Journal section: Oral Surgery
Publication Types: Review

doi:10.4317/medoral.24132

Therapeutic alternatives in the management of osteoradionecrosis of the jaws. Systematic review

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Received: 03/07/2020
Accepted: 28/09/2020

Camolesi GCV, Ortega KL, Medina JB, Campos L, Lorenzo Pouso AI, Gándara Vila P, *et al*. Therapeutic alternatives in the management of osteoradionecrosis of the jaws. Systematic review. Med Oral Patol Oral Cir Bucal. 2021 Mar 1;26 (2):e195-207.

Article Number:24132 http://www.medicinaoral.com/

eMail: medicina@medicinaoral.com
Indexed in:
Science Citation Index Expanded
Journal Citation Reports
Index Medicus, MEDLINE, PubMed
Scopus, Embase and Emcare
Indice Médico Español

Abstract

Background: to systematically review the literature, comparing the healing of osteoradionecrosis (ORN) among the therapeutic alternatives: surgical, pharmacological and combined.

Material and Methods: The review was organized according to the PRISMA protocol with regards to the following PICO question: patients with ORN of the jaws (P=Patient); all interventions reported (I = intervention); between all therapies (C=Comparison); healing of lesions (O=outcome).

Results: Surgical treatment was the most common choice (46.3%) followed by pharmacological treatment, exclusively (25.9%) or combined (26.9%). Treatment exclusively by surgical intervention seems to be most effective option, with 51.2% of the lesions healed, OR for healing of 5.7 (CI95% 1.9-16.9, p=0.002). Only 1 case (0.9%) corresponded to low level laser therapy.

Conclusions: It seems clear that early intervention with conservative surgical combined with pharmacological methods improves the prognosis of ORN.

Key words: *Osteoradionecrosis, radiotherapy bone necrosis, hyperbaric oxygen, pentoxifylline, teriparatide, low level laser therapy.*

Introduction

Radiotherapy (RT) alone or in combination with chemotherapy or surgery is an established form of therapy for the treatment of head and neck cancer (1). Nonetheless, it has significant limitations due to its short-term (such as mucositis, dry mouth and loss of taste) and long-term (subcutaneous soft-tissue fibrosis, neck muscle atrophy, swallowing abnormality, carotid damage, trismus, radiation caries, and osteoradionecrosis (ORN) side effects (2,3). Despite the use of 3D conformal RT (3D-CRT) and Intensity Modulated RT (IMRT), ORN of the jaws remains one of the most common resulting complications(4,5). The reported incidence of ORN in the population of irradiated head and neck patients is rather variable, ranging from 4.7% to 37.5% and it is considered a late event, with the vast majority of cases occurring in the first 3 years following treatment (6,7).

ORN can occur spontaneously due to genetic factors related to the TGF-β1 gene (8), or it can be the result of trauma (tooth extraction and denture-related irritations are common causes). Due to its low vascular nature and thicker cortical, mandibular ORN is more common than maxillary ORN (9-13). It is defined as irradiated and exposed bone tissue which fails to heal over a period of 3 months, without the presence of a residual or recurrent tumour (9,10,14,15). Although ORN can be observed without presenting bone exposure (16), normally clinically, it can range from a small area of intraoral bone exposure to extraoral fistulas and even pathological fractures. Pain, swelling, difficulties in mastication, paresthesia and facial deformities are possible sequelae of ORN and these have a significant impact on quality of life (7,17).

The pathogenesis of ORN remains unknown. Marx's initial proposal -the theory of hypoxia, hypovascularity and hypocellularity (3 Hs) leading to a non-healing wound- has recently been questioned, and likewise, it has not been supported by the results of several subsequent studies (9,18,19). In 2004, Delanian (20) proposed the radiation-induced fibroatrophic process (RIF) theory, which includes the formation of free radicals, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis, remodelling, and eventually bone and tissue necrosis.

The chosen treatment is based on the stage of the disease, as well as patient-related factors, however, the cure actually is not the desired outcome in the treatment of ORN, it is the abolition of symptoms and progression that is the goal. Several therapies have already been reported which have led to widespread opinions, nonetheless, there is still no universally accepted approach. More traditional or early-stage approaches include conservative treatments with oral hygiene control; hyperbaric oxygen (HBO) (prophylactically or therapeutically); the use of antibiotics over a variable period of time (although ORN is not an infectious process per se); and surgical debridement. Surgical management may be classified into minor and major procedures (21). In order to achieve satisfactory results, cases which do not respond to conservative treatment choices or those which present more advanced stages are treated with surgical resection, with or without the reconstruction of vascularised tissue(21). All of these treatments were guided mainly by Marx's theory (9). More recently and in light of the pathophysiology of the disease proposed by Delanian (20), pharmacological treatment with pentoxifylline-tocopherol with or without clodronate (PENTOCLO) (22), teriparatide (23) and low-level laser therapy (LLLT) (24) have been introduced.

Therefore, the aim of this paper is to systematically review the literature, comparing the healing of ORN with all the reported therapies: surgical, pharmacological and combined.

Material and Methods

- Protocol and registration

The design of this study was registered in PROSPERO (Ref. 159983). This review was carried out following the PRISMA guidelines and according to the PICO method (25): patients with ORN of the jaws (P=Patient); all interventions related (I = intervention); between all therapies (C=Comparison); healing of lesions (O=outcome).

- Selection criteria, sources of information and search

We conducted a bibliographic search in PubMed, Web of Science, Scopus, LiLACS, OVID, EMBASE, Cochrane Library, Clinical Trials, the five WHO regional bibliographic databases (AIM, LILACS, IMEMR, IMSEAR, WPRIM), and the Conference Proceedings Citation Index in order to identify relevant studies on ORN of the jaws between the first records found in the database and November 2019.

Inclusion criteria: All of the articles on case series, case reports, cohort studies, and case and control studies with no language limitation were included.

Exclusion criteria: Articles which do not deal with RT-induced osteonecrosis; unavailable abstract; complete maxillectomy; other systematic reviews; studies that have not been conducted on humans.

Selection of studies: Two independent researchers, MPS and GCVC, analysed the abstracts of the articles obtained in the search which had met the search criteria, that is to say, texts that dealt with patients with ORN of the jaws and their management. Both of the researchers subsequently read the full article in order to determine whether or not it met the inclusion criteria. A third researcher, LC, acted as a mediator in the case of any disputes.

Data collection process: Data from all the articles was collected by both researchers independently (in duplicate) and this data was corroborated by the third party who acted as a mediator in case of discrepancy or lack of agreement.

- Study variables

The following information was extracted from each study: First author, year of publication, type of study, location of cancerous lesion, dose used in RT, management of the lesion (surgical, pharmacological or combined), location (maxilla, jaw), region (anterior, posterior), quantity (single, multiple), and also the time from the end of RT to the diagnosis of ORN, time until healing, maximum follow-up time, and finally whether or not there were any recurrences.

- Risk of bias

The methodological quality and the risk of bias of the included studies were assessed using the Newcastle-Ottawa scale (NOS)(26). For studies, cohorts and cases and controls, which amounted to 4.6% of the included studies, the original NOS scale was used, and for the remaining 95.4%, that is to say, the case series and case report studies, Pierson and Bradford Hills' modified NOS scale (27) was used. This analysis was carried out independently by each of the two researchers and in the case of any disagreements the third researcher acted as a mediator.

- Statistical analysis

All of the variables were collected in a database and were analysed with SPSS v. 24.0 (IBM Inc., Madrid, Spain). Basic descriptive statistics were used for the univariate description, these included the mean, standard deviation, frequency and percentage. The relationship between the different categorical variables and healing was evaluated using Pearson's Chi-square. The relationship between the healing and the type of treatment and the quantitative variables was studied by using the ANOVA test to compare the means. The influence of the treatment type on the progression of ORN was assessed by using a univariate logistic regression analysis. The significance level was established at $p \leq 0.05$.

Results

The search process involved a total of 3,861 articles. After removing duplicates, 2,722 articles remained; of these 1,769 were subsequently excluded because they did not meet the inclusion criteria (Fig. 1). After fully reading the 542 articles, it was determined that 110 studies met all of the inclusion criteria and these were included.

Four of the articles were rated as high quality (3.6%), 103 as medium quality (93.6%), and 3 as low quality (2.7%) (Table 1). The summary of the data of all of the patients that was extracted from the studies is depicted in Table 2, and the full descriptive results can be found in Table 3.

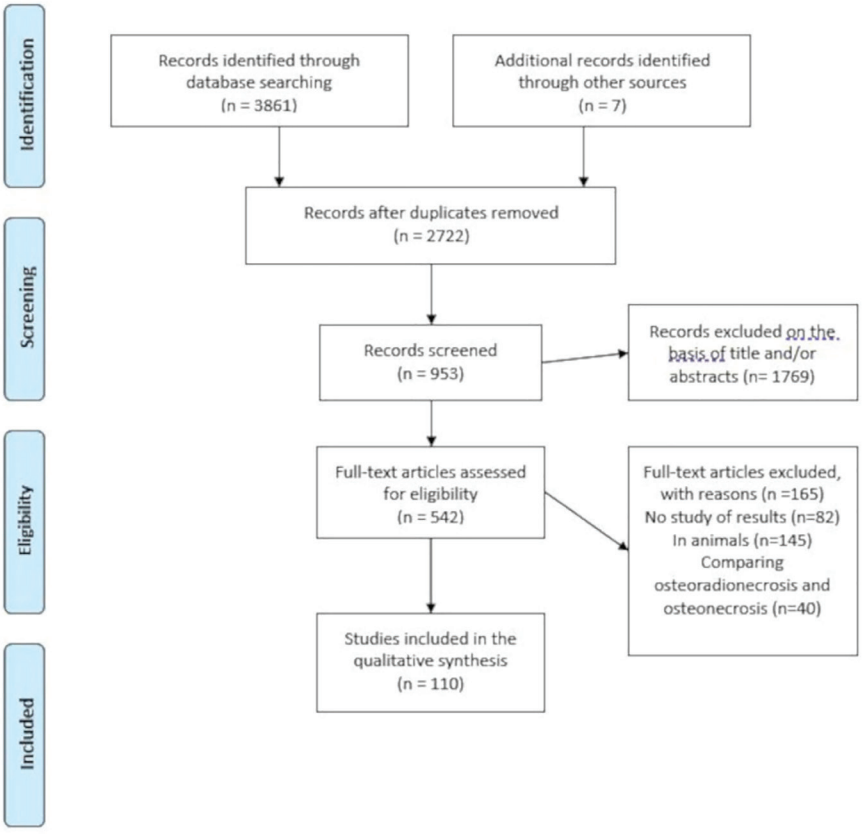

Fig. 1: PRISMA flow diagram.

Table 1: Classification of the studies in terms of risk of bias according to the NOS scale.

Author	Year	Number of Patients	Assessment
Alam *et al.*	2009	33	Medium
Ang *et al.*	2003	21	Medium
Baron *et al.*	2016	5	Medium
Baumann *et al.*	2010	63	Medium
Beech *et al.*	2016	1	Medium
Bettoni *et al.*	2019	11	Medium
Bettoni *et al.*	2019	49	Medium
Bianco *et al.*	2019	8	Medium
Bohn *et al.*	2015	3	Medium
Bouguila *et al.*	2015	22	Medium
Breik *et al.*	2019	2	Medium
Cannady *et al.*	2010	53	Medium
Cha *et al.*	2018	2	Medium
Chandarana *et al.*	2013	12	Medium
Chang *et al.*	2001	29	Medium
Chang *et al.*	2011	35	High
Chen *et al.*	2014	153	Medium
Chen *et al.*	2016	105	High
Chen *et al.*	2018	1	Medium
Chen *et al.*	2019	1	Medium
Chiapasco *et al.*	2006	59	Medium
Choi *et al.*	2014	1	medium
Chronopoulos *et al.*	2015	115	Medium
Coskunfirat *et al.*	2004	12	Medium
Curi *et al.*	1997	104	Medium
Curi *et al.*	2000	18	Medium
Curi *et al.*	2007	5	Medium
D'Hauthuille *et al.*	2008	59	Medium
Dai *et al.*	2015	120	Medium
Danielsson *et al.*	2019	17	Medium
David *et al.*	2001	51	Medium
De Felice *et al.*	2016	36	Medium
Delanian *et al.*	2005	18	Medium
Delanian *et al.*	2011	54	Medium
Dieleman *et al.*	2017	27	Medium
Dissard *et al.*	2019	27	Medium
D'Souza *et al.*	2007	23	Medium
D'Souza *et al.*	2009	58	Low
D'Souza *et al.*	2014	71	Medium
Epstein *et al.*	1997	26	Medium
Etezadi *et al.*	2013	1	Medium
Fan *et al.*	2016	31	Medium
Freiberger *et al.*	2009	65	Medium
Gal *et al.*	2003	30	Medium
Gallegos *et al.*	2015	25	Medium
Gallesio *et al.*	2015	10	Medium
Gavriel *et al.*	2017	21	Medium
Gevorgyan *et al.*	2013	14	Medium
Gupta *et al.*	2013	33	Medium
Haffey *et al.*	2019	8	Medium
Hamilton *et al.*	2012	14	Medium
Harris M *et al.*	1992	24	Medium
Hayashi *et al.*	2015	13	Medium
Hirsch *et al.*	2008	305	High

Table 1 cont.: Classification of the studies in terms of risk of bias according to the NOS scale.

Ioannides *et al.*	1994	28	Medium
Jacobson *et al.*	2010	1	Medium
Jenwitheesuk *et al.*	2018	84	Medium
Jisander *et al.*	1999	8	Medium
Kahenasa *et al.*	2012	1	Medium
Kildal *et al.*	2001	1	Medium
Kim *et al.*	2016	8	Medium
Kobayashi *et al.*	2000	4	Medium
Kraeima *et al.*	2018	3	Medium
Kumar *et al.*	2018	25	Low
LaDow C.S *et al.*	1950	1	Medium
Lyons *et al.*	2013	30	Medium
Magremanne M *et al.*	2018	1	Medium
Mainous *et al.*	2015	1	Low
Mainous *et al.*	2014	2	Medium
Man *et al.*	1975	14	Medium
Manimaran *et al.*	1973	1	Medium
Manzano *et al.*	2019	20	Medium
Manzon *et al.*	2015	2	Medium
Mao *et al.*	2004	11	Medium
Marwan *et al.*	1983	58	Medium
Marx RE *et al.*	2017	150	Medium
Mc Leod *et al.*	2012	12	Low
Milani *et al.*	2019	1	Medium
Militsakh *et al.*	2005	9	Medium
Moran *et al.*	1987	1	Medium
Mounsey *et al.*	1993	41	Medium
Mücke *et al.*	2013	94	Medium
Nabil *et al.*	2012	10	Medium
Nakatsuka *et al.*	1996	9	Medium
Notani *et al.*	2003	87	Medium
Oh *et al.*	2009	114	Medium
Ohba *et al.*	2013	12	Medium
Patel *et al.*	2016	62	Medium
Piccin *et al.*	2016	1	Medium
Pinto *et al.*	2017	21	High
Porcaro *et al.*	2015	1	Medium
Reuther *et al.*	2003	68	Medium
Ribeiro *et al.*	2018	20	Medium
Robard *et al.*	2014	27	Medium
Rommel *et al.*	2018	15	Medium
Santamaria *et al.*	1998	12	Medium
Scala *et al.*	2010	1	Medium
Shaha *et al.*	1998	6	Medium
Shan *et al.*	2015	5	Medium
Shimizu *et al.*	2012	2	Medium
Southerland *et al.*	1993	1	Medium
Suh *et al.*	2010	40	Medium
Sullivan e*t al.*	1989	17	Medium
Teixeira *et al.*	1991	8	Medium
Van Merkesteyn *et al*	1994	1	Medium
Van Merkesteyn *et al.*	1995	29	Medium
Vudiniabola *et al.*	2000	14	Medium
Wong *et al.*	1997	32	Medium
Woo *et al.*	2016	1	Medium
Young *et al.*	2016	4	Medium

Table 2: Descriptive summary of all of the articles.

Author	Year	Location of the cancerous lesion	RT dose (Gy)	ORN management	ORN location	ORN region	ORN lesions	Time from RT to ORN months	Healing	Follow-up time months	ORN recurrences
Alam *et al.*	2009	1,3,5,6,9	-	Surgical	Jaw	Anterior and Posterior	Multiple	47	No	-	Yes
Ang *et al.*	2003	3,6,7,9,10	60	Combined	Multiple	-	Single	48	No	79	Yes
Baron *et al.*	2016	12,1,9,4,2	-	Surgical	Jaw	Anterior and Posterior	Multiple	63.6	Yes	48	No
Baumann *et al.*	2011	-	66.5	Surgical	Jaw	Anterior and Posterior	Multiple	-	Yes	72	No
Beech *et al.*	2016	2	-	Surgical	Jaw	Posterior	Single	60	Yes	-	No
Bettoni *et al.*	2019	1,13,8,7,2	-	Surgical	Jaw	-	Single	48.5	Yes	83	No
Bettoni *et al.*	2019	-	63.6	Combined	Jaw	Anterior and Posterior	Multiple	57	No	-	Yes
Bianco *et al.*	2019	7,14,9,15,16,8	78	Pharmacological	Multiple	-	Multiple	23.2	Yes	12	No
Bohn *et al.*	2016	4,13,2	55.4	Pharmacological	Jaw	Anterior and Posterior	Multiple	72	Yes	12	No
Bouguila *et al.*	2015	5,13	72	Combined	-	-	-	48	Yes	-	No
Breik *et al.*	2019	9,2	70	Pharmacological	Jaw	Posterior	Single	10	Yes	-	No
Cannady *et al.*	2011	3,8	-	Surgical	Multiple	-	Single	-	Yes	-	No
Cha *et al.*	2018	2	60	Pharmacological	Jaw	Posterior	Single	180	Yes	-	No
Chandarana *et al.*	2013	-	-	Surgical	-	-	-	-	Yes	-	No
Chang *et al.*	2001	8, 2, 9, 7, 4, 16, 18, 15	67.7	Surgical	Jaw	-	Single	-	Yes	-	No
Chang *et al.*	2011	13, 20, 4, 2, 19, 16, 15,9	67.4	Surgical	Jaw	-	Single	46	Yes	36	No
Chen *et al.*	2014	-	87.4	Surgical	Jaw	-	Single	29.8	Yes	-	No
Chen *et al.*	2016	13, 20, 4, 2, 19, 16, 15, 9	74	Combined	Jaw	Posterior	Multiple	72	Yes	8	No
Chen *et al.*	2018	5	-	Surgical	-	-	-	-	Yes	-	No
Chen *et al.*	2019	2	72	Pharmacological	Multiple	Anterior and Posterior	Multiple	60	Yes	-	No
Chiapasco *et al.*	2006	11,2,4,10	53.5	Surgical	Multiple	Anterior and Posterior	Single	-	Yes	120	No
Choi *et al.*	2014	9	-	Surgical	Multiple	-	Single	84	Yes	-	No
Chronopoulos *et al.*	2015	4,2,6	63.4	Combined	Jaw	Anterior and Posterior	Single	-	No	-	Yes
Coskunfirat *et al.*	2004	5,3,10,2,21	65	Surgical	Multiple	-	Multiple	-	Yes	62	No
Curi *et al.*	1997	13, 2, 20, 4, 16, 15, 8, 5, 6, 7, 22	60	Combined	Multiple	-	Single	18	No	12	Yes
Curi *et al.*	2000	13, 2, 20, 4, 16, 15, 8, 9	6.2	Pharmacological	Multiple	-	Single	27.9	Yes	24.8	No
Curi *et al.*	2007	2,16,4	65	Surgical	Jaw	Anterior and Posterior	Single	45.6	Yes	-	No
D'Hauthuille *et al.*	2008	-	-	Surgical	Jaw	Anterior and Posterior	Single	-	Yes	-	No
Dai *et al.*	2015	2, 23, 4, 11, 10, 20, 16, 6, 22	68.1	Surgical	Multiple	Anterior and Posterior	Multiple	36	No	-	Yes
Danielsson *et al.*	2019	9,1,2,19,12	68	Surgical	Jaw	-	Single	37.2	No	12	Yes
David *et al.*	2001	2, 4, 16, 8, 19, 5, 11	51.8	Pharmacological	Jaw	-	Single	32	No	108	Yes
De Felice *et al.*	2016	3, 8, 7, 22, 28, 29	66.3	Combined	Multiple	Anterior and Posterior	Multiple	6	No	-	Yes
Delanian *et al.*	2005	3,8	65	Pharmacological	Jaw	Posterior	Single	7.25	Yes	-	No
Delanian *et al.*	2011	3,8	62.5	Pharmacological	Jaw	-	Single	15.5	Yes	36	No
Dieleman *et al.*	2017	4, 1, 2, 15, 14	60	Combined	Jaw	-	-	36	Yes	24	No
Dissard *et al.*	2019	2, 4, 3, 8, 18	65	Pharmacological	Jaw	Anterior and Posterior	Multiple	87.5	Yes	24	No

Table 2 cont.: Descriptive summary of all of the articles.

D'Souza *et al.*	2007	3, 8, 7, 18	64	Combined	Jaw	-	Single	48	Yes	30	No
D'Souza *et al.*	2009	-	-	Pharmacological	-	-	-	-	Yes	-	No
D'Souza *et al.*	2014	3, 8, 7, 18	64	Combined	Jaw	-	Single	25	Yes	69	No
Epstein *et al.*	1997	9	-	Combined	-	-	-	50	No	123	Yes
Etezadi *et al.*	2013	-	70	Surgical	Jaw	Posterior	Multiple	-	Yes	-	No
Fan *et al.*	2016	5, 4, 15, 2, 17, 8, 1, 9, 16, 7, 22	76.3	Surgical	Jaw	-	-	-	Yes	72	No
Freiberger *et al.*	2009	1, 12, 18	67.5	Combined	Jaw	Anterior and Posterior	Multiple	73.3	Yes	56	No
Gal *et al.*	2003	-	-	Combined	Jaw	-	Single	-	No	-	Yes
Gallegos *et al.*	2015	2, 9, 7, 8	-	Pharmacological	Jaw	Posterior	Single	24	No	36	Yes
Gallesio *et al.*	2015	22, 14, 16, 28, 30	-	Surgical	Multiple	-	Single	-	Yes	12	No
Gavriel *et al.*	2017	9, 2, 15, 18, 16, 19	53	Pharmacological	Multiple	-	Single	12	Yes	25.2	No
Gevorgyan *et al.*	2013	2, 4, 16, 7, 8, alveolus	-	Combined	Jaw	-	Single	26.9	No	26	Yes
Gupta *et al.*	2013	N/R	60	Pharmacological	Jaw	-	Single	7.5	Yes	12	No
Haffey *et al.*	2019	2, 1,9, 18	-	Surgical	Jaw	Posterior	Multiple	-	Yes	63	No
Hamilton *et al.*	2012	-	65	Combined	Jaw	Posterior	Multiple	19.8	Yes	-	No
Harris M *et al.*	1992	-	61.9	Surgical	Jaw	Anterior and Posterior	Single	-	Yes	-	No
Hayashi *et al.*	2015	2, 4, 16, 3, 11, 20, 8, 5, 18, 12	60	Pharmacological	Multiple	Anterior and Posterior	Multiple	-	No	-	Yes
Hirsch *et al.*	2008	-	66.5	Surgical	Jaw	Anterior and Posterior	Single	-	Yes	-	No
Ioannides *et al.*	1994	2, 4, 9, 20, 18	65	Surgical	Jaw	Anterior and Posterior	Multiple	-	Yes	84	No
Jacobson *et al.*	2010	-	-	Surgical	Jaw	Posterior	Multiple	-	Yes	-	No
Jenwitheesuk *et al.*	2018	5, 3 , 23	-	Pharmacological	Jaw	-	Multiple	-	Yes	6	No
Jisander *et al.*	1999	-	62.5	Combined	Jaw	Posterior	Multiple	119	Yes	93	No
Kahenasa *et al.*	2012	9, 1	70	Pharmacological	Jaw	Posterior	Single	6	Yes	-	No
Kildal *et al.*	2001	28	72	Surgical	Jaw	Posterior	Multiple	84	Yes	-	No
Kim *et al.*	2016	5, 19,12,18	71	Surgical	Jaw	Anterior and Posterior	Single	-	Yes	85	No
Kobayashi *et al.*	2000	2, 19,8	90	Surgical	Jaw	Posterior	Single	-	Yes	41	No
Kraeima *et al.*	2018	4	61	Combined	Jaw	Posterior	Single	11.5	No	-	Yes
Kumar *et al.*	2018	1, 4, 9, 2, 11, 7, 10	62	Surgical	Multiple	Anterior and Posterior	Single	48	Yes	-	No
LaDow C.S *et al.*	1950	9	51	Surgical	Jaw	Posterior	Single	36	Yes	-	No
Lyons *et al.*	2013	4, 2, 16, 31, 14, 10, 3, 8, 18, 15	62	Surgical	Multiple	-	-	-	No	-	No
Magremanne M *et al.*	2018	8	70	Pharmacological	Jaw	Posterior	Single	42	Yes	6	No
Mainous *et al.*	1973	4	80	Pharmacological	Jaw	Anterior and Posterior	Single	17	Yes	-	No
Mainous *et al.*	1974	2, 4, 20, 9, 15	70	Pharmacological	Jaw	Anterior and Posterior	Single	-	Yes	-	No
Man *et al.*	2015	14, 11	60	Surgical	Jaw	-	Single	-	Yes	-	No
Manimaran *et al.*	2014	16, 9	-	Combined	Jaw	Posterior	Single	36	Yes	24	No
Manzano *et al.*	2019	4, 5, 14, 19, 8, 1	60.1	Combined	Multiple	Anterior and Posterior	Multiple	6.5	No	-	Yes
Manzon *et al.*	2015	11	55	Surgical	Jaw	-	Single	-	Yes	-	No

Table 2 cont.: Descriptive summary of all of the articles.

Mao *et al.*	2004	-	-	Surgical	-	-	-	-	Yes	-	No
Marwan *et al.*	2017	1, 8, 4, 23	-	Surgical	-	-	-	-	Yes	-	No
Marx RE *et al.*	1983	-	-	Combined	Jaw	Anterior and Posterior	Single	-	Yes	-	No
Mc Leod *et al.*	2012	2	-	Pharmacological	-	-	Single	40	Yes	-	No
Milani *et al.*	2019	23, 3, 8, 29	-	Pharmacological	Jaw	Posterior	Single	60	Yes	12	No
Militsakh *et al.*	2005	1	71	Surgical	Jaw	Anterior and Posterior	Single	-	Yes	67	No
Moran *et al.*	1987	2, 4,19	55	Surgical	Jaw	Anterior and Posterior	Single	14	Yes	-	No
Mounsey *et al.*	1993	4, 2, 10	47.5	Pharmacological	Jaw	Anterior and Posterior	Multiple	39	No	-	Yes
Mücke *et al.*	2013	5, 2	69.3	Combined	Multiple	-	Multiple	-	No	12	Yes
Nabil *et al.*	2012	2, 8	-	Surgical	Multiple	Anterior and Posterior	Multiple	-	No	48	Yes
Nakatsuka *et al.*	1996	2, 22, 20, 13, 19	80	Surgical	Jaw	Anterior and Posterior	Multiple	-	Yes	61	No
Notani *et al.*	2003	2, 4, 15, 9, 19, 14, 6, 5, 121, 18, 13	90	Combined	Jaw	-	Single	-	Yes	444	No
Oh *et al.*	2009	2, 8, 16, 10	8.4	Combined	Jaw	-	Single	33	No	372	Yes
Ohba *et al.*	2013	8, 3, 6, 5	64	Pharmacological	Jaw	Anterior and Posterior	Single	13	Yes	30.3	No
Patel *et al.*	2016	8	-	Pharmacological	Jaw	-	Single	-	Yes	-	No
Piccin *et al.*	2016	4, 2, 8, 15	70	Combined	Jaw	Posterior	Single	-	Yes	-	No
Pinto *et al.*	2017	16	65.6	Surgical	Jaw	-	Single	-	No	40	Yes
Porcaro *et al.*	2015	2, 4, 14, 9, 16, 7, 13, 28	90	Surgical	Maxilla	Posterior	Single	24	No	12	Yes
Reuther *et al.*	2003	-	60	Combined	Multiple	-	Single	13	No	-	Yes
Ribeiro *et al.*	2018	3, 8	72	-	Multiple	Anterior and Posterior	Single	24	Yes	-	No
Robard *et al.*	2014	4, 27, 11, 9, 23, 8, 2	95	Surgical	Jaw	Anterior and Posterior	Single	60	Yes	-	No
Rommel *et al.*	2018	15, 16, 5, 12, 2, 4, 19	-	Surgical	Jaw	-	-	-	Yes	-	No
Santamaria *et al.*	1998	2	60. 35	Surgical	Jaw	Anterior and Posterior	Single	13	Yes	45	No
Scala *et al.*	2010	2, 1, 4	66	Pharmacological	Jaw	-	Multiple	48	Yes	24	No
Shaha *et al.*	1998	5, 8, 2	69.5	Surgical	Jaw	Anterior and Posterior	Single	104.5	Yes	80	No
Shan *et al.*	2015	5	66	Surgical	Jaw	Posterior	Multiple	104.5	Yes	90	No
Shimizu *et al.*	2012	2, 4	63	Surgical	Jaw	Anterior and Posterior	Single	48	Yes	-	No
Southerland *et al.*	1993	-	84	Combined	Jaw	Posterior	Multiple	-	Yes	-	No
Suh *et al.*	2010	-	-	Surgical	Jaw	-	Single	-	No	17.4	Yes
Sullivan e*t al.*	1989	2, 1, 17	-	Surgical	Jaw	-	-	-	Yes	15	No
Teixeira *et al.*	1991	18	78.3	Combined	Jaw	-	Single	-	Yes	-	Yes
Van Merkesteyn *et al*	1994	4, 2, 16, 15, 19, 9, 5, 13, 18, 26	67	Combined	Jaw	Posterior	Multiple	2	Yes	6.5	No
Van Merkesteyn *et al.*	1995	-	75	Combined	Jaw	-	Single	72	No	84	Yes
Vudiniabola *et al.*	2000	4, 2, 20, 14, 16, 9, 15, 8, 24, 7, 25	58	Combined	Multiple	-	Single	183	Yes	156	No
Wong *et al.*	1997	9	64	Pharmacological	Multiple	Anterior and Posterior	Single	-	Yes	36	No
Woo *et al.*	2016	-	72	Surgical	Jaw	Posterior	Single	-	Yes	-	No
Young *et al.*	2016	-	-	Pharmacological	-	-	-	-	Yes	-	No

Location of the cancerous lesion: 1.Base of the Tongue, 2.Tongue, 3.Oral cavity, 4. Floor of the mouth, 5.Nasopharynx, 6.Hypopharynx, 7.Larynx, 8.Oropharynx, 9.Amygdalin fossa, 10.Maxilla, 11.Jaw, 12.Submandibular gland, 13.Lips, 14.Alveolar ridge, 15.Retromolar trigone, 16.Soft palate, 17.Hard palate, 18.Parotid gland, 19.Oral mucosa, 20.Gingiva, 21.Nasolacrimal conduct, 22.Maxillar sinus, 23.Cheek, 24.Epiglottis, 25.Pyriform sinus, 26.Sublingual gland, 27.Uvula, 28.Minor salivary glands, 29.Major salivary glands, 30.Thyroid, 31. Tonsil.

Table 3: Descriptive summary of extracted categorical variables.

Variable		**N**	**%**
Treatment group	Surgical medical treatment	109	99.08
	LLLT	001	0.92
Treatment type	SURGICAL	051	46.8
	PHARMACOLOGICAL	028	25.6
	COMBINED	030	27.6
Surgical treatment	FREE FLAP	053	60.2
	PEDICULATED SOFT TISSUE	006	6.8
	ARTIFICIAL DERMAL SKIN	001	1.1
	DEBRIDEMENT	020	22.7
	BLOCK GRAFT	001	1.1
	SEGMENTAL OSTEOTOMY	007	7.9
	Total	088	100.0
Pharmacological treatment and hyperbaric medicine	PENTOCLO	005	8.5
	PENTOXIFYLLINE	006	10.2
	ANTIBIOTICS AND ANTISEPTICS ALONE	002	3.4
	PRGF	005	8.5
	HBO	033	55.9
	OZOSAN	002	3.4
	TERIPARATIDE	002	3.4
	COMBINED (2 OR MORE)	003	5.2
	Total	058	100.0
ORN Location	JAW	079	71.8
	MAXILLA	002	1.8
	MULTIPLE	020	18.2
	NOT SPECIFIED	009	8.2
	Total	110	100.0
Mandibular region	POSTERIOR	025	22.7
	ANTERIOR-POSTERIOR	037	33.6
	NOT SPECIFIED	048	43.6
	Total	110	100.0
Number of lesions	SINGLE	068	61.8
	MULTIPLE	028	25.5
	NOT SPECIFIED	014	12.7
	Total	108	100.0
Healing	NO HEALING	026	23.6
	HEALING	084	76.4
	Total	109	100.0

With regards to the characteristics of the ORN found, 9 (8.2%) of the articles did not specify the location of the lesion. Out of the 81 articles with a single lesion, 2 of them presented in the maxilla (1.8%), 79 in the jaw (71.8%), and 20 (18.2%) presented in both jaws. With regards to the number of lesions, 61.8% of the articles described single lesions, 25.5% described multiple simultaneous lesions, and in 12.7% of the articles this was not specified. In 22.7% of the cases, the lesions appeared solely in the posterior region, however in 33.6% of the cases these appeared both in the anterior and posterior sectors.

As far as the mean onset time, there was a significant variability in with a range from 2 months to 183 months, however the mean was 45.7 months (SD=36.2), that is to say 3.8 years. Evidently the appearance of the lesions depends on the maximum follow-up time, which, in this systematic review was broad and variable, ranging from 6 to 444 months, with a mean of 58.9 months (SD=76.5).

In terms of the therapeutic alternatives used, the surgical treatment was the most common choice representing 45.5% of cases, and pharmacological treatment, exclusively or combined, was the least common, with 26.1% and 28.4% of cases respectively. Only one study, that is to say 0.90% corresponded to the treatment of ORN by LLLT. Radical surgical treatment with free flap was the most used surgical alternative in 60.2% of the cases, followed by debridement (curettage and/or sequestrectomy or marginal resection) in 22.7%. In terms of exclusively pharmacological treatments, HBO accounted for 58.3%, followed by the use of pentoxifylline, with or without clodronate in 21.6% of the cases. The systematic review shows an overall healing of 77.2% of the lesions.

The healing of the ORN lesions is understood as the absence of relapse during the follow-up period, which as shown before, is very variable. This healing appears to vary depending on the type of treatment performed. Out of 88 cases which were treated by surgical intervention, only 73.7 % of the cases were cured, and likewise, 70.0% of the 60 cases, which were treated by pharmacological means were cured. Broadly speaking, treatment exclusively by surgical intervention seems to be effective option, with 51.2% of the lesions healed, whereas only 28.6% of the lesions of patients who were treated exclusively by pharmacological means, and 17.9% of the lesions in patients who underwent combined medical-surgical treatment (p=0.002) were healed. In the study conducted with LLLT therapy combined with antimicrobial photodynamic therapy (aPDT), 20 patients were treated and 100% of the patients were cured.

Statistically significant differences between healing and the type of surgical treatment were not observed, however, as we can see in Table 4, statistically significant differences were observed when using pharmacological treatment, Table 4. Pentoxifylline with/without clodronate made a major and significant contribution to the healing in 84,6 % of the cases where was used, with HBO healed in 62.8 % of the cases, whereas other alternatives, such as the exclusive use of antibiotics/anti-inflammatories/antiseptics failed in 100 % of the patients (p=0.043). By performing a binomial logistic regression analysis, we verified that the type of treatment is the only statistically significant factor related to healing. Therefore, taking the combined medical-surgical treatment as a reference, exclusive surgical treatment shows an OR for healing of 5.7 (CI95% 1.9-16.9, p=0.002) and 5.7 for pharmacological treatment (CI95% 1.5-20.2, p=0.009). Given that only one study was treated with LLLT, this has been excluded from the equation.

Table 4: Comparison of the healing process according to the different types of treatment gathered for ORN. AAA (Antibiotics, anti-inflammatories, antiseptics); PRGF (platelet rich growth factor).

Free flap	**Surgical treatment**						**Total**	***p* value**
	Pediculated soft tissue	**Artificial dermal skin**	**Debridement**	**Block graft**	**Segmental Osteotomy**			
NO HEALING	12 (52.2%)	2 (8.7%)	0	6 (26.1%)	0	3 (13.0%)	23 (100.0%)	**0.811**
HEALING	41 (63.1%)	4 (6.2%)	1 (1.5%)	14 (21.5%)	1 (1.5%)	4 (6.2%)	65 (100.0%)	
Total	53 (60.2%)	6 (6.8%)	1 (1.1%)	20 (22.7%)	1 (1.1%)	7 (7.9%)	88 (100.0%)	
Pentoxifylline	**Pharmacological treatment**						**Total**	***p* value**
	AAA	**PRGF**	**HBO**	**Teriparatide**	**Combined**			
NO HEALING	2 (11.1%)	2 (11.1%)	0	13 (72.2%)	0	1 (5.5%)	18 (100.0%)	**0.043**
HEALING	11 (26.2%)	0	5 (11.9%)	22 (52.4%)	2 (4.8%)	2 (4.8%)	42 (100.0%)	
Total	13 (21.6%)	2 (3.3%)	5 (8.3%)	35 (58.3%)	2 (3.3%)	3 (5.0%)	60 (100.0%)	

Discussion

ORN is a serious complication which is difficult and expensive to treat (21). In order to manage the disease in its early stages, the treatment must be conservative. The authors recommend oral hygiene, optimisation of the nutritional condition and a multidisciplinary management, which includes minor surgery, how the dental extraction, or debridement of the necrotic tissue and antibiotics (28).

In the 1960s, after its implementation by Marx (9), HBO began to be used as an additional treatment for ORN, as a complement for soft tissue flaps and in the management of radiated tissues. Although HBO initially showed promising results in the treatment of ORN (11), today's literature shows very disparate results in the use of this technique (29).

In the advanced stages or recurrences of the disease, a surgical reconstruction of the jaw is performed by means of the surgical resection and immediate transfer of the tissue to the disease, especially in stage III (30). The reconstruction of a free flap in the radiated jaw is difficult. The identification and dissection of the receiving vessels can be arduous and it requires for vessels to be selected from outside of the radiated field, generally from the contralateral neck (13).

Furthermore, it is an expensive procedure, due to hospital stay (21). Recently factors like appearance, swallowing, and chewing that interfere with the quality of life were analyzed and showed that the approach with adequate debridement, resection, and reconstruction may greatly improve QOL (31). The surgical treatments identified in the studies include sequestrectomy and debridement (32), free flap (33), pediculate soft tissue (34) and block grafting (35).

In this review, 21.6% of the studies presented ORN cases, which were treated with pentoxifylline and PENTOCLO. This management is used in both the early and advanced stages of the disease. The combined medical therapy showed a recovery rate of 88.9 % in the 13 presented studies, and in just 11.1 % of them (2 studies), the disease progressed and subsequent surgery was necessary for healing. Some of these studies presented patients whose recovery had already failed with other conservative therapies, such as the study conducted by Delanian (22), in which 16 out of 18 patients completely recovered and, out of these, 14 were fully recovered within 7 months. In 2011 (36), a subsequent study conducted by the same researchers on refractory ORN of the jaw treated by means of HBO and surgical intervention, studied the combination of pentoxifylline and vitamin E, together with clodronate, antibiotics and steroids as treatment. All of the patients (100 %) presented with a complete regression of the exposed bone and were fully recovered within 2 years after treatment, with 50 % of the patients recovering in just 6 months.

In research performed by D'Souza (7), the results of ORN patients who had received medical treatment with pentoxifylline, tocopherol and doxycycline were compared with those of patients who had been treated with HBO. 25% and 51% of the patients respectively showed a progression of the disease and required free flap reconstruction. Furthermore, in the group of patients that received medical treatment there were no recurrences of ORN following the resection and the free flap reconstruction, in comparison with a 20% recurrence in the group treated with HBO. This confirms the current understanding of the pathophysiology of ORN based on the fibrosis induced by radiation.

Recently, other alternatives for the management of ORN have been discussed in the literature, and these include plasmatic factors modified in all their versions (PRGF, PLT-gel, L-PRF), Teriparatide and LLLT. With regards to plasma rich in growth factors (PRGF), its use was suggested following reports in which it was demonstrated that its application as filling material in surgeries and pre-prosthetic implants presented excellent adjuvant and regenerative proprieties (37). The RIF process reduces the level of expression of the transforming growth factor beta (TGF-β). The use of PRGF formulations is based on the premise that the growth factors contained in platelet granules, which are released after activation are beneficial to improving the tissue regeneration (37). In a study, which was performed by Gallesio on 10 patients (38), on day 14 after surgery, the treated area presented complete wound closure.

Cha (23), presented a study in which Teriparatide -a recombinant human parathyroid hormone- was used, demonstrating its beneficial effects on bone regeneration of ORN of the jaw in advanced stages. However, the studies performed on rat models have shown a theoretical risk of osteosarcoma, therefore confirming the need for further studies (39).

The only LLLT report found in our review dated back to 2018 (24). The effectiveness of LLLT is supported by studies in which its effects on the healing process of the oral mucosa are highlighted. These studies have also demonstrated that it minimises the exudative phase, boosts healing and leads to the proliferation and transformation of fibroblasts and myofibroblasts that help in tissue repair, due to the release of growth factors (40). Ribeiro (24) presented a protocol for management with LLLT, in which the 20 treated patients presented with the pathology in early to advanced stages. 100 % of the reported cases were healed with no recurrence during the two follow-up years. This therapy is also non-invasive, atraumatic and no significant associated adverse effects have been reported in the literature.

Among the limitations to this systematic review, it is important to mention that it mostly consists of a retrospective group of cases and case reports, therefore mean-

ing that their heterogeneous nature and the absence of randomised trials is a limiting factor. As a consequence of these disadvantages, the possibility of carrying out a more objective analysis in which more powerful conclusions are drawn would prove challenging.

The results obtained out of all of the different treatments proposed for ORN, seem to indicate that the combined surgical and / or pharmacological treatment (PENTOCLO), is the treatment of choice and offers better healing rates. In case of recurrence, there is some evidence that resection surgery and reconstruction may also be considered, respecting the particular circumstances in which each should be used. What seems clear is that early intervention with conservative surgical and pharmacological methods improves the prognosis of ORN. In an attempt to expand less invasive treatment methods, we suggest more studies for conservative surgical management of hard tissue associated with LLLT therapy, based on controlled clinical studies, with well-distinguished control groups are necessary in order to establish a more efficient therapeutic pattern.

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Funding
None declared.

Conflict of interest
None declared.

Authors contributions
Gisela CV Camolesi: Was responsible for acquisition of data: literature search, analysis and interpretation of data collected and drafting of article.
Karem L. Ortega: Was responsible for the final approval of manuscript.
Janaina Braga Medina: Was responsible for the final approval of manuscript.
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Mario Pérez Sayáns: Was responsible for conception and design of review, acquisition of data: literature search, analysis and interpretation of data collected, drafting of article and/or critical revision, final approval of manuscript.