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Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review

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Abstract. This systematic review aims to identify and review the best available evidence to answer the clinical question 'What are the incidence and the factors influencing the development of osteoradionecrosis after tooth extraction in irradiated patients?'. A systematic review of published articles on post-irradiation extraction was performed via electronic search of the Medline, Ovid, Embase and Cochrane Library databases. Additional studies were identified by manual reference list search. Evaluation and critical appraisal were done in 3 stages by two independent reviewers and any disagreement was resolved by discussion with a third party. 19 articles were selected for the final analysis. The total incidence of osteoradionecrosis after tooth extraction in irradiated patients was 7%. When extractions were performed in conjunction with prophylactic hyperbaric oxygen, the incidence was 4% while extraction in conjunction with antibiotics gave an incidence of 6%. This systematic review found that while the incidence of osteoradionecrosis after post-irradiation tooth extractions is low, the extraction of mandibular teeth within the radiation field in patients who received a radiation dose higher than 60 Gy represents the highest risk of developing osteoradionecrosis. Based on weak evidence, prophylactic hyperbaric oxygen is effective in reducing the risk of developing osteoradionecrosis after post-radiation extractions.

Key words: osteoradionecrosis; systematic review; extraction.

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Radiotherapy is an established treatment modality in the management of malignant disease of the head and neck. Radiotherapy targets all cells with a high turnover rate, whether malignant or normal host tissue. A balance of tumour eradication and normal tissue preservation must be reached to achieve cure without further debilitating the patient. This adverse effect on normal tissue limits the dose and dose delivery rate of radiation therapy. Certain adverse effects of therapy may have to be accepted in exchange for cure of this lethal disease. Bone is radio-resistant compared with other tissues but, due to compromise in its blood supply and reparative ability, it remains a problem when irradiated.

Osteoradionecrosis (ORN) is recognized as one of the most severe complications of radiation therapy. ORN is difficult to treat and often leads to poor outcome and deformity. ORN is defined as an area of exposed devitalized irradiated bone that fails to heal over a period of 3–6 months in the absence of local neoplastic disease[11,28,35,56,76]. ORN can occur spontaneously, due to periodontal and apical disease and possibly after trauma induced by dentures, or after surgery or tooth extraction[11,19,29,57,61,79]. Extraction before

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or after irradiation is said to be the most common initiating factor in the development of ORN in irradiated jaws[57,79]. Incidence of ORN after tooth extraction in irradiated patients is estimated to be around 2–18%[58,78].

To prevent this complication after post-irradiation extraction, several methods have been tried. Antibiotic prophylaxis before the extraction procedure is the most common initiative to prevent ORN[41]. This is probably because it is easy to administer and widely available. Others have suggested using hyperbaric oxygen (HBO) before extraction[45,58,83]. The high oxygen level with HBO is thought to induce fibroplasia and angiogenesis in the hypoxic, hypocellular and hypovascular tissue, thus preventing the occurrence of ORN after tooth extraction[57]. Scarce availability possibly limits the routine use of HBO in the irradiated population needing tooth extraction. Recent suggestions include the use of pentoxifylline and tocopherol some weeks before extraction[51].

Intra-operatively, measures such as alveoloplasty, primary closure and limited periosteal trauma during extraction are said to be critical steps in avoiding ORN[9,28]. Limiting the number of teeth to be extracted in a single session and using low-adrenaline local anesthesia or avoiding certain local anesthetic (LA) agents are also used[59]. These suggestions are based on years of clinical experience with the disease.

The exact incidence of ORN after post-irradiation extraction is unknown. The effectiveness of the methods used to reduce the incidence of ORN is also unknown. Given the increase in the head and neck irradiated population and the devastating morbidity of ORN, a systematic review to determine the exact incidence of ORN post-extraction and identify the best prevention methods available appears timely.

Materials and methods

A systematic review of the best evidence available in the literature was performed to answer the following clinical question: 'What are the incidence and the factors influencing the development of ORN of the jaw bones after tooth extraction in irradiated head and neck cancer patients?'

An initial electronic search was performed using MEDLINE (1950 to April 2010) via Pubmed and Ovid. Further search was performed through Embase and The Cochrane Library database. A broad search strategy was undertaken using the following keywords: Osteoradionecrosis AND (Hyperbaric oxygen OR Extraction OR Prevention OR Antibiotics). The title and abstract (when available) of the articles retrieved using the described strategy were then screened by 2 reviewers. For studies appearing to be relevant, and for those with insufficient data in the title and abstract to make a clear decision, the full article was obtained. The reference lists from the selected articles were also screened and the full text of any relevant citation was retrieved to be included in the study selection phase.

The full text of all articles retrieved from the first round of search and the articles retrieved from the manual reference list search were evaluated independently by 2 reviewers. Articles reporting data regarding extraction of teeth in human adults after irradiation of the oral and maxillofacial region were accepted. Single case reports were excluded at this stage. Articles selected after the full text assessment were submitted to final eligibility assessment for inclusion in the review. The criteria described below were used to determine eligibility. Articles excluded from this phase and the reasons for exclusion were also reported.

All types of study with data assessing ORN occurrence after tooth extraction in patients who had radiation in the head and neck region with a minimum sample size of 5 patients were considered. No restriction on language, publication date or publication status was imposed. In order to avoid selection bias, studies had to include a consecutive group of patients who had radiation to the head and neck and underwent post-irradiation extraction.

Subjects who had teeth extracted after radiotherapy for treatment of a neoplasm of the head and neck region were eligible. Subjects could be treated by radiotherapy alone, chemoradiotherapy or as adjunct therapy with surgery. Subjects with irradiation of the head and neck region that did not include the maxilla or mandible were considered ineligible and were excluded. Subjects with ORN present before tooth extractions were also excluded.

Studies with or without intervention to prevent the occurrence of ORN after extractions in post-irradiated patients were accepted. Those without any intervention to prevent ORN were accepted as controls. The intervention, if any, had to be clearly described.

The primary outcome measure is the occurrence of ORN at the extraction socket. Diagnosis of ORN had to be made by a clinician after clinical examination. ORN for the purpose of this review was defined as an area of exposed devitalized irradiated bone that failed to heal over 3 months with no evidence of recurrence of local neoplastic disease. Abiding by this definition, unhealed sockets of individual subjects had to be followed-up for at least 3 months post-extraction. Articles reporting follow-up in a group of patients had to have a median/mean follow-up period of at least 6 months post-extraction to be included in this review. Other outcomes were: ORN incidence under different prevention/intervention methods; and analysis of risk factors (relation of interval between extraction and RT treatment, extractions in mandible/maxilla, radiation dose and radiation field) in the development of ORN after extraction in irradiated patients.

The data were collected in a Microsoft Excel table by the first reviewer. The second reviewer checked the extracted data to avoid any omissions or inaccuracies in the data extracted. Any differences were discussed by the 2 reviewers and disagreement managed by consultation with a third party.

Results

The electronic database search last updated on 30 April 2010 yielded 518 hits from Pubmed, 384 hits from Ovid, 167 hits from Embase and 2 from the Cochrane Library. 121 articles were considered relevant to the topic after title and/or abstract screening. A manual reference list search of the 121 selected articles yielded a further 23 articles. Full texts of these 144 articles were evaluated for the report-

Table 1. Eligibility criteria.

Eligibility criteria for inclusion in the final review
Minimum sample size of 5 patients
Radiotherapy in head & neck region affecting mandible, maxilla or both
No previous ORN at the extraction site
Consecutive group of patients undergoing extraction after RT
Diagnosis of ORN made after clinical examination by clinician
ORN occurred at site of extraction
For individual subjects with unhealed sockets follow-up must be at least 3 months and for group of subjects median/mean follow-up must be more than 6 months after extraction

Table 2. Articles excluded after eligibility assessment.

Year	Author	Title	Study type	Reason for exclusion	ORN/patient	%
2009	Kaur et al.[42]	Retrospective audit of the use of the Marx Protocol for prophylactic hyperbaric oxygen therapy in managing patients requiring dental extraction following radiotherapy to the head and neck	Retrospective	ORN was not diagnosed by clinician/clinical exam	1/26	3.8%
2007	Chang et al.[15]	Do pre-radiation dental extractions reduce the risk of osteoradionecrosis of the mandible?	Retrospective	Inadequate description of the ORN site	12/51	23.5%
2006	Wahl[84]	Osteoradionecrosis prevention myths	Review	No new data	–	–
2005	Bennet et al.[5]	Hyperbaric oxygen therapy for late radiation tissue injury	Systematic review	No new data	–	–
2004	Oh et al.[64]	Risk of osteoradionecrosis after extraction of impacted third molars in irradiated head and neck cancer patients	Retrospective	Less than 5 patients	1/4	25%
2004	Feldmeier[30]	Hyperbaric oxygen for delayed radiation injuries	Review	No new data	–	–
2003	Afanasyev et al.[1]	Removal of teeth in patients with malignant maxillofacial tumours during different periods of radiotherapy	Unclear	Inadequate description of the ORN site; Inadequate description/duration of follow up period	0/5	0%
2002	Feldmeier and Hampson[31]	A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach	Systematic review	No new data	–	–
1999	Vudiniabola et al.[83]	Hyperbaric oxygen in the prevention of osteoradionecrosis of the jaws	Prospective	Non-consecutive patient undergoing post-irradiation extraction (Data presented as any oral surgery procedure—unable to extract data on post-radiation extraction)	–	–
1998	Toljanic et al.[80]	Osteoradionecrosis of the jaws as a risk factor in radiotherapy: a report of an 8-year retrospective review	Retrospective	Less than 5 patients	0/4	0%
1997	Clayman[18]	Management of dental extraction in irradiated jaws: a protocol without hyperbaric oxygen therapy	Review	No new data	–	–
1995	Henrich et al.[36]	Untersuchungen zur problematik einer chirurgischen zahnsanierung im zusammenhang mit der bestrahlung maligner tumoren	Retrospective	Inadequate description/duration of follow up period	0/167	0%
1989	Widmark et al.[86]	Osteoradionecrosis of the jaws	Retrospective	Non-consecutive patients undergoing post-irradiation extraction	–	–
1986	Marciani and Ownby[55]	Osteoradionecrosis of the jaws	Retrospective	Inadequate description/duration of follow up period	0/17	0%

Table 2 (*Continued*)

Year	Author	Title	Study type	Reason for exclusion	ORN/patient	%
1985	Kraut[45]	Prophylactic hyperbaric oxygen to avoid osteoradionecrosis when extractions follow radiation therapy	Case report	Less than 5 patients; non-consecutive patients undergoing post-irradiation extraction	0/3	0%
1983	Horiot et al.[39]	Dental preservation in patients irradiated for head and neck tumours: A 10-year experience with topical fluoride and a randomized trial between two fluoridation methods	Prospective	Inadequate description/duration of follow up period	4/29	13.8%
1981	Horiot et al.[38]	Systematic dental management in head and neck irradiation	Prospective	Inadequate description/duration of follow up period; duplicate data	–	–
1980	Murray et al.[62]	Radiation necrosis of the mandible: a 10 year study. Part II. Dental factors; onset, duration and management of necrosis	Retrospective	Inadequate description/duration of follow up period	7/8	87.5%
1979	Beumer et al.[7]	Radiation therapy of the oral cavity: sequelae and management, part 2	Review	Duplicate data	–	–
1976	Regezi et al.[67]	Dental management of patients irradiated for oral cancer	Retrospective	Inadequate description/duration of follow up period	0/9	0%
1976	Bedwinek et al.[3]	Osteonecrosis in patients treated with definitive radiotherapy for squamous cell carcinomas of the oral cavity and naso- and oropharynx	Retrospective	Non-consecutive patients undergoing post-irradiation extraction (Data presented as combination of pre and post-radiation extraction-unable to extract data on post-radiation extraction)	–	–
1973	Carl et al.[14]	Oral surgery and the patient who has had radiation therapy for head and neck cancer	Retrospective	Non-consecutive patients undergoing post-irradiation extraction (data presented as combination of pre and post-radiation extraction—unable to extract data on post-radiation extraction); inadequate description/ duration of follow up period	–	–
1972	Beumer et al.[10]	Hard and soft tissue necroses following radiation therapy for oral cancer	Retrospective	Inadequate description/duration of follow up period	1/23	4.3%
1972	Carl et al.[13]	Oral care of patients irradiated for cancer of the head and neck	Retrospective	Duplicated data; Inadequate description/duration of follow up period	–	–
1972	Daly and Drane[21]	Osteoradionecrosis of the Jaws	Retrospective	Less than 5 patients; inadequate description/ duration of follow up period	3/3	100
1969	Hoffmeister et al.[37]	Radiation in dentistry–surgical comments	Retrospective	Inadequate description/duration of follow up period	14/24	58.3%
1968	Solomon et al.[74]	Extraction of teeth after cancericidal doses of radiotherapy to the head and neck	Prospective	Inadequate description/duration of follow up period	0/31	0%
1966	Grant and Fletcher[34]	Analysis of complications following megavoltage therapy for squamous cell carcinomas of the tonsillar area	Retrospective	Inadequate description/duration of follow up period	7/16	43.8%
				Total	50/420	11.9%

Table 3. Articles included in the final review.

Year	Author	Title	Study type	Number of patients	Intervention	Follow-up	ORN	Percentage
2008	Koga et al.[44]	Dental extraction related to head and neck radiotherapy: ten-year experience of a single institute	Retrospective	57	86% used antibiotics, 17.5% used HBO	Median 42.8 month	1	1.75%
2007	Ben-David et al.[4]	Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions	Retrospective	13	2 undergone HBO, others not mentioned clearly	Median 26 month	0	0%
2007	Lye et al.[50]	The effect of prior radiation therapy for treatment of nasopharyngeal cancer on wound healing following extractions: incidence of complications and risk factors	Prospective	40	Antibiotics; Chlorhexidine 0.2% mouthwash; LA without adrenaline; suturing	3 month	3	8%
2004	Chaux-Bodard et al.[16]	Extractions dentaires en territoire irradie	Prospective	107	Antibiotics; Alveoloplasty and primary closure; Chlorhexidine 0.2% mouthwash; Low-adrenaline anaesthesia	3 month	1	0.93%
2003	Sulaiman et al.[78]	Dental extractions in the irradiated head and neck patient: a retrospective analysis of Memorial Sloan-kettering Cancer Centre protocols, criteria and end results	Retrospective	107	7 received HBO; 65% did not receive antibiotic; 35% received antibiotic, suturing, Post-radiation extraction in multiple visits	mean 22m	2	1.87%
2001	David et al.[22]	Hyperbaric oxygen therapy and mandibular osteoradionecrosis: a retrospective study and analysis of treatment outcome	Retrospective	24	HBO	6 month	0	0%
2001	Chaves and Adkinson[17]	Adjunctive hyperbaric oxygen in irradiated patients requiring dental extractions: outcomes and complications	Prospective	40	HBO	12 month	4	10%
1999	Tong et al.[81]	Incidence of complicated healing and osteoradionecrosis following tooth extraction in patients receiving radiotherapy for the treatment of nasopharyngeal carcinoma	Retrospective	43	Antibiotics; Chlorhexidine 0.2% mouthwash; suturing +/− alveoloplasty in muktiple extraction	6 month	2	4.65%

Table 3 (*Continued*)

Year	Author	Title	Study type	Number of patients	Intervention	Follow-up	ORN	Percentage
1998	Carl and Ikner[12]	Dental extractions after radiation therapy in the head and neck area and hard tissue replacement (HTR) therapy: a prelimenary study	Prospective	8	Alveoloplasty and primary closure; hard tissue replacement; antibiotics	Minimum 7 month	0	0%
1997	Lambert et al.[46]	Management of dental extractions in irradiated jaws: a protocol with hyperbaric oxygen therapy	Retrospective	46	HBO; alveoloplasty and primary closure	Minimum 2 1/2 month	0	0%
1991	Maxymiw et al.[59]	Postradiation dental extractions without hyperbaric oxygen	Prospective	72	Antibiotics; low-adrenaline and non-lidocaine anaesthesia; less then 2 teeth persession	Minimum 2 1/2 month	0	0%
1987	Makkonen et al.[54]	Dental extractions in relation to radiation therapy of 224 patients	Retrospective	25	6 received antibiotics, 6 did not received antibiotics; 13 unclear	1–8 years	0	0%
1987	Epstein et al.[28]	Osteonecrosis: study of the relationship of dental extractions in patients receiving radiotherapy	Retrospective	42	Antibiotic; primary closure +/− alveoloplasty	3 month	3	7.14%
1987	Schweiger[73]	Oral complications following radiation therapy: a five-year retrospective report	Retrospective	24	Antibiotics	1 month	2	8.33%
1985	Marx et al.[58]	Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin	RCT	74	HBO versus antibiotic	6 month	13	17.57%
1983	Beumer et al.[9]	Postradiation dental extractions: A review of the literature and a report of 72 episodes	Retrospective	72	Alveoloplasty and primary closure for multiple tooth extraction, HBO in 4	3 month	16	22.22%
1981	Morrish et al.[60]	Osteonecrosis in patients irradiated for head and neck carcinoma	Retrospective	18	Not clear	3 month	9	50%
1976	Beumer et al.[8]	Radiation complications in edentulous patients	Prospective	11	Not clear	6 month	1	9%
1953	Wildermuth and Cantril[87]	Radiation necrosis of the mandible	Retrospective	5	Antibiotics in 4, none in 1	Minimum 1 month	0	0%
				828			57	6.88%

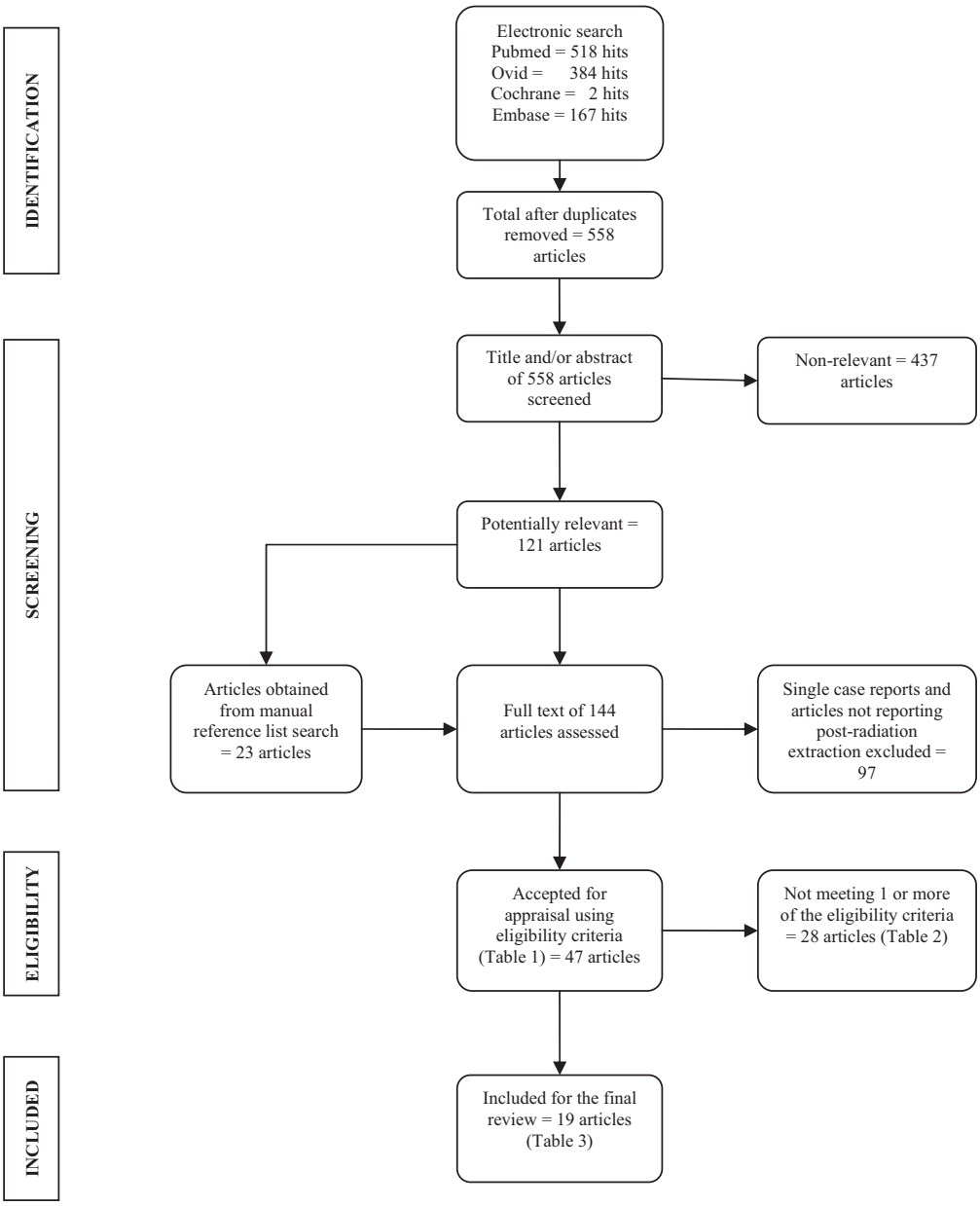

Fig. 1. Flow diagram for study selection (as adapted from PRISMA statement[48]).

ing of clinical data on tooth extraction in irradiated jaws. 47 articles were selected and entered for eligibility assessment, using the eligibility criteria in Table 1.

Of these 47 articles, 28 articles that did not meet one or more of the eligibility criteria were excluded; the reasons for exclusion are listed in Table 2. 19 articles were accepted for the final review (Table 3). They underwent a critical evaluation process to obtain the best available valid data for this review. A flow chart of the selection and evaluation process is presented in Fig. 1.

Among the 47 selected articles, there were two systematic reviews (SR), one randomized controlled trial (RCT) and 10 prospective studies reporting data on tooth extraction in irradiated jaws. The remaining articles were 28 retrospective studies, 4 reviews, 1 case report and 1 not clearly described. 19 articles were included in the final review. For the prevention of ORN, 8 reported the use of HBO, 12 used antibiotics and 2 failed to describe clearly the intervention used. There were also articles reporting alveoloplasty, primary closure, local anesthesia with low adrenaline and limiting the number of extractions per session combined with the measures described above.

11 articles reported clearly the relation of ORN occurrence to the number of teeth removed with 8 studies specifying the site of extraction as the maxilla or mandible. In 7 studies, mention was made of whether the tooth extracted was in the field of radiation or outside it. The radiotherapy dose received by the patient was clearly described in 9 studies.

Primary outcome

There were 57 ORN cases after post-radiation extraction in 828 patients. This gives a total incidence of 7% (Table 3). 11 of the 19 articles described the number of teeth extracted. There were 2766 tooth extractions and 54 of the extraction sockets later developed ORN (Table 4).

Table 4. ORN per tooth extracted.

Author	Teeth extracted	Incidence/tooth	Percentage
Lye et al.[50]	155	3	1.94%
Chaux-Bodard et al.[16]	287	1	0.35%
Sulaiman et al.[78]	647	2	0.31%
David et al.[22]	54	0	0%
Chaves and Adkinson[17]	371	6	1.62%
Tong et al.[81]	237	4	1.69%
Carl and Ikner[12]	44	0	0%
Maxymiw et al.[59]	449	0	0%
Makkonen et al.[54]	94	0	0%
Epstein et al.[28]	137	3	2.19%
Marx et al.[58]	291	35	12.03%
Total	2766	54	1.95%

Table 5. Incidence after antibiotics and HBO.

Author	HBO/pt	ORN	Antibiotic/pt	ORN	HBO/tooth	ORN	Antibiotic/tooth	ORN
Koga et al.[44]	10[a]	n.a.	49[a]	n.a.	n.a.	n.a.	n.a.	n.a.
Ben David et al.[4]	2	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Lye et al.[50]	0	0	40	2	0	0	155	3
Chaux-Bodard et al.[16]	0	0	107	1	0	0	287	1
Sulaiman et al.[78]	7	0	n.a.	n.a.	14	0	n.a.	n.a.
David et al.[22]	24	0	0	0	54	0	0	0
Chaves and Adkinson[17]	40	4	0	0	371	6	0	0
Tong et al.[81]	0	0	43	2	0	0	237	4
Carl and Ikner[12]	0	0	8	0	0	0	44	0
Lambert et al.[46]	46	0	0	0	n.a.	n.a.	n.a.	n.a.
Maxymiw et al.[59]	0	0	72	0	0	0	449	0
Makkonen et al.[54]	0	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Epstein et al.[28]	0	0	42	3	0	0	137	3
Schweiger[73]	0	0	24	2	n.a.	n.a.	n.a.	n.a.
Marx et al.[58]	37	2	37	11	156	4	135	31
Beumer et al.[9]	4	0	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Morrish et al.[60]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Beumer et al.[8]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Wildermuth and Cantril[87]	0	0	4	0	n.a.	n.a.	n.a.	n.a.
Total	160 3.75%	6	377 5.57%	21	595 1.68%	10	1444 2.91%	42

n.a., not described in articles.

[a] Excluded because ORN occurrence was not reported.

Table 6. Type of antibiotics used before extraction.

Year	Author	Used antibiotics	Type
2008	Koga et al.[44]	Yes	Not clear
2007	Ben-David et al.[4]	Not clear	–
2006	Lye et al.[50]	Yes	Preoperatively Pen V 2 g/clindamycin 600 mg and postoperatively Pen V/clindamycin with metronidazole for 1 week
2004	Chaux-Bodard et al.[16]	Yes	Postoperative amoxycillin for 8 days
2003	Sulaiman et al.[78]	Yes	Not clear
2001	David et al.[22]	No	–
2001	Chaves and Adkinson[17]	No	–
1999	Tong et al.[81]	Yes	Postoperative penicillin 250 mg qid for 1 week
1998	Carl and Ikner[12]	Yes	Postoperative clindamycin bid for 4 days
1997	Lambert et al.[46]	No	–
1991	Maxymiw et al.[59]	Yes	Preoperative Penicillin V 2 g and postoperatively 600 mg qid for 1 week
1987	Makkonen et al.[54]	Yes	Not clear
1987	Epstein et al.[28]	Yes	Not clear
1987	Schweiger[73]	Yes	Not clear
1985	Marx et al.[58]	Yes (one arm)	Preoperative 1mu IV Penicillin G and postoperative Penicillin V 500 mg qid for 10 days
1983	Beumer et al.[9]	Not clear	–
1981	Morrish et al.[60]	Not clear	–
1976	Beumer et al.[8]	Not clear	–
1953	Wildermuth and Cantril[87]	Yes	Penicillin

Table 7. Intra-operative measures to prevent ORN.

Procedure		Articles
Alveoloplasty and/or suturing	Performed	9, 12, 16, 28, 46, 50, 58, 81
	Not performed	59
	Not clear	4, 8, 17, 22, 44, 54, 60, 73, 78, 87
LA with no/low adrenaline	Performed	16, 50, 59
	Not performed	58
	Not clear	4, 8, 9, 12, 17, 22, 28, 44, 46, 54, 60, 73, 78, 81, 87
Limited extractions per-session	Performed	59, 78
	Not performed	–
	Not clear	4, 8, 9, 12, 17, 22, 28, 44, 46, 50, 54, 58, 60, 73, 81, 87

Table 8. Extraction performed in maxilla and mandible.

Author	Extraction in mandible	ORN at mandible	Percentage	Extraction in maxilla	ORN at maxilla	Percentage
Lye et al.[50]	89	2	2.25%	66	1	1.51
David et al.[22]	54	0	0%	0	0	0%
Chaux-Bodard et al.[16]	231	1	0.43%	56	0	0%
Tong et al.[81]	121	0	0%	116	4	3.45%
Carl and Ikner[12]	32	0	0%	12	0	0%
Maxymiw et al.[59]	252	0	0%	197	0	0%
Makkonen et al.[54]	66	0	0%	28	0	0%
Marx et al.[58]	291	35	12.03%	0	0	0%
Total	1136	38	3.35%	475	5	1.05%

Other outcomes

In the 8 articles reporting the use of HBO, 7 articles reported its relation with the occurrence of ORN in which the total incidence was 4%. HBO was described as breathing 100% oxygen at 2.4 ATM for 90 min. The protocol was 20 sessions pre-extraction and 10 sessions post-extraction as suggested by Marx et al.[58]. Extraction of 595 teeth with ORN occurring in 10 of the sockets (an incidence of 2% per tooth) was reported after using HBO. On the use of antibiotics, 9 of the 12 articles reporting the use of antibiotics clearly described the incidence of ORN in relation to its use. The overall incidence of ORN with the use of antibiotics was 6%. 1444 teeth were extracted in this group and ORN occurred in 42 of the sockets (incidence 3% per tooth) (Table 5). In these studies, the antibiotic regimens used were variable. The antibiotics most widely used were penicillin and clindamycin (Table 6).

The most common intra-operative measures performed with the intention to prevent ORN were alveoloplasty/alveolotomy and suturing, performed separately or in combination. Eight articles reported the use of alveoloplasty and/or suturing. One article did not use the procedure, while the remaining authors failed to mention clearly whether they used the procedure or not. Three articles reported the use of low adrenaline or non-adrenaline vasoconstrictor in the local anesthesia solution before performing the extraction. Limiting the number of extractions per-session in an effort to avoid ORN was reported in two studies (Table 7).

When extraction was performed in the maxilla, only 1% of the sockets developed ORN. The risk is 3 times higher in the mandible as 38 of 1136 sockets (3%) developed ORN post-extraction (Table 8).

Extraction of teeth included in the radiation field revealed an incidence of ORN of 3% while extraction of teeth outside the radiation field resulted in no ORN in any socket (Table 9).

Radiation doses reported were assessed for any correlation with the incidence of ORN. 29 patients received a radiation dose less than 60 Gy. Among these patients, none developed ORN. In the group receiving more than 60 Gy, 12% of patients developed ORN after post-irradiation extraction (Table 10).

Time interval from radiation to extraction was analyzed after dividing the patients into two groups. In the first group, in whom extractions were performed within 1 year of radiation, 8% of patients developed ORN. In group 2 (extractions more than 2 years after radiation), 16%

Table 9. Extraction in radiation field and outside radiation field.

Author	Extraction in radiation field	ORN in field	Percentage	Extraction outside radiation field	ORN outside field	Percentage
Chaux-Bodard et al.[16]	287	1	0.35%	0	0	0%
Sulaiman et al.[78]	344	2	0.58%	317	0	0%
David et al.[22]	44	0	0%	10	0	0%
Tong et al.[81]	38	4	10.50%	199	0	0%
Carl and Ikner[12]	19	0	0%	25	0	0%
Maxymiw et al.[59]	196	0	0%	253	0	0%
Marx et al.[58]	291	35	12.03%	0	0	0%
Total	1219	42	3.45%	804	0	0%

Table 10. Radiation dose and post-extraction ORN.

Author	Dose <60 Gy	ORN <60 Gy	Percentage	Dose >60 Gy	ORN >60 Gy	Percentage
Lye et al.[50]	0	0	0%	40	2	5%
Sulaiman et al.[78]	0	0	0%	7	0	0%
David et al.[22]	12	0	0%	12	0	0%
Tong et al.[81]	0	0	0%	43	4	9.30%
Carl and Ikner[12]	2	0	0%	6	0	0%
Lambert et al.[46]	15	0	0%	25	0	0%
Marx et al.[58]	0	0	0%	74	13	17.57%
Morrish et al.[60]	0	0	0%	18	9	50%
Wildermuth and Cantril[87]	0	0	0%	5	0	0%
Total	29	0	0%	230	28	12.17%

Table 11. Time of extraction post-radiation.

Author	Extraction within 1 year radiotherapy (ORN)	Extraction between 2 and 5 years radiotherapy (ORN)	Extraction after 5 years radiotherapy (ORN)
Carl and Ikner[12]	5(0)	3(0)	0(0)
Makkonen[54]	4(0)	21(0)	
Schweiger[73]	16(1)	8(1)	
Beumer et al.[9]	14(2)	48(12)	10(2)
Wildermuth and Cantril[87]	1(0)	2(0)	2(0)
Total	40(3)	53(12)	12(2)
		94 (15)	
Percentage	7.50%	22.60%	16.70%
		16%	

developed ORN (Table 11). When extraction after 2 years was further analyzed, the risk seemed to be highest in the period 2–5 years after radiotherapy.

Discussion

ORN has been a clinical problem in irradiated patients since the introduction of radiotherapy as a treatment modality for malignancy. ORN of the maxillofacial region was reported as early as 1922 by Regaud[66]. In the typical presentation, ORN starts with an exposed devitalized part of the jaw bone, later progressing to sequestrum formation, oro-cutaneous fistula[11,28] and finally to pathologic fracture[11,28,79,85]. Occasionally, the sufferer remains asymptomatic, but many complain of pain, swelling, dysaesthesia, halitosis, and dysgeusia[11,28,29,79].

The definition of ORN has not been agreed[76]. Most definitions rely on the clinical presentation of the disease, but inclusion of radiographic evidence in the diagnostic criteria has been suggested[76]. The main differences in defining the condition relate to the duration of bone exposure before the condition can be named ORN. Generally, ORN is defined as area of exposed devitalized irradiated bone that fails to heal over a period of 3–6 months with no signs of local neoplastic disease[11,28,35,56,76]. This variation in the diagnostic definition criteria for ORN has resulted in difficulties when estimating the true incidence of ORN after post-irradiation dental extraction. This has been overcome in this study by defining ORN as 'An exposed necrotic bone for more than 3 months with no signs of tumour recurrence in a previously irradiated area' for the purpose of this review.

In this review, ORN is accepted as any clinically diagnosed bone exposure of the socket of the extracted tooth that fails to heal for 3 months or longer. As the follow-up period is an essential part of diagnosing ORN, 3 months was selected as a minimum period in an attempt to avoid overestimating the occurrence of ORN. This is because exposure of bone for less than 3 months could simply be due to the delayed healing that is expected due to the compromised healing capacity of irradiated jaws. In studies reporting a follow-up period, a median/mean follow-up of more than 6 months was considered to have fulfilled this purpose. This minimum follow-up period and clinically diagnosed bone exposure should eliminate any possibility of misdiagnosis or over-estimation of the incidence of ORN. These strict criteria would give an accurate and valid estimation of the true incidence of ORN after post-irradiation extraction. Failure to comply with the minimum follow-up period criteria in the definition were the most common cause of non-validity of studies appraised in this review (Table 2).

Tooth extraction has long been considered one of the main risk factors for the development of ORN[11,20,57,79]. Some researchers found that when extraction is performed before radiation, the risk of developing ORN is higher[78] while others found post-irradiation extraction to be more risky[11,28,60,79]. Recently, the increase in dental awareness and use of fluoride has reduced the number of teeth requiring extraction after radiotherapy[39], but these efforts have not eliminated the need for extraction in the radiated population.

The exact incidence of ORN after post-irradiation extraction is unknown. By identifying articles with predefined validity criteria, the authors think that 7% is the most accurate estimate of the incidence of ORN post-extraction. The data show a downward trend of the risk of developing ORN after extraction in recent years. The incidence of ORN after post-irradiation extraction performed after 1990 was 2% compared with 16% before then. This finding can probably be attributed to significant advances in radiotherapy technology. For the risk of developing ORN per tooth extracted, only 54 sockets developed ORN after extraction of 2766 teeth. An ORN incidence of 2% per tooth extracted; so approximately 2 sockets will develop ORN after extraction of 100 teeth in radiated patients.

The pooled data show the incidence of post-extraction ORN is 3% in the mandible compared with 1% in the maxilla. The result of this review supports the finding of

most studies in the literature that the mandible has a higher risk of developing ORN compared with the maxilla[11,19,43,60,71,79]. The pattern of blood supply to the mandible has been implicated as a primary reason for this finding[37,79]. Other more simple explanations claim that the mandible is included in the radiation field more often than the maxilla[29,79,82]. It has been suggested that transection of the external maxillary artery and its branches during radical neck dissection predisposes the mandible to ORN[9]. All the evidence suggests that extraction of a tooth or teeth in the mandible should be recognized as a higher risk for developing ORN post-extraction.

HBO has a long history in the management of ORN. Suggested by MAINOUS et al. in 1973[53], it was initially used for the treatment of ORN. Marx later popularized the use of HBO based on the theory of hypoxic–hypocellular–hypovascular tissue[56]. It is said that in the hypoxic–hypocellular–hypovascular irradiated tissue, HBO as an adjunct to surgery would induce angiogenesis and increase fibroblast activity[57]. MARX et al. later suggested its use before extraction for the prevention of ORN in irradiated tissue[58]. According to the only randomized controlled trial[58], after the extraction of mandibular teeth located inside the radiation field in patients who received more than 60 Gy, ORN was prevented more effectively by HBO than by penicillin. This trial explored the use of HBO in this specific group. When HBO was used in a wider selection of patients, ORN developed in 4% of patients after prophylactic HBO, which is almost half the risk of developing ORN compared with the total ORN incidence of 7%. This finding further supports the use of HBO.

The limitation of HBO use is the long process required when applying HBO to prevent ORN. According to the protocol, 20 sessions lasting 90 min each are required before extraction[58]. This could mean 1 month of preparation before extraction. This makes it difficult to justify its use in a patient with acute pain or infection needing immediate extraction. Availability is also limited, especially outside main cities[83]. Adding the cost of the treatment further limits its possible use[83].

Another factor against the use of HBO is the associated complications. Common complications reported are middle ear barotrauma[17,83] and myopia[42]. More severe but less common complications include pneumothorax, arterial air embolism, oxygen toxicity seizure, pulmonary oxygen toxicity or acute pulmonary edema[33,47,49,83]. HBO is contraindicated in patients with chronic obstructive pulmonary disease, poorly controlled chronic heart failure or with active tumour[17], so it is not an option in many patients. With the low incidence of post-extraction ORN, one would need to consider whether it is worth taking the extra risk of complications and added cost for a small reduction in the incidence of ORN. This review indicates the effectiveness of HBO in preventing ORN in patients needing extraction, but judicious patient selection is important to maximize the benefit of HBO. Patients receiving more than 60 Gy and needing extraction of mandibular tooth/teeth within the radiated field in the absence of contraindications to HBO appear to benefit most.

Antibiotic prophylaxis for ORN has high acceptance among surgeons and patients[41] and has become a standard in managing extractions in irradiated patients. In this review, 12 articles reported the use of antibiotics pre- or postoperatively. 7 articles clearly reported the type of antibiotic used. Those most widely used were penicillin and clindamycin. The widespread use of antibiotics for prevention of ORN has not been supported by its pathophysiology. Since infectious organisms have been relegated to the role of contaminants[56] only in ORN, the use of antibiotics is questionable. It could be agreed that antibiotics are not used to prevent ORN, but to prevent infection in impaired tissue. Antibiotic prophylaxis is a normal part of preoperative preparation before extraction in the irradiated population. The pooled incidence for post-extraction ORN with the use of antibiotics is 6%.

Other preventive options such as ultrasound[68] and the use of pentoxifylline and tocopherol have been suggested[51] but no publications reporting and advocating these techniques to prevent ORN are available. Ultrasound has been suggested[68] because of its ability to induce angiogenesis in the bone[27,70]. Ultrasound has also been shown to induce fibroblast and osteoblast proliferation in irradiated tissue[27,69]. Promising results have been reported with its use for the management of established ORN[35]. Ultrasound has the advantage of being cheaper, easier to tolerate and associated with fewer complications than HBO[68].

Pentoxifylline and tocopherol have been shown to be effective when treating radiation tissue injury[23,26,32] followed by good results in the management of established ORN[24,25]. These impressive findings prompted suggestions for their combined use as a prophylaxis to prevent ORN[51]. Supported by the potential benefit achieved using pentoxifylline as prophylaxis to prevent radiation tissue injury[2,52,65], it was suggested that pentoxifylline 400 mg twice daily and tocopherol 1000 IU once daily, be given 1 week before extraction and continued for a further 8 weeks[51]. These drugs are well tolerated with few side effects, which include dyspepsia, nausea, headache or vertigo, asthenia, hot flushes, epigastralgia and allergy in some patients[2,26,32,52]. Until data on the effectiveness of these modalities for the prevention of ORN become available, physicians are limited to the traditional options of HBO and antibiotics because using HBO, ultrasound, pentoxifylline or tocopherol requires weeks of preparation, which could be an issue in cases of pain or acute infection.

Intraoperative efforts have been made to prevent ORN after extraction. Most authors suggest extraction should be performed with minimal trauma or atraumatically to reduce the risk of developing ORN[28,42,45,50,59,73,74,78,81]. Atraumatic extraction is best described as limited mucoperiosteal disruption[7,55,59] and minimal bone injury. An atraumatic extraction can be impossible in difficult cases due to tooth-root morphology, impaction or deeply retained roots. The logic behind the atraumatic approach is to preserve the integrity of the periosteum, an important source of vascularity especially in impaired tissues[7].

Alveoloplasty and suturing of the socket are commonly performed to avoid ORN[9,12,16,28,46,50,58,74,81]. This procedure attempts to trim off sharp bony spicules and provide soft tissue cover for the sockets to prevent bone exposure[3,21,75]. NIEBEL and NEENAN suggested that alveoloplasty should be done to reduce the clot size[63]. Another reason is that the alveolar ridge will not readily remodel in this compromised tissue resulting in an irregular ridge that would cause increased risk of bony exposure when wearing a denture in the future[6,14]. Limiting the number of teeth extracted per-session has been suggested to prevent ORN by avoiding overburdening the already limited blood supply[9,14,59]. Other less popular suggestions include avoiding lidocaine or adrenaline-containing local anesthesia[16,50,59], the use of a nasogastric tube during the postoperative period[39], elastic or orthodontic extraction[63,72] and chlorhexidine mouthwash[50,81]. These measures have not been supported by evidence as no specific studies have been performed to assess their effectiveness in preventing

ORN in post-radiation extraction. They are often performed simultaneously causing difficulties in assessing the benefit or harm of each of these actions individually. Future studies are needed to assess the effectiveness of these empirical efforts in preventing ORN.

The clinician responsible for tooth extraction in the irradiated population should have specific knowledge of the radiation field. This review shows that the risk of developing ORN after extraction of teeth outside the field of radiation is almost non-existent. None of the patients who had extraction outside the radiation field developed ORN compared with 3% of patients developing ORN after extractions inside the radiation field. This agrees with findings from THORN et al. who found that, of 80 consecutive ORN cases; only one patient (1%) had developed ORN outside the radiation field[79]. This indicates a great possible benefit of new radiation delivery and planning techniques such as intensity modulated radiation therapy and three-dimensional conformal radiotherapy[4,77]. Their ability to exclude the jaws from the field of radiation could eliminate the risk of ORN. This finding also suggests any extractions outside the radiation field could be performed safely.

The radiation dose is an important risk factor for the development of ORN[11,19,60,61]: the higher the dose given, the higher the risk of developing ORN[19,79,86]. This review found that none of the patients receiving less than 60 Gy developed ORN, but this finding should be accepted cautiously in view of the limited sample size available. Previous studies have shown that even though patients receiving a higher radiation dose appear to be at a higher risk of developing ORN, the risk is not absent when doses below 60 Gy were given[79,86]. Others found that the occurrence in patients receiving doses below 60 Gy is considerably higher[19]. Based on this systematic review, the risk of developing post-extraction ORN is minimal in patients receiving RT doses less than 60 Gy.

The total dose prescribed can be an indicator, albeit not an accurate one, of the risks of developing ORN after post-radiation extraction[11]. The authors think that the amount of radiation absorbed by the mandible or maxilla would be a better guide to the risk of developing ORN after tooth extraction. There are differences in the prescribed dose and the absorbed mandible dose in radiotherapy for head and neck neoplasms[40], which can explain why ORN can occur at prescribed doses of less than 60 Gy. Beside the total dose, other factors such as dose rate and fractionation could also play a role[28,29,86]. According to this review, few authors tried to use the absorbed dose to predict the occurrence of ORN after extraction[8,12,50,59]. The authors were unable to analyse the relation of absorbed dose to the occurrence of ORN due to the differences in the way the absorbed dose was reported. The prescribed dose is more readily available in the radiation records, so the clinician responsible for carrying out the extractions could use the 60 Gy threshold as an indicator of the risk of a patient developing ORN after extraction.

The authors tried to assess the importance of the time interval between extraction and completion of radiotherapy. Previous findings tended to agree that the risk of developing spontaneous ORN is higher within the first 2 or 3 years after radiotherapy[57,79]. The relation of time interval after radiotherapy to the risk of trauma-induced ORN has been more controversial. The risk of developing trauma-induced ORN remains for many years after radiotherapy[19,29,57,79]. THORN et al. discovered in a collection of 80 ORN cases that most late-onset ORN were trauma-induced with the latest one being 16 years post-radiotherapy[79]. Other researchers found a bimodal peak of incidence relating to trauma-induced ORN[19,57]. Marx and Johnson suggested that the first peak occurs within the first 3 months, which is related to trauma before or during radiation and the second starting after 2 years and peaking at 5 years[57]. This second peak is probably due to the increasing number of patients needing extraction due to tooth breakdown a few years after radiotherapy. The risk of ORN increases over time[57]. The present findings support the notion that the risk of developing ORN persists for years after radiotherapy. The period 2–5 years after radiotherapy had the highest incidence of ORN after post-radiation extraction. Further studies are needed to ascertain the relation of time interval between extraction and radiotherapy to the risk of developing ORN after extraction.

This systematic review was performed according to strict standards, but these efforts cannot mask the overall quality of the data collected. The nature of retrospective studies inevitably introduces bias. The lack of well conducted RCTs or prospective studies hampered the authors' efforts to provide more accurate analysis. The authors think that the outcome of this review is the best available valid finding on this subject at this time.

This review estimates that 7 of 100 patients undergoing post-radiation tooth extraction will develop ORN (Table 12), and that 2 of 100 teeth extracted would lead to ORN (Table 13). The risk is relatively low, especially in the last 20 years. By considering the risk factors in this review, it is possible to identify the patients at most risk and apply the best prophylaxis available to prevent ORN. The surgeon or dentist in charge of performing the extraction in this irradiated population should have access to the radiation records of each patient needing extraction under his/her care. With this knowledge of radiation dosage and radiation field, a reliable assessment of the risk of developing ORN post-extraction can be made. This review found that extraction of mandibular teeth in the radiation field after receiving more than 60 Gy represents the highest risk. Based on the current best evidence, HBO has a place in preventing ORN in high risk patients. Further studies are needed to widen the scope of use of HBO or the use of different modalities

Table 12. Summary of ORN incidence in relation to number of patients.

	Patient undergoing extraction	ORN per patient	Percentage
Total patient undergone post-radiation extraction	828	57	6.88%
Patient undergone post-radiation extraction with HBO	160	6	3.75%
Patient undergone post-radiation extraction with antibiotics	377	21	5.57%
Patient receiving more than 60 Gy	230	28	12.17%
Patient receiving less than 60 Gy	29	0	0%
Extraction within 1 year post-radiotherapy	40	3	7.50%
Extraction within 2–5 years post-radiotherapy	53	12	22.64%
Extraction after 5 post-radiotherapy	12	2	16.70%

Table 13. Summary incidence of ORN in relation to number of teeth extracted.

	Number of teeth extracted	ORN per socket	Percentage
Total teeth extracted	2766	54	1.95%
Extraction in mandible	1136	38	3.35%
Extraction in maxilla	475	5	1.05%
Extraction in radiation field	1219	42	3.45%
Extraction outside radiation field	804	0	0%
Extraction with HBO	595	10	1.68%
Extraction with antibiotics	1444	42	2.91%

with wider scope of applicability to prevent ORN.

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