Imaging Science in Dentistry 2021; 51: 223-35
https://doi.org/10.5624/isd.20210011

Head and neck radiotherapy-induced changes in dentomaxillofacial structures detected on panoramic radiographs: A systematic review

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ABSTRACT

Purpose: This study aimed to summarize the impact of neck and head radiation treatment on maxillofacial structures detected on panoramic radiographs.
Materials and Methods: In this systematic review, the authors searched PubMed Central, Embase, Scopus, Cochrane Central Register of Controlled Trials, Web of Science, and Google Scholar for original research studies up to February 2020 that included the following Medical Subject Headings keywords: words related to "radiotherapy" and synonyms combined with keywords related to "panoramic radiography" and "oral diagnosis" and synonyms. Only original studies in English that investigated the maxillofacial effects of radiotherapy via panoramic radiographs were included. The quality of the selected manuscripts was evaluated by assessing the risk of bias using Cochrane's ROBINS-I tool for non-randomized studies.
Results: Thirty-three studies were eligible and included in this review. The main objectives pertained to the assessment of the effects of radiation on maxillofacial structures, including bone architecture alterations, periodontal space widening, teeth development abnormalities, osteoradionecrosis, and implant bone loss. The number of participants evaluated ranged from 8 to 176.
Conclusion: The interaction between ionizing radiation and maxillofacial structures results in hazard to the tissues involved, particularly the bone tissue, periosteum, connective tissue of the mucosa, and endothelium. Hard tissue changes due to radiation therapy can be detected on panoramic radiographs. ***(Imaging Sci Dent 2021; 51: 223-35)***

KEY WORDS: Radiotherapy; Radiograph, Panoramic; Diagnosis, Oral; Radiation Effects

Introduction

Essential treatment approaches for head and neck malignant neoplasms include radiotherapy, chemotherapy, and surgery, which may be performed independently or combined depending on the type of neoplasm and the extent of disease progression. Radiotherapy is usually the first-line approach for patients with head and neck cancer and is frequently applied as a complement to surgical tumor resection. There are three distinct types of radiotherapy: external beam radiation, brachytherapy, and radioisotope therapy.[1] Radiotherapy protocols vary according to the histological type, location, and stage of the tumor,[1] and frequently consist of 50-70 Gy for a period of 4 to 7 weeks.[2] The aim of radiotherapy is to eliminate or ablate the neoplasm while minimizing damage to the surrounding healthy tissue; however, healthy tissue injury is an unavoidable consequence of radiotherapy.[1]

Tissue changes induced by radiotherapy result from decreased tissue perfusion and tissue fibrosis, as well as capillary obstruction.[3] Capillary obliteration leads to decreased osteoblastic and osteoclastic activity, which affects bone repair and remodeling.[3] Hence, post-radiotherapy alterations in maxillary bones, as well as in other mineralized

Received January 18, 2021; Revised February 17, 2021; Accepted February 26, 2021
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Imaging Science in Dentistry · pISSN 2233-7822 eISSN 2233-7830

tissues such as tooth structures, are observed in patients undergoing radiation treatment. These include widening of the periodontal ligament space[4] and aggressive tooth decay.[5] Furthermore, the destruction of acinar cells in salivary glands decreases the production of saliva and leads to other changes in the oral cavity.[5]

The deleterious effects of radiation on mineralized tissues have been studied by many investigators, mainly using panoramic radiographs, which is the most requested imaging examination in dentistry. Panoramic radiographs have a number of advantages, including the ability to provide a range of essential information about the status of the oral cavity and related bones.[6] Hence, knowledge of the effects of radiotherapy in the maxilla and mandible, as detected using panoramic radiographs, is necessary for the treatment of patients who have undergone this oncologic treatment.

Thus, the objective of this study was to review the literature regarding radiotherapy-induced changes in dentomaxillofacial structures, as detected on panoramic radiographs, in patients undergoing head and neck radiotherapy. Specifically, this review addressed the following questions: 1) "What have researchers investigated regarding changes in dentomaxillofacial structures due to radiotherapy treatment for head and neck cancer based on panoramic radiographs?" and 2) "What results have researchers obtained?"

Materials and Methods

The present systematic review was registered with the National Institute for Health Research International Prospective Register of Systematic Reviews (registration number: CRD4201913058). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist was adopted.[7]

Studies published up to February 2020 were screened for inclusion in this review by searching PubMed Central (United States National Institutes of Health's National Library of Medicine), Embase (Excerpta Medica Database), Scopus (Elsevier), the Cochrane Central Register of Controlled Trials, Web of Science (Institute of Scientific Information - Clarivate Analytics), and Google Scholar (Google) databases. The Boolean operator "AND" was used to combine search keywords. Itemized search strategies for each database were organized on the basis of the following search keywords: radiotherapy AND panoramic radiograph, radiotherapy AND oral manifestations, radiotherapy AND jaw; radiotherapy AND jaw diseases, radiotherapy AND mandible, radiotherapy AND maxilla, radiotherapy AND oral diagnosis, radiotherapy AND oral diseases, radiation effects AND panoramic radiograph, radiation effects AND oral manifestations, radiation effects AND jaw, radiation effects AND jaw diseases, radiation effects AND mandible, radiation effects AND maxilla, radiation effects AND oral diagnosis, radiation effects AND oral diseases, radiation effects AND panoramic radiograph, radiation effects AND oral manifestations, radiation treatment AND jaw, radiation treatment AND jaw diseases, radiation treatment AND mandible, radiation treatment AND maxilla, radiation treatment AND oral diagnosis, radiation treatment AND oral diseases, targeted radiation therapy AND panoramic radiograph, targeted radiation therapy AND oral manifestations, targeted radiation therapy AND jaw, targeted radiation therapy AND jaw diseases, targeted radiation therapy AND mandible, targeted radiation therapy AND maxilla, targeted radiation therapy AND oral diagnosis, targeted radiation therapy AND oral diseases. A summary of the keyword combinations is presented in Figure 1.

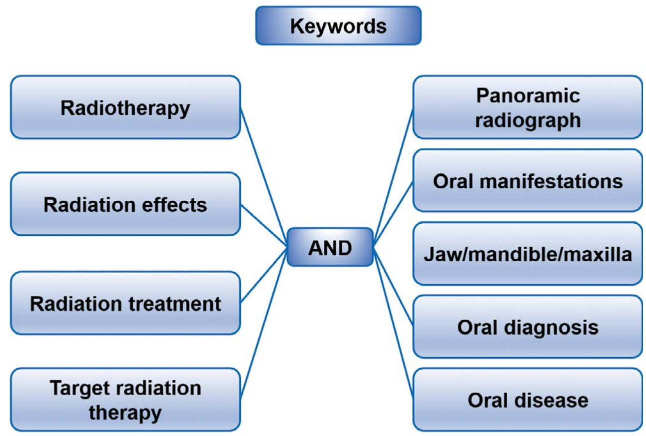

Fig. 1. A summarized representation of the keywords selected in this review.

Only original studies were considered suitable for inclusion. Abstracts, case reports, oral presentations, technical notes, abstracts, and literature reviews were excluded. Research articles that investigated the maxillofacial effects of radiotherapy, but not via panoramic radiographs, were not eligible. Moreover, studies in which the main objective was to test protocols, techniques, treatment for osteoradionecrosis, software, and assessment tools were excluded. If the use of panoramic radiographs was not clearly described in a given study, the study was not considered eligible. Additionally, non-English-language articles and non-human studies were not included. All studies with publication dates until February 2020 were included.

Research groups of patients who underwent radiotherapy as adjuvant treatment for head and neck cancer were inclu-

Table 1. Research results: authors, objective pertaining to radiotherapy assessment using panoramic radiographs, size of the sample studied, radiation dose applied in each study, and type of radiotherapy applied

Authors	Objective	Sample studied	Radiation dose/ type of radiotherapy
Palma et al.[9]	To evaluate the impact of RT on mandibular bone tissue in HNC patients	30 patients who underwent RT	Total: $\leq$59 Gy - 70 Gy/ 3-DCR
Hoogeven et al.[10]	To assess the late effects of chemotherapy and radiotherapy in pediatric HNC rhabdomyosarcoma survivors	42 survivors up to 25 years old	Not detailed/ not reported
Hachleitner et al.[11]	To describe a procedure for temporary mandibulotomy and the impact of postoperative treatments involving RT	57 patients.	42.5 Gy - 71.4 Gy/ 3-DCR and IMRT
Kilinç et al.[12]	To determine the frequency of dental anomalies in pediatric cancer patients at the ages $<$5 years and between 5 and 7 years	93 pediatric patients	Not reported/ not reported
Li et al.[13]	To compare the outcomes of deep circumflex iliac artery and free fibula flaps in RT-treated patients.	154 patients	59.5 Gy - 62.4 Gy/ not reported
Mattos et al.[14]	To evaluate the long-term alterations of teeth and cranial bones in long-term pediatric survivors HNC rhabdomyosarcoma who were treated with RT and chemotherapy between the ages of 0 and 5 years	27 long-term survivors	Total: 41.4 Gy - 50.4 Gy/ 2-DPRT and 3-DPRT
Pellegrino et al.[15]	To evaluate the clinical and radiological outcomes of a group of patients who underwent mandibular reconstruction with fibula free flap, RT, and rehabilitation.	21 patients; 108 osseointegrated dental implants	60 Gy - 63 Gy (pre- and/or post-surgery)/ IMRT
Markman et al.[16]	To verify whether head and neck RT may induce calcified carotid artery atheroma in HNC patients and to compare socio-demographic/clinical characteristics	180 with panoramic radiographs taken before and after RT	$<$50 Gy - $\geq$70 Gy/ not reported
Owosho et al.[17]	To determine the correlation between the radiation dose, periodontal status, alcohol use, and smoking in patients with ORN	44 HNC patients who received RT	Not reported/ not reported
Tanaka et al.[18]	To investigate the association between age at the time of cancer treatment and abnormalities in childhood cancer survivors.	55 patients	Less than 50 Gy/ not reported
Bengtsson et al.[19]	To evaluate whether preservation of the periosteum during mandibulotomy would decrease postoperative complications in patients who were treated with RT	32 patients	45 Gy - 60 Gy/IMRT
Chan et al.[20]	To assess changes to the appearance of the mandible	126 patients	50 Gy - 70 Gy/IMRT
Ernst et al.[21]	To evaluate changes in the marginal bone level of dental implants in edentulous patients with SCC who received RT	36 edentulous patients	Mean: 45 Gy/IMRT
Owosho et al.[22]	To investigate dentofacial long-term effects among HNC rhabdomyosarcoma survivors	13 patients	55 Gy - 72 Gy/IMRT
Proc et al.[23]	To investigate the incidence of dental complications in childhood cancer survivors	61 panoramic radiographs	Not reported/ not reported
Pompa et al.[24]	To evaluate the survival of dental implants placed after ablative surgery or adjunctive RT	34 patients	45 Gy - 54 Gy/IMRT
Dediol et al.[25]	To analyze the complications of mandibulotomy fixation methods in SCC patients who underwent surgical treatment and RT	85 patients	Not specified/ not reported

Table 1. Continued

Authors	Objective	Sample studied	Radiation dose/ type of radiotherapy
Karagozoglu et al.[26]	To investigate the incidence of periosteal ossification of the vascular pedicle in patients with defects of the mandible or maxilla reconstructed with fibular free flaps	112 (part of the sample underwent RT)	$<$60 Gy or $>$60 Gy/ not reported
Shen et al.[27]	To demonstrate an algorithm to assist surgeons in selecting different modes of the double-barrel vascularized fibula graft	45 patients	Not reported/not reported
Cubukcu et al.[28]	To evaluate the dental development of childhood cancer survivors (treated under the age of 10 years) who received RT	37 childhood cancer survivors	25 - 59 Gy/not reported
Hommez et al.[5]	To analyze the effect of the radiation dose on the presence of apical periodontitis	36 patients	66.0 Gy - 70.2 Gy/ IMRT or SI3FT
Khojastepour et al.[29]	To examine radiologic changes in the mandible in patients who received RT for HNC	48 patients	50 Gy - 60 Gy/ not reported
Gomez et al.[30]	To analyze post-RT dental caries in HNC patients in whom a hyperbaric camera was not used	168 patients	3,960 cGy - 7,200 cGy/ IMRT
Ben-David et al.[31]	To assess the prevalence and dosimetric and clinical predictors of mandibular ORN in HNC patients who received parotid gland-sparing IMRT.	176 patients	65 Gy - 70 Gy/IMRT
Bonan et al.[32]	To assess the dental status of HNC (SCC) patients with low socioeconomic level who received dental care prior to RT.	40 patients	4,500 to 9,000 cGy/ tele RT
Lopes et al.[33]	Assessment of the prevalence of dental morphological changes in children who received chemotherapy alone or concomitant RT.	137 patients (83: lymphoproliferative neoplasia; 54: solid tumors)	Not reported/ not reported
Eisen et al.[34]	To determine whether postoperative RT of the mandibulotomy site carries an increased risk of early and late complications	30 patients	60 Gy/conventional RT
Freymiller et al.[35]	To verify the incidence of calcified atheroma in HNC patients treated with RT	17 patients	45 Gy - 71 Gy/ not reported
Marunick et al.[36]	To verify whether primary or adjuvant neutron-beam RT results in a significantly increased rate of ORN	9 patients	1050 to 2040 cGy/ neutron beam RT
Carl and Ikner.[37]	To assess the effects of hard tissue replacement on HNC patients treated with RT who underwent teeth extraction and hard tissue replacement.	8 patients	4000 Gy - 7440 Gy/ not reported
Friedlander et al.[38]	To determine whether individuals with ORN due to RT are more likely to have calcified carotid artery atheromas	61 patients	40 Gy - 72 Gy / not reported
Friedlander et al.[39]	To determine whether patients who received RT are more likely to have calcified atherosclerotic lesions	33 patients	40 Gy - 72 Gy / not reported
Murray et al.[40]	To determine the association between dental disease existing before irradiation and subsequent mandibular radiation necrosis in HNC patients who received RT	46 patients	Not reported to all sample/ not reported

RT: radiotherapy, HNC: head and neck cancer, SCC: squamous cell carcinoma, ORN: osteoradionecrosis, 3-DCR: 3-dimensional conformational radiotherapy, IMRT: 3-dimensional conformational radiotherapy and intensity-modulated radiation therapy, 2-DPRT: conventional 2-dimensional plan radiotherapy, 3-DPRT: 3-dimensional plan radiotherapy, SI3FT: single-isocenter 3-field technique ded. Any patients in a given study's sample who had not received radiotherapy in the head and neck region were excluded.

Data extraction was performed by 2 independent reviewers who evaluated the full text of each investigation to select potentially eligible investigations after screening the titles and abstracts. A third reviewer verified each investigation before conclusively considering it as eligible. Disagreements among reviewers were solved by discussion, and when agreement could not be achieved, another collaborator was consulted. The authors or coauthors of the selected investigation were contacted when the full text was not available.

The following data were extracted and recorded: author information, the number of participants evaluated, radiation dose, and type of radiotherapy (Table 1). Details including the timing of the radiographic assessment, main results, and conclusions (Table 2) were also summarized and presented in tables.

The quality of the selected manuscripts was evaluated using the Cochrane ROBINS-I tool for assessing the risk of bias in non-randomized intervention studies.[8] ROBINS-I evaluates bias in studies according to 7 distinct domains (organized using "signaling questions," described as: confounding selection of participants; classification of the interventions, biases due to deviations from intended interventions, missing data, measurement of outcomes, selection of the reported missing data, measurement of outcomes, and selection of the reported result).[8] The bias assessment results are demonstrated in Table 3.

Results

A total of 13,261 research articles were initially found in the databases after searching for all keywords. After applying the eligibility criteria and removing overlapping studies, 13,228 investigations were excluded, and a total of 33 studies[5,9-40] on the oral and maxillofacial effects of radiotherapy, as assessed by panoramic radiographs, were included. Table 1 summarizes the details of the selected studies.

The oldest study was published in 1980,[40] while the most recent ones were published in 2020.[9,10] The number of participants evaluated in the sample studied ranged from 8[37] to 176,[31] and the samples included were highly heterogeneous. Patients with head and neck cancer were often included in the investigated samples,[5,17,19,22,24,28-37,40] as were patients with hematopoietic neoplasms (such as leukemia),[12,18,23,28,33] although those with neck cancer were also studied independently.[38,39] Some studies were exclusively dedicated to patients with oral squamous cell carcinomas,[21,25,32] rhabdomyosarcoma survivors,[10,14,22] patients with osteoradionecrosis,[17,36,40] and patients in whom the outcomes of surgical procedures such as mandibulotomy[11,19,34] or the use of mandible reconstruction methods were investigated.[13,15,26,27]

Regarding the objectives of investigations pertaining to head and neck radiotherapy, 4 studies focused on determining whether radiotherapy may induce calcified carotid artery atheroma in patients with head and neck cancer,[16,35,38,39] and 2 studies exclusively examined patients with osteoradionecrosis by imaging.[17,31] The effects on oral structures such as teeth in children survivors of head and neck rhabdomyosarcoma was the subject of 4 investigations.[10,14,22,33] Surgical outcomes or complications in patients who received radiotherapy were evaluated in 10 studies,[9,11,13,15,19,25-27,34,37] while changes in marginal bone levels or survival rates of implants were investigated in 2 studies.[21,24] Lastly, the appearance of the mandible,[20,29] apical periodontitis,[5] and dental abnormalities or dental status alterations due to radiotherapy[18,23,28,30,32,33] were also assessed using panoramic radiographs.

The main results and conclusions pertaining to the effects of head and neck radiotherapy and the timing of panoramic assessments in each study are presented in Table 2. In 11 studies, panoramic radiographs were performed before and after radiotherapy,[9,10,16,17,19,20,30,31,33-35] particularly when the primary objective of the study was to investigate the effects of radiotherapy that could be evaluated by panoramic radiographs. Distinct results and conclusions were obtained by the researchers, reflecting the aim of each investigation (Table 2).

The radiation type and dose applied in radiotherapy treatment are also summarized in Table 1. The radiation dose varied from 41.4 Gy14 to 74 Gy.[38,39]

Four studies included patients with benign lesions in their samples;[15,24,26,27] in these studies, evaluating the effects of radiotherapy was a secondary objective, and the studies focused on post-surgical calcification of the pedicle in cases of mandibulotomy[26] and a broad range of surgical outcomes,[13,27] as well as on implant placement or survival.[15,24]

Regarding the quality assessment, we found that most missing data in the manuscripts involved a lack of information about the type of radiotherapy and radiation dose used (Table 3). We considered that research articles without such information entailed a "critical" or "serious" risk of bias.[12,18,23,27,33,40] Regarding studies where the type of radiotherapy was missing, we assumed that conventional radiotherapy had been used.[10,12,13,16,18,19,23-29,33,35,37-40] Neverthe-

Table 2. Main results and conclusions pertaining to the effects of head and neck radiotherapy and the timing of the panoramic assessment performed in the studies

Authors	Timing of the panoramic radiographic assessment	Results	Conclusions
Palma et al.[9]	Before RT: 1-3 weeks, after RT: 3-35 months	Statistically significant decreases were observed in the mean pixel intensity and fractal dimension values after RT.	3D conformational radiotherapy for HNC negatively affected the trabecular microarchitecture and mandibular bone mass.
Hoogeven et al.[10]	Post-RT	There was a correlation between the location of the target area, the developmental stage of the dental tissues and the severity of the effect on dental development. If the dose was high and a root had not yet formed, the root formation seemed to be halted.	Radiation therapy had dental consequences, with age-dependent specific regional effects.
Hachleitner et al.[11]	Post-surgery	Minor complications occurred in 2 patients in the early postoperative period.	Complications causing bony non-union, leading to postponed postoperative radiotherapy, were not noted in this cohort.
Kilinç et al.[12]	Post-RT	The patients in the study group presented distinct dental abnormalities and patients from the control group presented only enamel defects. Root malformation was more common in patients receiving chemotherapy and radiotherapy than in those receiving only chemotherapy.	Pediatric patients who received cancer treatment before the age of 7 years constituted a high-risk group for dental abnormalities. The frequency of microdontia and hypodontia increased even more when the patient was treated for cancer before 5 years of age.
Li et al.[13]	Post-surgery	No statistically significant difference was found between surgical techniques considering the ORN rates.	The decision of which bony flap to use should not be influenced by the potential risk of ORN.
Mattos et al.[14]	After RT and chemotherapy	The more observed dental alterations were root shortening and anodontia. The highest frequency of dental alterations was found in patients with paranasal sinus, nasopharyngeal, and nasal cavity tumors and in patients who were treated and diagnosed at ages 0-5.	Chemotherapy and radiotherapy for the treatment of head and neck rhabdomyosarcomacan result in alterations to dental and bone development, especially when treatment occurs at a young age (<5 years). The results suggest that chemotherapy alone can also affect bone and dental growth and development.
Pellegrino et al.[15]	Immediately after implant placement (baseline) and at the time of prosthetic loading and then annually	Implant failure was more common in the subgroup that had implants placed after radiation therapy.	Radiotherapy negatively impacts survival and success, in particular in the short and medium-term follow-up. Relevant peri-implant bone resorption does occur over time and ultimately influences implants success, and it is mainly related to peri-implant gingival hyperplasia.
Markman et al.[16]	Before and after head and neck RT	35% of the HNC patients presented calcified carotid artery atheroma. No significant difference in calcified carotid artery atheroma before and after RT was observed.	RT did not alter the prevalence of calcified carotid artery atheroma in patients with HNC during this time of follow-up.
Owosho et al.[17]	Post-RT	Patients with oropharyngeal cancer were prone to develop ORN earlier and received higher radiation doses.	Higher radiation dose, poor periodontal status, and alcohol use were significantly associated with ORN.
Tanaka et al.[18]	Post-RT	Several oral and maxillofacial abnormalities were observed in childhood cancer survivors. In total, 73.2% of patients demonstrated some form of oral and maxillofacial abnormality, particularly developmental abnormalities.	Childhood cancer survivors were found to be at an increased risk of dental disturbances, which may be predicted by the period of treatment for the primary disease.

Table 2. Continued

Authors	Timing of the panoramic radiographic assessment	Results	Conclusions
Bengtsson et al.[19]	Before treatment and at follow-up (12 months)	The major complications observed were ORN, nonunion, and infection of the microvascular transplant. No difference between surgical techniques were observed considering complication development.	This study found more persistent complications in the subperiosteal group compared with the supraperiosteal group at 12-month follow-up, which could imply that a more tissue-preserving surgical technique promotes mandibular healing in patients undergoing mandibular access osteotomy in combination with radiotherapy.
Chan et al.[20]	Before and after treatment (5 to 60 months)	60% of the patients had changes due to RT, and the most frequently observed change was widening of the periodontal space. Mean mandibular body doses of 45 Gy or greater were the 3 variables found to be statistically significant for widened periodontal ligament space detection over time.	Postradiotherapy widening of the periodontal space changes should be recognized and differentiated from both odontogenic-related and cancer-induced types of widening of the periodontal space.
Ernst et al.[21]	After implant placement, after 12 months, and after 36 months (radiation therapy was completed a minimum of 6 months before implant placement)	Radiation therapy was found to have an effect on crestal bone loss. There was a period of increased bone loss during the first 12 months, followed by a phase of stagnation with almost stable levels of crestal bone.	Mean amounts of crestal bone changes in irradiated patients were twice as high as those in non-irradiated patients.
Owosho et al.[22]	After treatment (intensity-modulated radiotherapy and chemotherapy)	Patients with dentofacial developmental abnormalities were $\leq$7 years of age at treatment	Dentofacial developmental abnormalities are a sequela that can be observed after intensity-modulated radiotherapy. As the prognosis of childhood malignancy improves and more patients become long-term survivors, these late dentofacial sequelae among childhood cancer survivors will be common.
Proc et al.[23]	After RT and chemotherapy treatment (exact timing not mentioned)	Dental anomalies were much more prevalent in cancer survivors than in healthy children. The most severe anomaly, hypodontia, was 3 times more common among cancer patients than control subjects.	Anticancer treatment has a significant impact on tooth development, particularly in small children.
Pompa et al.[24]	Post-RT	Implant loss was dependent on the position and location of the implants; implant survival was dependent on whether the patient had received radiotherapy. Better outcomes were observed when the implant was not loaded until at least 6 months after placement.	A delayed loading protocol will give the best chance of implant osseointegration, stability and, ultimately, effective dental rehabilitation.
Dediol et al.[25]	1 week, 1 month, and 3 months postoperatively	The type of mandible fixation method used had no influence on the decision to use radiotherapy.	Radiotherapy did not cause serious complications and is not regarded as hazardous in midline mandibulotomy patients.

Table 2. Continued

Authors	Timing of the panoramic radiographic assessment	Results	Conclusions
Shen et al.[27]	Every 3 months during the first post-operative year to assess bony union	The authors do not recommend a condylar prosthesis for reconstruction of mandibular ramus because the incidence rate of condylar prosthesis exposure was higher in patients treated with RT.	Good aesthetic and functional results can be achieved after dental rehabilitation by following the authors' algorithm when choosing the different modes of double-barrel vascularized fibula graft for mandibular reconstruction.
Cubukcu et al.[28]	After RT and chemotherapy treatment (exact timing not mentioned)	In children treated with chemotherapy and RT, only 6.7% of mature permanent teeth were classified as unaffected, in contrast to 68.2% in the children who received chemotherapy alone. Children who received chemotherapy alone did not have more missing teeth than children administered chemotherapy and RT combination. Microdontia was more often observed in patients treated with combined RT and chemotherapy when compared to those who received chemotherapy only.	Children treated for solid tumors and lymphomas are at considerable risk of some disturbances in developing dental structures. The severity of disturbances induced by chemotherapy was increased by head and neck radiotherapy.
Karagozoglu et al.[26]	Initial: 1 month after surgery; other: regular imaging for follow up	Periosteal ossification of the pedicle was found on the postoperative panoramic radiographs of 27% of patients. It was more common among younger patients and patients who had not been given high doses of radiotherapy (>60 Gy).	Periosteal ossification of the pedicle is age-related and radiotherapy-related phenomenon, and it may cause a diagnostic dilemma for clinicians who are not aware of it as it may mimic metastatic disease.
Hommez et al.[5]	Post-RT	Radiation dose was found to be the only explanatory variable in the presence of apical periodontitis.	In zones with a higher radiation dose, inflammation of the jawbone due to bacterial infection of the root canal is more likely to develop, probably due to post-RT bone changes.
Khojastepour et al.[29]	Post-RT	There was a significant relationship between the number of years after RT and the complaint of limitation of mouth opening. The width of the mandibular canal and the thickness of the cortex, as well as the amount of maximum jaw opening, were significantly lower in patients exposed to RT than in controls.	Reduction of width of mandibular cortex and dimensions of the inferior alveolar canal could be considered to be among the post-RT effects on mandibular bone of head and neck RT. These changes may be a predictor of the risk of future ORN in irradiated subjects.
Gomez et al.[30]	Pre- and post-RT	A mean parotid dose of >26 Gy was predictive of subsequent dental caries, whereas a maximum mandibular dose >70 Gy and a mean mandibular dose >40 Gy were correlated with dental extractions after RT.	The mechanisms for radiation-induced dental caries and dental extractions differ, with the incidence of dental caries being more related to the dose to the salivary glands, and dental extractions being a consequence of radiation directly to the mandible.
Ben-David et al.[31]	Pre- and post-RT	The average gradient (in the axial plane containing the maximal mandibular dose) was 11 Gy (range 1-27 Gy, median 8 Gy). At a median 34-month follow-up, there were no cases of ORN.	The use of a strict prophylactic dental care policy resulted in no cases of clinical ORN.

Table 2. Continued

Authors	Timing of the panoramic radiographic assessment	Results	Conclusions
Bonan et al.[32]	Pre-RT	Despite new RT techniques, Brazilian patients with low socioeconomic levels who are diagnosed with head and neck SCC need dental extractions before radiotherapy due to severe periodontal disease and caries. Osteoradionecrosis, as a multifactorial process, is still an important problem associated with high total doses, poor systemic and oral health, as well as tobacco smoking and alcohol use.	ORN was associated with a multifactorial etiology (high doses of radiation, heavy tobacco and alcohol use, poor systemic condition, malnutrition, and even local trauma) in 3 cases; 1 was mainly associated with dental extraction before radiotherapy presenting a non-healed alveolus, and 1 was associated with a mandibulectomy performed during cancer treatment.
Lopes et al.[33]	Post-RT	Children who received chemotherapy and radiotherapy greater than or equal to 2,200 cGy before age 5 presented the highest rates of dental abnormalities.	The findings suggest that immature teeth were at a higher risk for developmental disturbances than mature teeth and that dental abnormalities may be closely related to the stage of dental development.
Eisen et al.[34]	Pre- and post-RT	Complications of mandibulotomy occurred in 20% of the patients.	Mandibulotomy can be safely performed in patients who are likely to require postoperative external radiation.
Freymiller et al.[35]	Pre- and post-RT	There was a statistically significant difference in the prevalence of atheromas in post-irradiation patients when compared to the healthy control individuals.	Individuals who have received therapeutic irradiation to the neck are more likely to develop carotid artery atheromas after treatment than are risk-matched control patients who have not been irradiated.
Marunick et al.[36]	Not reported	ORN did not develop in the 5 patients who received primary neutron-beam RT. However, ORN developed in all patients who received adjuvant neutron-beam RT after surgical resection.	The use of adjuvant neutron-beam RT should be considered with caution due to the risk of ORN.
Carl and Ikner.[37]	Post-RT, after dental extractions	Graft particles appeared to provide a matrix for soft tissue.	Hard tissue replacement particles appear to provide a matrix for fibrous connective tissue formation.
Friedlander et al.[38]	Post-RT	A statistically significant difference in the presence of atheroma in ORN patients was verified, in comparison with healthy patients.	Individuals who receive radiation doses sufficient to cause ORN of the mandible are at significantly higher risk of developing carotid artery atherosclerotic lesions than controls.
Friedlander et al.[39]	Post-RT	Patients that received RT for HNC had a higher risk of the development of calcified carotid artery atherosclerotic lesions than control individuals.	The ability to detect "therapeutically induced/early-onset" atherosclerosis by panoramic dental radiography augments the profession's responsibilities to this group of patients.
Murray et al.[40]	Pre and post-RT	The incidence of necrosis was significantly greater in patients with dental disease.	Dental disease must be eliminated in patients with a history of dental neglect, poor oral hygiene, and smoking or drinking alcohol before RT to avoid ORN.

Gy: Gray, RT: radiotherapy, HNC: head and neck cancer, SCC: squamous cell carcinoma, ORN: osteoradionecrosis

Table 3. Risk of bias assessment according to the Cochrane ROBINS-I tool for assessing the risk of bias in non-randomized intervention studies[8]

Authors	D1	D2	D3	D4	D5	D6	D7	Overall
Palma et al.[9]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Hoogeven et al.[10]	Low	Low	Serious	Low	Moderate	Low	Low	Serious
Hachleitner et al.[11]	Low	Low	Low	Low	Low	Low	Low	Low
Kilinç et al.[12]	Low	Low	Critical	Low	Moderate	Low	Low	Critical
Li et al.[13]	Low	Low	Serious	Low	Moderate	Low	Low	Serious
Mattos et al.[14]	Low	Low	Low	Low	Low	Low	Low	Low
Pellegrino et al.[15]	Low	Low	Low	Low	Low	Low	Low	Low
Markman et al.[16]	Low	Low	Serious	Low	Moderate	Low	Low	Serious
Owosho et al.[17]	Low	Low	Low	Low	Low	Low	Low	Low
Tanaka et al.[18]	Low	Low	Critical	Low	Moderate	Low	Low	Critical
Bengtsson et al.[19]	Low	Low	Serious	Low	Serious	Low	Low	Serious
Chan et al.[20]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Ernst et al.[21]	Low	Low	Low	Low	Low	Low	Low	Low
Owosho et al.[22]	Low	Low	Low	Low	Low	Low	Low	Low
Proc et al.[23]	Low	Low	Critical	Low	Moderate	Low	Low	Critical
Pompa et al.[24]	Low	Low	Serious	Low	Low	Low	Low	Serious
Dediol et al.[25]	Low	Low	Serious	Low	Low	Low	Low	Serious
Karagozoglu et al.[26]	Low	Low	Serious	Low	Moderate	Low	Low	Serious
Shen et al.[27]	Low	Low	Critical	Low	Low	Low	Low	Critical
Cubukcu et al.[28]	Low	Low	Serious	Low	Low	Low	Low	Serious
Hommez et al.[5]	Low	Low	Low	Low	Low	Low	Low	Low
Khojastepour et al.[29]	Low	Low	Serious	Low	Low	Low	Low	Serious
Gomez et al.[30]	Low	Low	Low	Low	Moderate	Low	Low	Low
Ben-David et al.[31]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Bonan et al.[32]	Low	Low	Low	Low	Low	Low	Low	Low
Lopes et al.[33]	Low	Low	Critical	Low	Low	Low	Low	Critical
Eisen et al.[34]	Low	Low	Low	Low	Low	Low	Low	Low
Freymiller et al.[35]	Low	Low	Serious	Low	Moderate	Low	Low	Serious
Marunick et al.[36]	Low	Low	Low	Low	Moderate	Low	Low	Moderate
Carl and Ikner.[37]	Low	Low	Serious	Low	Low	Low	Low	Serious
Friedlander et al.[38]	Low	Low	Serious	Low	Low	Low	Low	Serious
Friedlander et al.[39]	Low	Low	Serious	Low	Low	Low	Low	Low
Murray et al.[40]	Low	Low	Critical	Low	Low	Low	Low	Critical

D1: bias due to confounding, D2: bias due to selection of participants, D3: bias in classification of interventions, D4: bias due to deviations from intended interventions, D5: bias due to missing data, D6: bias in measurement of outcomes, D7: bias in selection of the reported result

less, the radiation dose was essential information that could not be deduced. The assessment results of the risk of bias are presented in Table 3.

Discussion

Head and neck neoplasms are usually treated with radiotherapy, which applies ionizing radiation. Radiotherapy primarily targets malignant cells through the production of free radicals that damage the genetic material of vulnerable malignant cells.[41] However, it also damages healthy cells, particularly those that are fast-dividing, resulting in radiation-induced adverse effects.[42]

Bone architecture alterations,[14,29] periodontal space widening,[20] tooth development abnormalities,[10,12,18,22,28,33] osteoradionecrosis,[13,17,36] and peri-implant bone loss[15,21,24] are examples of the interactions of ionizing radiation with maxillofacial hard structures, which can be detected by panoramic radiographs. Moreover, radiotherapy for head and neck neoplasms has an unfavorable impact on patients' quality of life, especially as it negatively affects oral health and oral function commitment. Hyposalivation,[30] reduced mouth opening, mucositis, oral pain, dental caries, and osteoradionecrosis are examples of the deleterious oral effects of radiotherapy, even when using modern radiotherapy techniques.[43]

Regarding alveolar bone changes, patients who receive irradiation show crestal bone changes,[21] which increase the peri-implant bone resorption.[15] Periodontal space widening is a finding often reported in the literature when describing maxillomandibular imaging changes in these patients. Although its pathophysiological process is unknown, it is postulated that the inflammatory changes that lead to the enlargement of the periodontal ligament space are associated with resorption of the adjacent bone and subsequent filling with fibrotic tissue.[20] When the inflammation is resolved, the periodontal ligament maintains its width.[20]

Other local complications of radiotherapy include changes in the shape, number, and developmental abnormalities in the teeth of children who receive radiotherapy and chemotherapy for head and neck cancer,[10,12,14,18,22,23,28,32,33] such as rhabdomyosarcoma.[10,14,22] The multimodal approach for childhood head and neck cancer includes systemic multiagent chemotherapy, local surgery, and/or radiotherapy.[22] This treatment results in significant alterations in the developing teeth and maxilofacial bones, which persist during the patient's life, especially when the treatment is administered at a young age (less than 5 years old).[10,14,44] This is because immature teeth are at higher risk for developmental disturbances.[33] The most common reported alterations are root shortening, anodontia, microdontia, and taurodontia.[14] The frequency and intensity of these alterations seem to be proportional to the treatment's intensity and duration (i.e., a higher amount of ionizing radiation used and a longer duration of the radiation treatment lead to worse alterations) and the child's age at diagnosis (i.e., a younger age is associated with worse alterations), while chemotherapy without head and neck radiotherapy has been shown to result in the least severe abnormalities.[28,44]

Osteoradionecrosis was mentioned by the analyzed studies,[13,17,32,40] which showed it to be associated with alcohol and tobacco use, high radiation doses, poor oral hygiene, and dental disease.[13,17,32] Osteoradionecrosis has also been investigated as a complication of radical and reconstructive maxillofacial surgery.[11,13,19,25,26,34] A study proposed that the pathophysiological mechanism of bone tissue breakdown in osteoradionecrosis is associated to hypoxia, hypovascularity, and hypocellularity in bone tissue due to radiation exposure.[45] This negative effect was also reflected in the study of Palma et al.,[9] who, by using panoramic radiographs and pixel analysis, verified that mandibular bone microarchitecture is affected by radiotherapy. In addition to evaluating the effects of radiotherapy as assessed by panoramic radiographs, some of the analyzed studies' primary objective was to investigate whether radiotherapy induces or increases the risk of developing calcified carotid artery atheroma in patients without[16,35,38,39] or with osteoradionecrosis.[31] The formation of atheromatous plaques and their further calcification result from chronic vascular inflammation, which may be induced by low-density lipoprotein cholesterol, free radicals from chronic smoking, and deleterious metabolic effects from diseases such as diabetes or hypertension.[16]

Lastly, implant survival and success after radiotherapy have also been assessed.[15,24] Overall, radiotherapy negatively impacts the implant's osseointegration and stability.[24] It also leads to progressive vessel and soft-tissue fibrosis, reducing the healing capacity of the bone tissue.[24] The time of loading is associated with implant success; thus, delayed loading is desirable to achieve adequate osteointegration.[24]

Regarding the radiotherapy techniques used in the analyzed studies, most studies did not specify the type of radiotherapy applied in their investigations;[10,12,13,16,18,19,23-29,33,35,37-40] thus, we assumed that these studies used conventional radiotherapy. Other studies mentioned the use of intensity-modulated radiotherapy (IMRT),[9,14,15,17,20-22,30,31] and 1 study included a mixed sample of patients treated with IMRT by conventional radiotherapy.[14] The objective of these previous investigations and of the present review was not to compare different radiotherapy techniques, their effects, or the radiation-induced changes observed in panoramic radiographs; nonetheless, certain differences among these techniques can be appreciated. IMRT delivers a minimal, homogeneous radiation dose into the neoplasm with maximum protection of tissues at risk,[46] thereby improving the outcome when compared to that of conventional radiotherapy.[47] If the studies' samples and objectives were more homogeneous, direct comparisons could have been performed to evaluate the effects of radiotherapy detected on panoramic radiographs.

The interaction between ionizing radiation and maxillofacial structures results in hazard to the tissues involved, particularly the bone tissue, periosteum, connective tissue of the mucosa, and endothelium. Radiation-induced effects that can be detected on panoramic radiographs include tooth development abnormalities, mandibular or maxillary bone architecture alterations, peri-implant bone loss, hyposalivation, reduced mouth opening, and osteoradionecrosis. Tooth development abnormalities and mandibular or maxillary bone architecture alterations induced by radiotherapy occur when the radiation treatment is performed during craniofacial development. Dentists should be aware of these side effects in order to provide proper oral treatment to patients with a history of radiotherapy treatment.

Conflicts of Interest: None

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