Journal of Dentistry & Oral Disorders

Open Access

Austin Publishing Group

Research Article

Experimental Irradiation of the Mandible in the Adult Rabbit: A Systematic Review of the Literature

Desoutter A[1], Deneuve S[2], Langonnet S[3], Claude L[4], Bera JC[5] and Chaux-Bodard AG*[1-3,5,6]

[1]Léon Bérard Cancer Center, Head and neck Unit, Surgery department, 28 Rue Laennec 69008 Lyon, France; Labtau – Inserm 1032 151 Cours Albert Thomas 69008 Lyon and ICE (Experimental Surgery Institute) Léon Bérard Cancer Center, 28 Rue Laennec 69008 Lyon, France

[2]Léon Bérard Cancer Center, Head and Neck Unit, Surgery Department, 28 Rue Laennec 69008 Lyon, France

[3]ICE (Experimental Surgery Institute) Léon Bérard Cancer Center, 28 Rue Laennec 69008 Lyon, France

[4]Léon Bérard Cancer Center, Department of Radiotherapy, 28 Rue Laennec 69008 Lyon, France

[5]Labtau – Inserm 1032 151 Cours Albert Thomas 69008 Lyon, France

[6]University Claude Bernard Lyon I, Faculty of Dentistry, 11 rue Guillaume Paradin, 69008 Lyon, France

***Corresponding author:** Chaux-Bodard AG, Léon Bérard Cancer Center, Head and neck Unit, Surgery department, 28 Rue Laennec 69008 Lyon, France; Labtau – Inserm 1032 151 Cours Albert Thomas 69008 Lyon and ICE (Experimental Surgery Institute) Léon Bérard Cancer Center, 28 Rue Laennec 69008 Lyon, France; Léon Bérard Cancer Center, Head and Neck Unit, Surgery Department, 28 Rue Laennec 69008 Lyon, France; ICE (Experimental Surgery Institute) Léon Bérard Cancer Center, 28 Rue Laennec 69008 Lyon, France; Labtau – Inserm 1032 151 cours Albert Thomas 69008 Lyon, France; University Claude Bernard Lyon I, Faculty of Dentistry, 11 rue Guillaume Paradin, 69008 Lyon, France

Received: June 25, 2020; **Accepted:** July 27, 2020; **Published:** August 03, 2020

Abstract

External radiotherapy is widely used in the treatment of head and neck cancers. Its main delayed adverse effect is osteoradionecrosis, which may be prefaced with bone alterations. The aim of this review is to focus on mandibular irradiation in the adult rabbit and to report which radiation protocol was used and which results were reported to try to harmonize a protocol with reproducible results.

A bibliographic search was performed for rabbit studies involving mandibular irradiation and published from 1975 to 2019. The radiation scheme, type of surgery, use of adjuvant therapies and main effects observed were reported.

The search resulted in 145 publications, including reviews and experimental studies. After selection, 24 publications remained for analysis. Surgery, mostly including distraction osteogenesis, concerned the lateral part of the mandible. Radiation schemes were numerous, in terms of dose, sessions, and time interval for sacrifice and bone analysis. Time interval between surgery and radiotherapy or sacrifice was also various. Concerning adjuvant therapies, the administration of hyperbaric oxygen seems to induce neoangiogenesis and thus accelerate bone healing. Five weekly sessions delivering 8.5 or 9 Gy each seems to be a valuable radiation scheme for studying bone alterations and the role of adjuvant therapies.

Keywords: Radiotherapy; Mandible; Rabbit; Late side effects

Abbreviations

Gy: Gray; IMRT: Intensity Modulated Radiotherapy; PMMA: Polymethylmethacrylate; HA: Hydroxylapatite; HBO: Hyperbaric Oxygen; MeV: Megaelectronvolt; microCT: Micro Computed Tomography (microscanner); PET: Positon Emission Tomography

Introduction

External radiotherapy is widely used in the treatment of head and neck cancer, and its adverse effects are well described. One of the most quality of life threatening delayed side effect is osteoradionecrosis. Despite improved radiotherapeutics techniques, such as Intensity-Modulated Radiotherapy (IMRT), this complication remains rare (<5%) but severe [1]. External radiotherapy decreases vascularization, increases the collagen excretion and has an important effect on osteoblasts and osteocytes as it seems to decrease their activity at doses of 20 Gy or more [2]. These alterations lead to bone dystrophy, which makes bone weaker and unable to heal properly, and may lead to osteoradionecrosis. The presentation of osteoradionecrosis after radiotherapy varies from small, asymptomatic bone exposure that may remain stable for months or years or heal with conservative management, to severe necrosis necessitating surgical intervention and free flap reconstruction [1-3]. Thus, osteoradionecrosis and radio-induced bone alterations remain partially unknown; they might compromise the patient's prognosis and quality of life. Preventive and curative therapies are still missing, and preclinical studies are mandatory.

Poort [4] performed a review on the irradiation of facial bones in animals, including craniofacial irradiation and large animals such as sheep. He reported that the use of the rabbit might be sufficient for initial experimental evaluation, as it could be a good model in terms of ease of use and management. The authors insisted on the various protocols in the literature and the need to standardize the evaluation of results.

This paper aims to review the different protocols for modeling

Citation: Desoutter A, Deneuve S, Langonnet S, Claude L, Bera JC and Chaux-Bodard AG. Experimental Irradiation of the Mandible in the Adult Rabbit: A Systematic Review of the Literature. J Dent & Oral Disord. 2020; 6(6): 1147.

mandibular therapeutic irradiation in the adult rabbit to study the different radiation schemes, the type of surgery performed, the time interval between surgery and radiotherapy, the different adjuvant therapies used and the main bone alterations (such as osteodystrophy, delayed bone healing or osteoradionecrosis) observed. It allowed identifying a radiation protocol with reproducible adverse effects on bone comparable with human therapeutic doses.

Material and Methods

Search

A bibliographic search was performed for rabbit studies published between 1975 and December 2019 involving mandibular irradiation. The protocol is available on demand. Databases used were Medline via PubMed, Web of Science, Cochrane, Embase and Scopus. Additional sources were also used, as for sources from the selected publications, and scientific non-indexed journals (from the grey literature). The search terms used were both MeSH terms ([and]) and synonyms ([or]). Terms were: ("radiotherapy" [or] "irradiation" [or] "radiation therapy") [and] ("experimental" [or] "experimental study") [and] ("mandible" [or] "mandibular jaw" [or] "oromandibular irradiation") [and] ("rabbit" [or] "rabbits" [or] "lagomorpha"). Only references with full text publication available were included and reported in a standardized form for data recording and study selection.

Data selection

The criteria used for the selection were following the PICO search strategy: "Population" was adult rabbits; "Intervention" was external radiotherapy on the mandible; "Comparison" was on the different reported protocols and their reported interference with bone healing; "Outcome" was to select a valid and reproducible protocol for mandibular irradiation in the adult rabbit. Research questions were: what type of irradiation scheme was used? What type of surgery was studied? Is there a main model for mandibular irradiation in the adult rabbit that generates bone alterations? Did the authors use adjuvant therapies (such as hyperbaric oxygen therapy) to increase bone healing and what were the results?

Data extraction

For each study, two authors extracted independently the following data: year of publication, number of animals, aim of the study, type of intervention, location of the surgery, radiation dose, fractionation and irradiation source, type of analyses (histological, radiological, histomorphological and others), time between surgery and radiotherapy, time between radiotherapy and euthanasia, adjuvant treatments (such as hyperbaric oxygen therapy), and bone alterations. Reasons for exclusion were: no report of radiotherapy, mandible not in the irradiated filed, growing animal, articles in another language than English, different aim of the study, quality score under 2, number of samples inferior to 10.

Risk of bias – quality of the studies

A standardized form was used (Figure 1) to report the data and analyze the quality and the bias of the studies, regarding the level of evidence, modified from the SYRCLE's (SY: Stematic Review Center for Laboratory animal Experimentation) risk of bias tool for animal studies [5]. Particular attention was given to the most frequent radiation schemes used and their results. A global quality score depending on the SYRCLE's evaluation was given to each study by 2 independent reviewers. In case of discrepancy, a 3rd reviewer analyzed the article. Based on the 7 points of the SYRCLE's assessment tool, a score ranging from 0 to 2 revealed a poor quality; from 3 to 4, a moderate to good quality; and over 5, a high quality. The result was balanced with number of animals and samples, and the significance of the results and conclusions.

Results

Number and quality of the studies

The search resulted in 145 publications, including reviews and experimental studies. The flow chart is presented in Figure 2. 71 duplicates (from the different databases) were removed, and on the 74 remaining studies, 13 were excluded because they did not focus on the rabbit. Of the 61 remaining publications, 37 were excluded. Reasons for exclusions were: no report of radiotherapy (N=13), mandible not included in the radiation field (N=13), full-text available only in Russian or Chinese (N=3), radiation delivered to young growing rabbits (N=2), number of animals or samples under 10 (N=3), quality score under 2 (N=3). Among the 24 remaining publications for analysis, 2 authors published 4 to 6 manuscripts each, with the same protocol [6,8,9,13,17,19,20,22]. Year of publication ranged from 1978 to 2019. Four studies were older than 20 years, 9 between 10 and 20 years, and 11 were published in the past 10 years.

Concerning the quality of the studies, all were experimental studies with control group; studies with number of animals inferior to 10 were excluded. Using the simplified grid inspired from the SYRCLE's tool 5, the studies were allowed the global quality scores: 20 studies had a moderate quality score; 5 studies had a high quality score [8,9,17,35]. Missing datas (i.e. eq dose and number of sessions per week, or randomization and blindness of the examinators) were highlighted. No meta-analysis was performed due to the differences between the reports and the design of the studies.

Animals

Number of animals ranged from 10 to 102 (mean: 28.5). In recent (<10 years) papers, the mean number of animals was 19. The sex of the animal was generally not specified (Supplementary file).

Surgical procedures

Surgery concerned the lateral part of the mandible, between the incisors and the molars in 20 studies, the basal bone in 1 study and the mandibular angle in 1 study, the vascularization in 1 study and was not available in 1 study. 14 studies concerned distraction osteogenesis, 4 Polymethylmethacrylate (PMMA) graft or Hydroxyl Apatite (HA) implants or bone grafts, 4 were postextractional or defect-healing studies, 1 was aiming to create an osteosarcoma, and 1 studied periostal flap. In 8 studies, Hyperbaric Oxygen Therapy (HBO) as adjuvant treatment was performed after completion of the radiotherapy.

Radiotherapy

Radiation schemes were numerous. The used irradiation source was Cobalt60 in 9 studies, photons in 8 studies (4 MeV in 4 studies, 6 MeV in 3 studies and 18 MeV in 1 study), and non-available in 7 studies. Six studies proposed a single-dose radiotherapy, with 1 session ranging from 10 (1 study), 15 (3 studies) to 28 Gy (2 fields of 15 Gy) and 30 Gy. Of these 6 studies, the radiation source was Co60 in 4 studies, photons in 1 study and was not specified in the last one.

Year of publication	Language	Aim of the study	Radiation therapy on the mandible	Surgery performed	Radiation scheme	Adult rabbit	Number of samples

SYRCLE's simplified form

Study number:

Authors:

Title:

1- Were the groups similar at baseline? Yes No N/A

2- Was the allocation adequately concealed during? Yes No N/A

3- Were the animals randomized? Yes No N/A

4- Were the caregivers or investigators blinded? Yes No N/A

5- Were incomplete outcome data adequately addressed? Yes No N/A

6- Are reports of the study free of selective outcome reporting? Yes No N/A

7- Was the study apparently free of other problems that could result in high risk of bias?

Yes No N/A

Number of animals (total / per group):

Additional comments:

Score of the study:

Inclusion in the review: **Y / N**

Figure 1: Form used for each study for the assessment of the eligibility criteria and the quality of the studies (Simplified from the SYRCLE's risk of bias assessment tool).

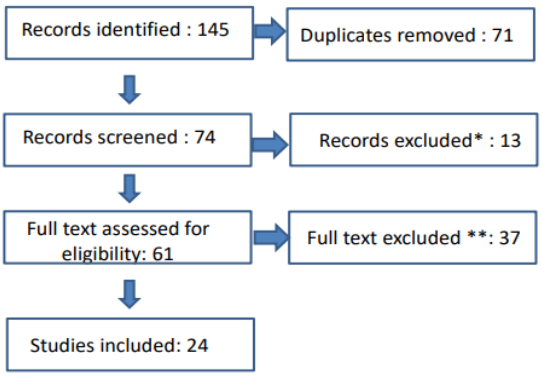

Figure 2: Flow chart: Selection of the studies. Records were excluded because of report of another animal, article in another language than English. Full text exclusion criteria were another animal (not stated in the abstract), another part of the body than the mandible, no report of radiotherapy, or a different aim of the study.

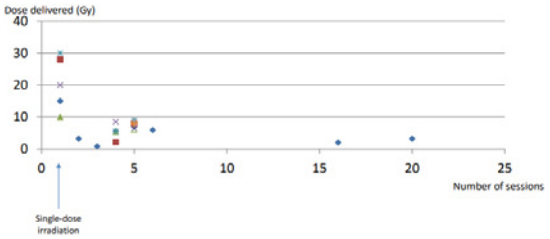

Figure 3: Radiation Schemes: X axis: number of sessions; Y axis: dose delivered per session. The graphic highlights that single dose radiotherapy delivered from 10 to 30 Gy, whereas most of the studies reported 4 to 6 sessions delivering 6 to 9 Gy.

The 17 remaining studies proposed fractionated radiotherapy, from 1 session per week to 5 sessions per week, with a dose per session from 2.2 to 9 Gy (Figure 3). The total dose of radiation ranged from 22.4 to 60 Gy. The equivalent-dose was given in 10 studies and ranged from 2x23 (1 study), 50 Gy (7 studies), 64 Gy (1 study), 70 Gy to 110 Gy (1 study), with an alpha/beta ratio of 3 for late effects. Duration of the fractionated radiation therapy ranged from 1 to 6 weeks. No study used chemotherapy (adjuvant or concomitant).

Time interval

Time interval between surgery and radiotherapy was various: in 4 studies the radiotherapy was completed after surgery, with a delay ranging from 5 days to 28 days. Other studies irradiated the rabbits first, and then proceeded to the surgery, with a time interval ranging from 1 week to 12 months (mean: 1.3 months). Mean time between surgery and euthanasia of the rabbits was 9 weeks. Time between radiotherapy and euthanasia of the rabbit ranged from 0 days to 12 months (Mean: 12.03 weeks, i.e. 3 months).

Analyses performed

Analyses were multimodal and mainly consisted in radiographic examination (9 studies), or in anatomical pathology examination with gross examination (5 studies), with histologic examination (18 studies) and histomorphometry with micro CT (11 studies). Other studies also proposed immunohistochemistry, real time PCR, pet-scan or microangiography. At least clinical and radiological or histological and radiological examinations were performed.

Discussion

The techniques and irradiation models reported in the literature are diverse and non-consensual. In our review, studies concerning growing animals were excluded due to the possible influence of growth on bone healing. Studies from 1975 to 2019 were included, as radiation schemes and particles were at least partially comparable,

whereas older studies could not be compared due to the evolution of radiation therapy. Three studies [16,24,25] were excluded because of the small number of samples for analysis (respectively, per radiation dose: 1, 4 and 6 samples), leading in a lack of consistency in the results (due to the possible interindividual variability between the animals).

Radiotherapy

The dose delivered was mostly equivalent to a minimum of 50 Gy total dose, because beyond this threshold the adverse effects of radiotherapy dramatically increase [6]. A higher dose was once used (70 Gy, 90 Gy and 110 Gy eq dose) to onset osteoradionecrosis [7]. Fractionation seemed to be a point to be discussed [8,9] and one author wondered if one session of radiotherapy per week is enough due to the high healing potential of the rabbit. Hypofractionation schedule seemed to be a better experimental schedule to mimic human radiotherapy [7]. On the contrary, single-dose irradiation did not allow the tumor cells recovery (and its differential effect between normal and tumor cells) which may mislead the clinical acute and subchronical adverse effects [10]. The main radiation schedules used were either single dose irradiation or 5 sessions of radiotherapy, mostly once or twice a week. Only one study delivered 5 daily sessions [15]. One study [16] (excluded from the review due to a low quality score) delivering 5 sessions of 5.5 Gy each did not find relevant bone alterations, but it is noticeable that no surgery was performed. Of the 6 studies with single-dose schedules, all but one study concerned grafts (implants, hydroxylapatite, or bone graft). Fractionated schedules mostly concerned distraction osteogenesis. It is likely that a fractionated scheme, allowing a better assessment of bone healing, better reproduces radiotherapy in humans [7].

Surgical procedures

The location of the surgery mostly concerned the lateral part of the mandible, between the incisors and the molars, chosen as it is the only part without teeth roots [11]. Only 3 studies [7,12,27] reported teeth extraction, probably because it is risky on the rabbit, requiring a closer follow up as the rabbit is not always able to eat properly. Thus, the surgical access was mostly extra oral, in the preangular area. One study aimed to reproduce osteoradionecrosis conditions, and thus used a higher dose of radiotherapy and tooth removal as surgical procedure (eq dose: 70-110 Gy) [7]. Despite a different aim of this study, the paper was analyzed to highlight the limitation doses for osteoradionecrosis.

Time interval

Concerning the time interval between radiotherapy and surgery and/or euthanasia, some authors considered that a time interval of six weeks in the rabbit could be equivalent to a time of 18 to 24 weeks in the human [14]. Furthermore, Zhang [17] suggested that one month in a rabbit's life span was equivalent to 6 months in humans, which corroborates Clark's [15] opinion who estimates that rabbit's bone turnover is 3 times faster, and thus healing 3 to 4 times faster compared to humans [18]. Therefore, time for observation must be shortened in rabbits [7]. Even when surgery was performed before radiotherapy, bone healing and peri-implant bone contact was reduced [11]. Alterations seemed to be correlated with a short time interval (i.e. the shorter the interval, the more severe the alterations).

Adjuvant therapies

Use of HBO therapy was proven to increase osteoblastic activity and angiogenic response, although not to restore the observed level in non-irradiated bone [19-21]. Furthermore, HBO increased the percentage of bone fill after distraction osteogenesis between the distracted segments. Its benefit was increased with time interval between completion of HBO and examination [15,21,22]. The use of stem cells also seemed to present a benefit in irradiated bone healing [22]. Only few adjuvant therapies aiming to increase the bone healing have been studied in the rabbit. It mainly consisted in HBO, which seemed to induce neoangiogenesis thus accelerating bone healing. Many other adjuvant therapies could be proposed to enhance bone healing, such as low level laser therapy, or low intensity pulsed ultrasounds.

Analyses performed

Despite the different analysis modalities and the different radiation schemes, the available literature is consistent with some of radiotherapy side-effects. Osteoblastic activity was inversely related to radiation dose [24]. Newly-formed bone was less mature and worse organized after radiotherapy [25]. Peri implant bone formation was delayed after radiotherapy, and the titanium-bone contact was better than the HA-bone contact with 2 HA-implants failure [26], and a delayed bone-contact formation [27]. Ninety days post operatively, sequestration, necrosis and failure to heal were observed after a 28 Gy single dose [14]. The bone turnover was greatly reduced, with trabecular and cortical bone alteration and a decrease in the expression of Metalloproteinases, Tissue Inhibitors of Metalloproteinases, Bone Morphogenic Proteins, Vascular Endothelial Growth Factor and basic Fibroblast Growth Factor [9,17,28,29]. Scattered islands of cartilage were also reported [17]. Bone alterations were correlated with the radiation dose. Fibrosis, severity of cortical destruction and number of myofibroblasts increased with the radiation dose, whereas osteocyte number, bone metabolism and bone mineralization decreased [7]. It seemed that after high doses, the cortical bone was more immature and bone formation was delayed [8]. After radiotherapy, the newly bone formation was not regular, with areas of bone deprivation and vascular decrease. In the non-irradiated group, healing seemed to be complete at 16 weeks [28]. After a 50 Gy total dose, there was a rarefaction of the trabeculae, no more sign of Haversian system or osteoclasts and a restricted bone formation [18].

It is remarkable that no studies report early or late effects on mucosa or skin, Zhang [8,17] suggesting that a higher dose is required to observe adverse effects of radiotherapy on these tissues with rapid turnover, cell renewing and high healing capacity.

Radiological evaluation was mainly done with micro CT but lateral radiographs, 90° to the occlusal plane, were also performed in many studies [8,21,29-31]. The bone callus formation was reduced after radiotherapy and was of inferior quality with higher doses and longer interval between radiotherapy and grafting. Thus, the time interval between radiotherapy and surgery seemed to be important [30,32]. PET imaging following 18F activity in osteoblasts and thus global osteoblastic activity showed that it is inversely related to the radiation dose [19]. Fixation of Tc99 was also increased in irradiated bone, highlighting the impairment of bone remodeling after radiotherapy, but not in the distracted site [33].

On micro CT scan, studies [15] showed that bone density was correlated to the radiation dose, the time interval between

radiotherapy and examination, and the use of HBO.

Histological evaluation was mostly performed with decalcification; the only study performing it without it being aimed to differentiate mineralized and non-mineralized bone and relayed therefore on histomorphometry [34]. It showed absent osteocytes and a decrease of osteoblasts 3 months after radiotherapy [34]. Endosteal osteoblasts seemed to have a relative resistance to radiation [30]. The initial phenomenon seemed to be fibroatrophy [7]. Nonetheless, there was a huge inter and intra variability of histological analyses between the different studies in term of techniques used. Because only descriptive studies were available, even if some of them used semi-quantitative methods (i.e. cell counts), the interpretation of the results was difficult.

Marx [36] recommends to interprete the data cautiously, especially in terms of dose equivalent in case of single dose irradiation. Indeed, a single 15 Gy dose may be mathematically equivalent to 23 sessions of 2Gy each, but not biologically. Thus, fractionated radiotherapy is mandatory to mimic human irradiation.

Conclusion

Rabbits are docile, cheap, and easy handled animals. They can provide enough tissue samples for studies and for surgical procedures. Therefore, they seem to be an appropriate model for studying osteoradionecrosis [7] and radiation-induced bone damages. A radiation dose of 5 weekly sessions at 8.5 or 9 Gy seems to be a radiation scheme that impairs bone union and maturity [8]. Another proposition could be 20 sessions of 3.2 Gy, 2 days per week, for 10 weeks [36] or 6 sessions delivering 6 Gy each [35], thrice a week. In these propositions, the fractionation and dose per fraction delivered is important, and to be correlated with the number of fractions per week. The first proposition could be a good option to combine both predictable radio-induced bone alterations and a reasonable experimental scheme, with a shorter treatment duration (5 weeks versus 10 weeks) and a better tolerance for the animals with only one session per week. Concerning the sacrificing period after radiotherapy, Soares [37] recommends a time interval from 14 to 21 days for the evaluation of bone microarchitecture changes.

Based on this analysis of the literature, and despite a great heterogeneity that render comparisons difficult to interpret, it seems that 5 weekly sessions delivering 8.5 Gy each is a valuable radiation scheme to study long term adverse effects of mandibular radiotherapy and test the effects of loco regional adjuvant therapies to increase the bone healing.

Funding

The authors thank the IFRO (Institut Français pour la Recherche Odontologique) [2012 and 2019] for its support.

References

1. Mendenhall WM. Mandibular Osteoradionecrosis. J Clin Oncol. 2004; 22: 4867-68.
2. Lyons A, Ghazali N. Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. Br J Oral Maxillofac Surg. 2008; 46: 653-60.
3. Jacobsson AS, Buchbinder D, Hu K, Daniel Buchbinder, Kenneth Hu, Mark L Urken. Paradigm shifts in the management of osteoradionecrosis of the mandible. Oral Oncol. 2010; 46: 795-801.
4. Poort L, Lethaus B, Böckmann R, Lucas J, Bernd L, Roland B. Experimental studies on the irradiation of facial bones in animals: a review. Int J Oral Otolaryngol Head Neck Surg. 2014; 3: 113-27.
5. Hooijmans CR, Maroeska MR, De Vries RBM, Leenaars M, Ritskes-Moitiga M. SYRCLE's risk of bias tool for animal study. BMC Medical Research Methodology. 2014; 14: 43.
6. Muhonen A, Säämaänen AM, Peltomäki T, Muhonen A, Säämänen AM, Peltomäki T, et al. The effect of irradiation and hyperbaric oxygenation (HBO) on extracellular matrix of the condylar cartilage after mandibular distraction osteogenesis in the rabbit. Int J Oral Maxillofac Surg. 2006; 35: 79-87.
7. Zong C, Cai B, Wen X, Bolei C, Syed A, Yuanli C, et al. The role of myofibroblasts in the development of osteoradionecrosis in a newly established rabbit model. J Cranio Maxillofac Surg. 2016; 44: 725-33.
8. Zhang WB, Zheng LW, Chua D, Denial Chua MD, Lim Kwong C, et al. Bone regeneration after radiotherapy in an animal model. J Oral Maxillofac Surg. 2010; 68: 2802-9.
9. Zhang WB, Zheng LW, Chua DTT, Li Wu Z, Daniel Tsin T, Wen Biao Z, et al. Treatment of irradiated mandibles with mesenchymal stem cells transfected with bone morphogenetic protein 2/7. J Oral Maxillofac Surg. 2012; 70: 1711-6.
10. Fowler JF, Harari PM, Leborgne F, et al. Acute radiation reactions in oral and pharyngeal mucosa: tolerable levels in altered fractionation schedules. Radiother Oncol. 2003; 69: 161-8.
11. Campillo VE, Langonnet S, Pierrefeu A, et al. Anatomic and histological study of the rabbit mandible as an experimental model for wound healing and surgical therapies. Lab Anim. 2014; 48: 273-7.
12. Kudo M, Matsui Y, Ohno K, et al. A histomorphometric study of the tissue reaction around hydroxylapatite implants irradiated after placement. J Oral Maxillofac Surg. 2001; 59: 293-300.
13. Muhonen A, Peltomaki T, Hinkka S, et al. Effect of mandibular distraction osteogenesis on temporomandibular joint after previous irradiation and hyperbaric oxygenation. Int J Oral Maxillofac Surg. 2002; 31: 397-404.
14. Eppley BL, Connolly DT, Winkelmann T, et al. Free bone graft reconstruction of irradiated facial tissue: experimental effects of basic fibroblast growth factor stimulation. Plast Reconstr Surg. 1991; 88: 1-11.
15. Clark CL, Strider J, Hall C, et al. Distraction osteogenesis in irradiated rabbit mandibles with adjunctive hyperbaric oxygen therapy. J Oral Maxillofac Surg. 2006; 64: 589-93.
16. Bodard AG, Debbache S, Langonnet S, et al. A model of mandibular irradiation in the rabbit: preliminary results. Bull Group Int Rech Sci Stomatol Odontol. 2013; 52: 12-17.
17. Zhang WB, Zheng LW, Chua DT, et al. Expression of MMP-1 and TIMP-1 in irradiated mandibles during distraction osteogenesis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012; 114: 698-703.
18. Ma Y, Shen G. Distraction osteogenesis after irradiation in rabbit mandibles. Br J Oral Maxillofac Surg. 2012; 50: 662-7.
19. Muhonen A, Peltomäki T, Knuuti J, et al. Osteoblastic activity of the rabbit temporomandibular joint during distraction osteogenesis assessed by [18F] fluoride positron emission tomography. Eur J Oral Sci. 2002; 110: 144-8.
20. Muhonen A, Muhonen J, Minn H, et al. The effects of irradiation and hyperbaric oxygen on bone formation during rabbit mandibular distraction. Arch Oral Biol. 2002; 47: 701-7.
21. Muhonen A, Haaparanta M, Grönros T, et al. Osteoblastic activity and neoangiogenesis in distracted bone of irradiated rabbit mandible with or without hyperbaric oxygen treatment. Int J Oral Maxillofac Surg. 2004; 33: 173-8.
22. Buchholz TA, Mc Cabe K, Cobb J, et al. TP53 overexpression in radiation-induced osteosarcoma of the rabbit mandible. Rad Res. 1999; 51: 278-82.
23. Soares MM, Segreto H, Aloise A, et al. Adipose derived stem cell on the regeneration of irradiated mandible of adult rabbit submitted to distraction osteogenesis. J Pharm Pharmacol. 2018; 6: 113-22.
24. Shao Z, Liu B, Liu Y, et al. Distraction osteogenesis in the irradiated rabbit

mandible. J Plast Reconstr Aesthet Surg. 2006; 59: 181-7.

25. Schön R, Ohno K, Kudo M, et al. Peri-implant tissue reaction in bone irradiated the fifth day after implantation in rabbits: histologic and histomorphometric measurements. Int J Oral Maxillofac Implants. 1996; 11: 228-38.

26. Matsui Y, Ohno K, Michi K, et al. Histomorphometric examination of healing around hydroxylapatite implants in 60Co-irradiated bone. J Oral Maxillofac Surg. 1994; 52: 167-72.

27. Jegoux F, Aguado E, Cognet R, et al. Alveolar ridge augmentation in irradiated rabbit mandibles. J Biomed Mater Res . 2010; 93: 1519-26.

28. Muhonen A, Muhonen J, Lindholm TC, et al. Osteodistraction of a previously irradiated mandible with or without adjunctive hyperbaric oxygenation: an experimental study in rabbits. Int J Oral Maxillofac Surg. 2002; 31: 519-524.

29. Zhang WB, Zheng LW, Chua DT, et al. Expression of bone morphogenetic protein, vascular endothelial growth factor, and basic fibroblast growth factor in irradiated mandibles during distraction osteogenesis. J Oral Maxillofac Surg. 2011; 69: 2860-71.

30. Morales MJ, Marx RE, Gottlieb CF. Effects of pre- and postoperative irradiation on the healing of bone grafts in the rabbit. J Oral Maxillofac Surg. 1987; 45: 34-41.

31. Lye KW, Tideman H, Wolke JCG, et al. Biocompatibility and bone formation with porous modified PMMA in normal and irradiated mandibular tissue. Clin Oral Impl Res. 2013; 24: 100-109.

32. Nathanson A, Wersall J. Effects of Co60-gamma-irradiation on the early ingrowth of an autogenous bone inlay into an artificial defect in the rabbit mandible. Scand J Plast Reconstr Surg. 1978; 12: 139-49.

33. Lind MG, Nathanson A. 99Tcm-DP accumulation in rabbit skull bones after 60Co Gamma irradiation. Acta Radiologica Therapy Physics Biology. 1977; 16: 489-96.

34. Yachouh J, Breton P, Roux JP, et al. Osteogenic capacity of vascularized periosteum: an experimental study on mandibular irradiated bone in rabbits. J Plast Reconstr Aesthet Surg. 2010; 63: 2160-7.

35. Piotrowski SL, Wilson L, Dharmaraj N, Hamze A, Clark A, Tailor R, Hill LR, Lai S, Kasper K, Young S. Development and characterization of a rabbit model of compromised maxillofacial wound healing. Tissue Eng: part C. 2019; 25: 160-67.

36. Marx RE. Histomorphometric examination of healing around hydroxylapatite implants in 60Co irradiated bone. Discussion. J Oral Maxillofac Surg. 1994; 52: 172-3.

37. Soares PBF, Soares CJ, Limirio PHJO, et al. Effect of ionizing radiation after-therapy interval on bone: histomorphometric and biomechanical characteristics. Clin Oral Investing. 2019; 23: 2785-93.