balance oncological efficacy with the risk of complications.

The 13 studies included in this systematic review employed a variety of criteria for the grading of ORN severity, reflecting the significant diversity in clinical presentation and severity observed across the studies. The studies frequently employed the Common Terminology Criteria for Adverse Events (CTCAE) and the Notani scoring system for the classification of ORN. It is notable that the CTCAE grades ranged from Grade 1 (asymptomatic, no intervention required) to Grade 3 (severe symptoms, limiting self-care, surgical intervention required). Similarly, Notani scores provide a detailed progression from Grade 1 (characterized by minor symptoms without significant clinical findings) up to Grade 3 (characterized by severe cases with pain, infection, or both, requiring extensive medical management). Most studies reported a combination of ORN grades, with a considerable proportion of patients experiencing symptoms that necessitated clinical intervention. This emphasizes the clinical significance and the diverse impact of ORN across the patient cohort. The observed variability highlights the necessity of a detailed and standardized approach to reporting ORN in order to accurately assess treatment outcomes and guide clinical management strategies (Table 2).The incidence of ORN identified in our studies was overall 8%. This is higher than the reports found in the literature. Nabil *et al.* [39] identified an incidence of 2% for osteoradionecrosis. The differences can be explained by the time periods during which the cohorts were analyzed and the ORN defining criteria used in each study. Regarding gender distribution, except for one study, the majority included more male subjects. This can be explained by a higher incidence of smoking and the associated risk of oncological pathologies. There has been a decline over the past few decades, attributed to the availability of more conformal techniques such as IMRT, as demonstrated by the study by Ben-David *et al.* [40].

In a recent study by Kovarik et al. (2023), a comprehensive analysis of extra-mandibular ORN outcomes was conducted, expanding the understanding of ORN beyond the mandibular region. The study documented an 8% incidence of ORN among a cohort of 2,303 head and neck cancer patients, specifically noting cases in the maxillary and temporal bones. Importantly, the median interval from the end of radiotherapy to the onset of ORN was detailed, providing insights into the timeline of ORN development [37].

4.2. Tumor Localization

Studies by Chronopoulos *et al.* and Curi *et al.* emphasized that the proximity of primary tumors to the mandible in the oral cavity or oropharynx significantly increases the risk of ORN, due to the higher radiation doses these areas typically receive. Analysis of large case series, each including over 100 ORN cases, reveals that approximately 85-90% of ORN occurrences are in patients with tumors of the oral

cavity or oropharynx. ORN is most observed following radiation therapy for primary tumors located in the oral tongue, floor of the mouth, alveolar ridge, retromolar trigone, and tonsils. This association is due to the significant volume of the mandible exposed to high radiation doses in these tumor types, and the surgical removal of tumors from these areas often necessitates mandibular osteotomies or mandibulectomies, which can be traumatic to the bone tissue [38,41]

These findings underscore the importance of careful monitoring and appropriate management of patients with tumors in the oro-maxillofacial region to prevent and manage complications associated with ORN.

4.3. Smoking

The study by Giardi *et al.* found a higher prevalence of active smokers following the start of radiotherapy in the case group compared to the control group (12 (63.1%) vs. 13 (30.2%) ($p = 0.04$)). Univariate analysis showed that active smoking was linked to a 3.95-fold increased risk of developing ORN ($p = 0.01$). In the study by Pereira *et al.*, 92.5% of patients with ORN had a history of tobacco use. The study also found that quitting smoking was a protective factor against ORN. Patients who had stopped smoking exhibited a significantly lower incidence of ORN. This effect may be attributed to the negative impact of tobacco on the healing process and its harmful effects on the oral mucosa [42,43]. These findings underscore the importance of smoking cessation and careful monitoring of radiation doses to reduce the risk of developing ORN among head and neck cancer patients treated with radiotherapy.

4.4. Radiation Dose

Previous studies have emphasized the link between administered radiation dose and mandibular ORNJ risk. Patients receiving high radiation doses, especially in the 60-75 Gy range, show a significantly increased risk of ORNJ [30, 26-35].While previous studies, such as those by Chen et al., Chang et al.[43-44] and others, have established a clear link between higher radiation doses and increased risk of mandibular ORN, it is crucial to balance these findings with the primary goal of radiation therapy: eradicating cancer. The therapeutic window for radiation dose is finely tuned to maximize tumor control while minimizing complications. Patients receiving radiation doses in the 60-75 Gy range, particularly those with tumors close to critical structures like the mandible, are shown to have a higher risk of developing ORN. However, reducing doses below therapeutically effective levels could jeopardize cancer control, potentially leading to suboptimal oncological outcomes. Gómez et al. investigated the impact of radiation dose on subsequent dental events and extractions, highlighting an association between maximum dose > 70 Gy and mean dose > 40 Gy with increased event rates [46]. Aarup-Kristensen *et al*. found that mean dose was significantly associated with ORNJ development [47]. Tsai *et al.* and Caparrotti *et al.* suggested that minimizing the values of V50 and V60 (volume receiving 50 Gy and 60 Gy, respectively) was associated with a reduction in the rate of osteoradionecrosis of the jaw (ORNJ) development in patients with oropharyngeal cancer. These findings were obtained by an equivalent case-control study [48,49]. Therefore, these studies highlight the importance of controlling and optimizing the administered radiation dose, especially in the maxillary region, to minimize the risk of ORNJ. By carefully identifying and monitoring the radiation dose, it is possible to contribute to reducing the complications associated with radiotherapeutic treatment and improving the quality of life for cancer patients.

4.5. Jaw surgical procedures

According to a systematic review, the incidence rate of ORN following dental extraction in patients who underwent radiotherapy was 7% [39]. Wang *et al.* study [50] suggested that dental extraction performed post-radiotherapy is associated with

an increased risk of developing ORN, peaking at approximately 4-5 years after ionizing radiation treatment. An earlier metal analysis found that patients who underwent dental extractions before radiotherapy had a lower incidence rate of osteoradionecrosis (4.16%) [51]. To prevent the development of ORN, it is recommended to wait for a period of 10-14 days between dental extraction and the commencement of radiotherapy. Another study conducted by Muraki *et al.*[52] reported that dental interventions such as dental assessment, prophylactic dental extraction, and maintaining good dental hygiene both before and after radiotherapy have significant effects in preventing the development of osteoradionecrosis (ORN). These preventive measures can contribute to reducing the risk and severity of complications associated with ORN in patients undergoing radiotherapy in the head and neck region. In the study conducted by Lee *et al.*, the frequency of ORN was 13 patients, representing 6.6% of cases. Among these, eight patients who underwent mandibular surgery developed ORN at the site of the surgery. Univariate analysis indicated that mandibular surgery and the use of Co-60 were significant risk factors for ORN ($p = 0.01$ and 0.04, respectively). In multivariate analysis, mandibular surgery was found to be the most important factor ($p = 0.001$) [53]. The incidence of ORN after extractions in the study conducted by Nadella *et al.* is approximately 5%. This risk is three times higher in dentate patients compared to edentulous patients, primarily due to extraction-related injuries and infections from periodontal disease [54]. The likelihood of developing ORN is greater for extractions of posterior mandibular teeth with roots located below the mylohyoid line and when atraumatic extraction techniques cannot be performed [55].

4.6 - Collaborative Approaches to Minimize ORN in Radiotherapy

Recent advances in radiotherapy techniques highlight the critical importance of interdisciplinary collaboration, particularly with radiation oncologists, to optimize treatment outcomes and minimize complications such as ORN. For example, Wagenaar et al (2019) investigated the benefits of composite minimax robust optimization (CMRO) in volumetric modulated arc therapy (VMAT) for patients with head and neck cancer. Their study demonstrated that CMRO significantly improves target coverage while reducing dose to non-target tissues, potentially reducing the risk of ORN. This approach is consistent with our findings, suggesting that meticulous radiation planning, including robust optimization techniques, can significantly impact the incidence of ORN by achieving precise dose distributions that spare the mandible and other critical structures [56].

Furthermore, van Bruggen et al. (2024) detailed the clinical implementation of a deep learning-based automated treatment planning system for intensity-modulated proton therapy (IMPT) in oropharyngeal cancer patients. Their blinded clinical trial compared manual plans with deep learning plans and found a high preference for the latter, highlighting the role of advanced planning technologies in improving treatment efficiency and precision. Importantly, their work demonstrates that deep learning algorithms can robustly optimize IMPT plans, reducing planning time while maintaining or improving dose accuracy and patient safety [57].

Both studies reflect a shift towards more personalized and precise radiotherapy protocols and highlight the need for ongoing collaboration between clinicians and researchers to refine radiotherapy strategies. The integration of such advanced computational techniques into clinical practice not only supports the primary goal of maximizing tumor eradication, but also crucially minimizes the risk of serious complications such as ORN. These findings reinforce our review's recommendation to monitor and adjust radiation dose to ensure that each patient's treatment plan is optimized to balance efficacy with potential adverse effects.

4.7. Strengths and limitations of current study

The risk of bias for studies estimated through a questionnaire obtained a response of yes or probably yes for most questions. However, this method is subjective and requires evaluation of multiple investigations to obtain more representative data for studies.

The limitations of this work primarily consisted of restricted access to literature, as only studies with full-text access could be opened. Regarding study eligibility, most excluded studies did not have a sufficiently long median follow-up period to be included in the final review.

Nevertheless, the main strength of this work lies in its timeliness through research on studies published in the last 10 years on this topic, which is important considering the changes in therapeutic regimens in oncology and the emergence of increasingly extensive management options for complications.

In this review, we consider the limited data on tooth extraction before radiotherapy. Although the available evidence is limited, it suggests an association between tooth extraction before radiotherapy and an increased risk of ORN. These conclusions are based on the clinical relevance and consistency observed across studies. We have interpreted these findings cautiously, considering the wider context of ORN risk factors, to ensure that our conclusions are robust and provide a balanced basis for future research and clinical decision making.

5. Conclusions

This systematic review highlights the need to balance effective cancer treatment by minimizing adverse effects such as ORN in head and neck cancer treatment. Our analysis suggests that although higher radiation doses increase the risk of ORN, indiscriminate reduction of radiation doses is not advocated. Instead, we emphasize the importance of personalized treatment planning that optimally balances tumor control with protection of surrounding tissues. Advanced radiation technologies such as IMRT and VMAT are critical to achieving these goals.

Collaboration with radiation oncologists and a multidisciplinary approach are essential to tailor radiotherapy protocols that ensure effective cancer treatment while reducing the risk of ORN. Our findings support a strategic, patient-specific approach to radiation dosing aimed at maximizing therapeutic outcomes and improving long-term quality of life for patients.

Supplementary Materials: Dataset available on request from the authors.

Author Contributions: Conceptualization AMC, AK and DG; methodology SED; software AK and EI; validation, AI and SB; formal analysis DG and EI; investigation AK, AZ and SED; resources, AZ.; data curation SB and AI.; writing—original draft preparation AK and AZ; writing—review and editing SED and AMC.; visualization AI.; supervision SB and A.Z.; project administration AK and AZ. All authors have read and agreed to the published version of the manuscript.

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