SECIB

DENTAL CARE FOR PATIENTS WITH ORAL CANCER

EDITED BY MEDICINA ORAL S.L. C.I.F. B 96689336

PRESENTATION OF THE SECIB.

The Spanish Society of Oral Surgery (Sociedad Española de Cirugía Bucal [SECIB]) is a non-profit society of a scientific nature, with its own legal personality and full capacity to act nationally, which brings together professionals in Dentistry, Stomatology and Medicine who have a clinical or scientific interest in Oral Surgery. It is in this environment where the approach and implementation of this Clinical Practice Guideline (CPG) should be framed, which seeks to jointly evaluate the available evidence on the management of patients with coagulation disorders, in order to organise and present it in an appropriate way to both the professional and the patient. Likewise, it is used to generate recommendations based on scientific evidence that can be disseminated through the relevant social and scientific media, so that they can be applied by oral surgeons in Spain and around the world in their clinical practice, thus benefiting the patient.

2. AUTHORSHIP.

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3. INTRODUCTION OF THE WORKING GROUP.

The SECIB has commissioned an Expert Group to develop a Clinical Practice Guideline on dental care for patients with oral cancer. The group is made up of teaching and research experts and clinicians in this field, forming a multidisciplinary group, in line with the therapeutic approach to oral cancer in the 21st century.

The guide aims to provide recommendations for the proper diagnosis and treatment of patients affected by oral cancer, including appropriate actions in the pre-cancer treatment period, during and after cancer treatment, from a dental point of view. These recommendations will be based on the best available clinical evidence.

This SECIB Clinical Practice Guideline aims to be the reference for the proper clinical management of patients who have been diagnosed with oral cancer, from the moment the lesion is identified. It is aimed primarily at dentists and stomatologists, as the professionals responsible for the oral health of their patients.

It can also be used by maxillofacial surgeons, otorhinolaryngologists and primary care physicians. The group is made up of teaching and research experts and clinicians in this field, forming a multidisciplinary group, in line with the therapeutic approach to oral cancer in the 21st century.

4. METHODOLOGY

The aim of this project is to draw up a CPG on the dental care of cancer patients, following a rigorous methodological process based on the indications of the document "*Elaboración de Guías de Prácticas Clínica en el Sistema Nacional de Salud*. *Manual Metodológico*" (Development of Clinical Practice Guidelines in the National Health System. Methodological Manual) and the recommendations available in *Guía Salud* (Health Guide).

In order to respond to this CPG, questions were developed that were structured following the PICO question format, consisting of a population group or patients, an intervention to be performed, a comparison of this intervention with other available alternatives, and the results obtained. The advantage of formulating specific clinical questions in the PICO format is that they unambiguously define what is sought to be known and assist in the bibliographical search.

With regard to the sources of information, Medline/PubMed and Embase/Elsevier have been used in this case.

In the integration of a CPG, it is of vital importance to conduct an information search protocol. We followed the EUnetHTA methodological guide "Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness" developed by the Institute for Quality and Efficiency in Health Care (IQWiG) in Germany, which requires experience in the search.

The study selection process was performed through a flow chart using the PRISMA template. The references were stored and managed in a private group of the bibliographic reference manager Mendeley.

The team collaborating on the guide is made up of 2 expert technicians in Methodology and Evidence-Based Health Care, one specialised in the methodology of clinical practice guidelines and care processes, and a Librarian specialised in the field of Health.

The critical reading of the references located was carried out using the SIGN checklist (to evaluate systematic reviews and meta-analyses, cohort studies, case and control studies, diagnostic test studies and economic evaluations); the OSTEBA sheets (to evaluate case series) and the AGREE (to evaluate CPG).

The recommendations were made according to the GRADE methodology, a tool for assessing the quality of evidence and grading the strength of recommendations in the context of the development of clinical practice guidelines, systematic reviews or health technology evaluations.

5. SCOPE AND OBJECTIVES OF THE CPG.

Background information.

Head and neck cancers affect the hard and soft tissues of the head and neck area, including the oral cavity. They account for 6% of all cancers, with an incidence of approximately 670,000 new cases diagnosed annually worldwide. Approximately 90% of these cancers are diagnosed as squamous cell carcinoma, which has a poor prognosis. Treatment includes surgery, chemotherapy and radiotherapy, administered independently or in combination.

Effects of cancer treatment on the oral cavity.

Tooth enamel is composed mainly of calcium phosphate crystals (hydroxyapatite), together with other minerals such as fluoride. Its surface is constantly forming as a result of a combination of demineralisation and remineralisation processes. Saliva, on the other hand, is secreted by the major and minor salivary glands, and is a complex fluid with numerous functions including lubrication and maintenance of mucous membranes, buffering and remineralising capacity.

It has been proven that some chemotherapy agents may contribute to hyposalivation, although it is mainly caused by radiation. It has been determined that hyposalivation begins to appear from the first week of radiotherapy treatment, with salivary flow decreasing mainly when radiation affects the parotid gland. Hyposalivation is affected in several ways, including altering the microflora, which leads to a reduction in the self-cleaning action of the oral cavity. Hyposalivation or decreased salivary flow in patients undergoing radiation is often accompanied by xerostomia or dry mouth sensation, which has the risk of developing a highly destructive type of caries later on. Radiotherapy changes the quality, quantity and composition of saliva, resulting in a reduction of salivary flow, as well as its buffering capacity and levels of electrolytes and immunoproteins.

The severity and frequency of xerostomia and hyposalivation depend on the radiation dose and the volume of irradiated glandular tissue. The dose used depends on the size of the tumour, its location and stage. More radiosensitive tumours such as lymphomas require lower doses of radiation than carcinomas. A frequent effect of this therapy is the decrease in salivary function. When the major salivary glands are exposed to high radiation, hyposalivation becomes a problem leading to xerostomia, this oral environment makes tooth maintenance difficult and increases the risk of caries. Dental extractions resulting from post-radiation caries can increase the risk of osteoradionecrosis in these patients, which can have potentially serious complications.

Therefore, in order to maintain the best possible quality of life for these patients, prevention to maintain oral health becomes more important. The prevention of caries is multifactorial and includes the maintenance of meticulous hygiene, the use of fluorides and a change in diet to minimise the consumption of cariogenic or acidic foods.

Justification of the CPG.

Oral cancer is the sixth most common malignant neoplasm worldwide, with a high mortality rate of over 50% at five years and high morbidity (sequelae). Oral squamous cell carcinoma constitutes over 90% of malignant oral neoplasms, and in a significant percentage of cases it arises from previous diseases that are currently grouped under the denomination of "Potentially Malignant Oral Disorders".

As we have seen above, the influence of cancer treatment on the oral cavity is extensive, and at multiple levels. Knowing these effects, anticipating and preventing them is fundamental in avoiding an increase in the oral pathology associated with cancer treatment, preserving the patient's quality of life and improving the efficacy of the cancer treatment itself. Evaluating the best available evidence to answer

clinical questions in this area is fundamental for all those involved in the process: for the entire oncological multidisciplinary therapeutic team, for the dentist in particular, and above all, and finally, for the patient and the quality of their clinical treatment.
Although there is a history of Clinical Practice Guidelines in the field of oral cancer, none of them focus on the more specific aspects of the role of the dentist, and even less so in our national scope of action, focusing on the therapeutic aspects of the dentist's competence.
This guide has been produced because there are no other guides on this oral disorder with the same focus. There are currently many studies published on the different aspects of this disease, both in terms of its significance and its diagnosis, prognosis and treatment.
For this reason, the preparation of this Clinical Practice Guideline with its analysis and recommendations can be very important in order to strengthen and identify the role of the dentist in the management of the cancer patient, all based on the best available evidence.

6. CLINICAL PROBLEMS ANALYSED.

1. Are smoking and alcohol abuse related to a higher rate of oral complications in adult oral cancer patients? Is there a limit to this effect?

Squamous Cell Carcinoma (SCC) is the oral cancer that develops the most in the oral cavity (1-14). It is also associated with a higher mortality and morbidity rate (1-10), especially when it occurs in young patients (1, 8, 10). The main risk factors associated with this type of cancer are tobacco and alcohol consumption, HPV infections and sun exposure (1, 7), with studies reporting a synergistic effect between the first two factors mentioned (1-13). Cellular alterations that arise as a consequence of exposure to carcinogens can progress to malignancy leading to malignant neoplasms due to genetic and molecular changes (1, 2). Tobacco is known to contain a large number of carcinogenic compounds that have been associated with genetic mutations, loss of cell cycle control mechanisms, apoptosis, etc. (2, 3, 13). The form of consumption is also a determining factor, with smokeless tobacco consumption being more harmful, in some studies, due to the prolonged exposure of the compounds to oral tissues and the absorption of these substances through saliva (2, 9). Alcohol, specifically the acetaldehyde resulting from its metabolism and reactive oxygen species, is capable of damaging DNA. However, alcohol consumption alone does not appear to have as much of a detrimental effect locally as when consumed concomitantly with tobacco (2, 12, 13).

EVALUATION AND SUMMARY OF THE EVIDENCE

A total of 40 articles were selected for full text reading from the 81 articles resulting from the primary search. Of the 40 articles, 14 were ultimately used to respond.

Exclusive use of tobacco

Tobacco is considered to be one of the main risk factors for the development of oral cancer (2) and perioperative complications, as well as recurrences. More specifically, the systematic review by A. Fonseca *et al.* (1), who performed a gene expression study, verified the higher frequency of repair gene polymorphisms in squamous cell lesions in smokers versus non-smokers. However, as to which type of tobacco (smoked or smokeless) may have a greater detrimental effect and thus a greater likelihood of developing SCC, there seems to be controversy, as the systematic review and meta-analysis by F. Mello *et al.* (2) found a higher likelihood of development in patients who used smoked versus smokeless tobacco, but the systematic review and meta-analysis by S. Asthana *et al.* (3) found it in patients who used chewing tobacco. In either case, the study by R. Abrahao *et al.* (7) reports a worse survival in former or current smokers, worse TNM staging characteristics and a 2,026-fold increased risk of developing a disease according to P.R. *et al.* (9). They define tobacco as an independent and aggressive risk factor in the pathogenesis of oral cancer. With regard to quitting or not after diagnosis and/or treatment, the study by Scott *et al.* (4) shows that most of the patients who continued to smoke were from more marginalised areas. The scarcity of data from Shingler's systematic review (6) means that it is not possible to draw conclusions about the effectiveness of therapies for quitting tobacco and alcohol use, nor the effects of these interventions on survival or the progression of the disease. On the other hand, the onset of smoking also appears to be a determinant in the development of SCC. Starting smoking before the age of 13 appears to double the odds of cancer compared to starting after the age of 20 (10).

Exclusive consumption of alcohol

According to the systematic review and meta-analysis by Mello *et al.* (2), exclusive alcohol consumption is not significantly associated with the onset of SCC. The results regarding alcohol consumption are often controversial and even more contradictory than might be expected. Borsetto's cohort study (5) showed a significant reduction in the risk of death in patients who consumed alcohol moderately compared to heavy drinkers and suggests that the better prognosis of moderate consumers may be due to a less aggressive oncophenotype than those who abstain.
According to Abrahao *et al.* (7), alcohol is not related to survival rates. Morais *et al.* (8) found only a weak association between alcohol consumption and the onset of SCC. Along this same line, Petti *et al.* (12) state that alcohol consumption does not appear to be an underlying risk for the development of cancer. They even speak of a reverse association. Adeyemi *et al.* (13) also found no significant increased risk of developing SCC in patients who exclusively consume alcohol.

Consumption of both tobacco and alcohol

Concomitant tobacco and alcohol abuse is the main risk factor for the development of oral cancer. In terms of the type of tobacco use, it appears that smoked tobacco together with alcohol has a greater detrimental effect than smokeless tobacco and alcohol (2). According to the study by Adeyemi *et al.* (13), tobacco and alcohol users had a relative risk of 1.6 for developing SCC. The effect of the use of both on the development of SCC in young patients remains unclear due to the short period of exposure in these patients (8). VHS *et al.* (11) found a significant excess mortality from secondary cancers, cardiovascular, respiratory and gastrointestinal diseases related to excessive alcohol and tobacco intake.
Petti *et al.* (12) report that 55% of oral cancer cases were attributable to concomitant consumption and not only to drinking or smoking.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

According to the results of the literature analysed, it can be confirmed that tobacco consumption in all its forms, smoked or chewed, is closely related to the development of squamous cell carcinoma of the oral cavity **(Grade of Recommendation B).** The effect of the exclusive consumption of alcohol is less clear **(Grade of Recommendation B).** The concomitant use of tobacco and alcohol has a synergistic effect, increasing the likelihood of developing this type of oral cancer **(Grade of Recommendation B)**. Tobacco and alcohol do not appear to be the main risk factors for the development of oral cancer in young patients, and the exposure time may be a limiting factor for these habits **(Grade of Recommendation B)**. Patients who continue smoking after diagnosis and/or treatment are more likely to experience cancer recurrence or second primary malignant neoplasms **(Grade of Recommendation C)**.
In the near future, it would be interesting to conduct detailed research, in randomised controlled clinical trials, on complications arising perioperatively or during chemo-radiotherapy treatment of patients with oral cancer who continue to smoke and drink alcohol. Likewise, it would be useful to develop new effective methods for quitting these habits and learning about the direct effects during the follow-up of cancer patients.

2. In the preoperative period, when is the best time for dental treatment?

The execution of dental treatments in patients with oral cancer who are going to undergo radiotherapy or chemotherapy will be determined by the risk of osteonecrosis of the jaw, hence why it is considered essential to know the ideal moment to carry out each dental treatment in order to minimise or avoid the development of osteoradionecrosis (ORN). Classically, the dental procedure associated with the highest risk of ORN is post-radiotherapy tooth extraction, hence many oral treatments in these patients are aimed at avoiding the need to perform it in the post-irradiation period. Pre-radiotherapy and pre-chemotherapy dental treatments include, in addition to tooth extraction, tartrectomy, the use of topical antiseptics such as chlorhexidine, local application of fluoride gel, scaling and root planing, surgery, caries restoration

and endodontic treatment. There are very few published studies that have assessed the most favourable timeline for each dental treatment modality in order to minimise complications and not influence the quality of life and survival of patients with oral cancer. Although the literature supports the fact that patients with oral cancer should receive a multidisciplinary oral assessment and diagnosis prior to radiotherapy or chemotherapy (1), there is disagreement about the influence of each type of dental treatment and the timing of its execution on the risk of ORN, on the delay in starting RT and on the patient's own quality of life.

EVALUATION AND SUMMARY OF THE EVIDENCE

Of the 28 articles selected to answer this question, we have included the 10 studies with the highest level of scientific evidence in the evaluation.

With regard to tooth extraction, all the studies analysed (3-6, 7,9-10) agree in stating that there is an association between the execution of the extraction and the occurrence of ORN, showing their differences with regard to the time of its execution. While for Huang *et al.* (3), Wang *et al.* (4) and Chang *et al.* (5), the occurrence of ORN is influenced by the timing of the extraction, Beech *et al.* (7), Wanifuchi *et al.* (9) and Bastone *et al.* (10) state that this association is independent of the time elapsed between the extraction and RT. Huang *et al.* (3) found that tooth extraction less than 2 weeks prior to starting RT significantly increased the risk of developing ORN. Likewise, those who were treated with a tooth extraction within 1 to 3 months post-RT had a higher risk of ORN. The authors suggest avoiding extractions within 2 weeks prior to RT and 1-3 months post-RT. Wang *et al.* (4) found a significantly higher risk of ORN in patients undergoing post-radiotherapy extractions, with the risk increasing over time, reaching the highest peak of occurrence in extractions performed 4-5 years after RT. The authors point out that performing extractions pre-radiotherapy is a safer method than performing them post-radiotherapy. According to Chang *et al.* (5), the risk of ORN in patients undergoing pre-radiotherapy extractions is significantly higher than in those not undergoing extractions. On the other hand, Beech *et al.* (7), in a retrospective observational study of 29 cases with ORN, noted that cases of ORN occurred in patients who underwent extractions regardless of whether they were performed pre- or post-radiotherapy. In the same vein, Wanifuchi *et al.* (9), in their study of 33 patients with ORN, observed no influence of the time elapsed between extraction and RT on the development of ORN. The study by Bastone *et al.* (10), in reference to prophylactic pre-radiotherapy extractions of healthy mandibular molars located in the irradiation field, reports that there is no association between the pre-radiotherapy timing of extractions and the occurrence of ORN. The authors highlight a high occurrence of ORN and emphasise the fact that the prophylactic extraction of healthy teeth would not be justified for preventing ORN. Elyias *et al.* (11) conducted a Cochrane review, but the authors found no randomised clinical trials that provided answers to this question. On this basis, the authors add that none of the current practices recommend the systematic extraction of healthy teeth pre-radiotherapy.

In reference to periodontal treatment, Huang *et al.* (3) state that patients who received tartrectomy and subgingival curettage had a significantly higher risk of ORN than those who did not receive this type of treatment, especially if it was performed within 3 to 6 months post-radiotherapy. In the study by Chang *et al.* (5), the authors found that patients who underwent tartrectomy within 2 weeks prior to RT experienced a significantly increased risk of developing ORN. The risk was reduced in patients who received this treatment from 2 weeks to 6 months pre-radiotherapy. Contrary to these authors, Wang *et al.* (4) found no association between periodontal treatment and the occurrence of ORN.

The association between the use of CHX rinses and the development of ORN was analysed by Chang *et al.* (5), reporting that patients with oral cancer who used CHX rinses had, during the study period, a higher occurrence of ORN than those who did not use chlorhexidine rinses, constituting a 1.96-fold increased risk.

In terms of endodontic treatment, in the study by Huang *et al.* (3), patients who received pre-radiotherapy root canal treatment had a higher prevalence of ORN than those who received it during RT treatment, followed by those who received it post-radiotherapy. Pre-radiotherapy endodontic treatment was associated with a significantly higher risk of ORN compared to those who did not undergo this treatment. On the contrary, Wang *et al.* (4) found no association between endodontic treatment and the risk of ORN.

Studies analysing the association between oral surgery and ORN (3-5) agree that the risk is significantly higher in patients undergoing oral surgery, with the risk increasing if the surgery is performed between 3 months pre-radiotherapy and 6 months post-radiotherapy.

The topical application of fluoride gel (before and/or during RT) (4) as well as the **restorative treatment of caries** and the timing of the treatment did not show any association with ORN (3).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

In patients with oral cancer, the ideal time to perform pre-radiotherapy extractions is between 2 and 4 weeks beforehand, avoiding the 15 days prior to the start of RT **(Grade of Recommendation B)**. Performing them in the pre-surgery period or at the same time as cancer surgery significantly reduces the delay in starting radiotherapy treatment **(Grade of Recommendation C)**. Tartrectomy and subgingival curettage should be avoided in the 15 days prior to the start of RT and should be performed earlier **(Grade of Recommendation B)**. Patients exposed to CHX mouth rinse during and after surgical and/or radiotherapy treatment are at increased risk of developing ORN, so its use is not recommended in patients with oral cancer undergoing RT **(Grade of Recommendation B)**. There does not seem to be an association between endodontic treatment and an increased risk of ORN, although some authors suggest avoiding endodontic treatment between 2 weeks and one month pre-radiotherapy **(Grade of Recommendation B)**. Oral surgery, performed in the pre-radiotherapy period, is associated with a significantly increased risk of developing ORN, and should therefore be avoided if not necessary for cancer-related reasons **(Grade of Recommendation B)**. The topical application of fluoride gel and restorative treatment of caries can be performed at any time during cancer pre-treatment, as they are not associated with an increased risk of ORN **(Grade of Recommendation B)**.

A larger number of studies analysing the detailed chronology of the execution of the different dental treatments in the period elapsing between the diagnosis of oral cancer and the start of cancer treatment would be necessary in order to provide a more comprehensive answer to this question. Incorporating data on the type, dose and exact location of irradiation into the dental pre-assessment would help to reconsider both the indications for dental treatment and its timing.

3. What actions in the pre-treatment period can reduce the occurrence of mucositis in adult oral cancer patients?

One of the main adverse effects of radiotherapy (RT) and/or chemotherapy (CT) treatments is the development of oral mucositis. Oral mucositis (OM) is defined as an inflammation of the oral mucosa caused by cancer therapy and is accompanied by erythema, ulceration, swelling and atrophy (1). The occurrence of OM in head and neck cancer (HNC) patients, including oral cancer (OC) patients, depends on the type of treatment they undergo. In patients undergoing RT treatment, this is estimated to be 75%, whereas in those undergoing CT, it is 40%. This percentage reaches 80% in patients who are treated simultaneously with RT/CT (2). This process can present varying degrees of intensity and can cause a significant loss of quality of life in patients who suffer from it, as it can cause severe pain and limit oral feeding. It is estimated that between 10-15% of patients with mucositis have to interrupt their cancer treatment, which can affect their survival (2). One aspect that would significantly improve the quality of life of oral cancer patients is to prevent the onset of OM. This would result in lower healthcare costs, as it would generate a lower consumption of analgesics, less possibility of requiring parenteral feeding and less demand for care during cancer treatment. In this particular section, we will analyse the existing evidence regarding the interventions applicable before starting cancer treatment.

EVALUATION AND SUMMARY OF THE EVIDENCE

A total of 23 articles were selected to answer this clinical question (1-25).

We referenced recommendations and systematic reviews published in 2019 and 2020 by the *Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) (3-8).* In these documents, this working group provides an up-to-date and critical review of the different types of treatment proposed for managing oral mucositis.

Preventive treatment of oral mucositis with growth factors and cytokines.

In 2019, Logan *et al.* (3) studied the role of palifermin, concluding that it is not possible to make any kind of recommendation on its use. With regard to the granulocyte-macrophage colony-stimulating factor (G-CSF), they reach the same conclusion.

Preventive treatment of oral mucositis with anti-inflammatory agents.

In 2019 (4), Ariyawarda *et al.* recommended benzydamine rinses in patients with HNC who were to receive doses of less than 50 Gy of RT. When analysing the efficacy of celecoxib, no differences were found with respect to the degree of OM, pain, diet or opioid consumption.

Preventive treatment of oral mucositis with natural agents.

The reviews by Yarom et al., both published in 2019 (5) and 2020 (6), conclude that no recommendation can be made regarding the use of zinc as a preventive for mucositis. These authors also studied the use of glutamine, suggesting its use in head and neck cancer patients undergoing RT/CT. These data differ from those presented by Shuai *et al.* in their systematic review published in 2020 (10) on the efficacy of glutamine in preventing OM in HNC patients undergoing RT. The use of honey as a preventive agent for OM has been studied in 2 included systematic reviews (6,11), with conflicting data. In the trial conducted by Aghamohammadi *et al.* in 2018 (12), they found benefit in the use of Zataria multiflora rinses before RT sessions, compared to a control group. However, it is true that this is an isolated result in the literature and the group is mostly made up of patients with nasopharyngeal cancer and oral cancer. In the study conducted by Onseng *et al.* in 2017 (13), it is shown that the use of 0.2% melatonin rinses before the RT session, accompanied by the intake of 20 mg of melatonin per day, while not influencing the occurrence of OM, did prove to be associated with a shorter duration of OM, with statistically significant differences.

Preventive treatment of oral mucositis with laser (photobiomodulation).

The systematic review prepared by Zadik *et al.* in 2019, which is the MASCC/ISOO reference document, includes 56 papers that give rise to the recommendations (7). With regard to patients with HNC who are going to undergo RT, the use of laser as a preventive treatment for OM is recommended. In the systematic review and meta-analysis conducted by Peralta-Mamani *et al.* in 2019 (15), the different parameters in the protocols on managing laser therapy in patients with HNC who are going to undergo RT are analysed, reaching the conclusion that the laser is effective in all cases, regardless of the parameters used, in the following ranges: Wavelength from 632.8 nm to 685 nm, energy density from 1.8 J/cm2 to 3.0 J/cm2, power from 10 mW to 60 mW and total energy from 0.8 J to 3.0 J. These favourable data on the use of laser as a preventive measure in patients with HNC who are going to undergo RT are supported by the systematic review and meta-analysis conducted by Peng *et al.* in 2020 (16), where they observed that patients who undergo laser therapy have a lower occurrence of OM. If we consider patients with HNC who are going to undergo RT/CT, the results observed in all studies analysed show the efficacy of the laser (7,16-19).

Preventive treatment of oral mucositis by reducing the RT dose.

The results obtained by Wang *et al.* in 2012 (20) support the use of intensity-modulated RT with preservation of the oral mucosa in patients with tongue cancer.

Preventive treatment of oral mucositis through basic oral healthcare.

In the MASCC/ISOO systematic review and recommendations document published by Hong *et al.* in 2019 (8), with regard to professional oral care, 3 RCTs and 6 experimental comparative studies were included. Two RCTs and one comparative study demonstrated a reduction in OM in patients who had prior dental care. Even with these results, the

authors indicate that it is not possible to establish a solid recommendation on professional dental care, given the variations in relation to the protocols described and types of interventions performed. Although it is true that the expert committee indicates that it is desirable for all patients to have a dental check-up prior to cancer treatment in order to avoid the risk of dental-related local or systemic infections. It is suggested that oral health protocols be implemented in patients with HNC who are going to undergo RT. This section includes the systematic review and subsequent consensus document generated by 40 experts following the Delphi method, published by De Sanctis *et al.* in 2016 (22). This study points out that poor oral hygiene and active periodontal disease can lead to an aggravation of the condition of OM. Therefore, it is indicated that dental treatment prior to starting cancer treatment could improve the control of OM, recommending the integration of the dentist into the dental management protocols. With regard to saline or sodium bicarbonate rinses, Hong *et al.* (8) indicate that no recommendation can be made, although the expert panel suggests that these rinses may increase oral cleanliness and improve patient comfort. The role of chlorhexidine rinses as a preventive for OM was analysed in the systematic review and meta-analysis conducted by Cardona *et al.* in 2017 (23) with no improvement in terms of mucositis, leading to the suggestion not to use chlorhexidine in these patients. **(Level of Evidence III)**.

Other preventive pharmacological treatments for oral mucositis.

In 2018 (23) and 2019 (24), Anderson *et al.* published two phase Ib/IIa and IIb clinical trials of the drug GC4419 as a preventive of OM in patients with HNC who are going to undergo RT/CT. These studies show a reduction in the time to onset of severe MO, for doses of 90 mg versus placebo, as well as in its occurrence.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The use of low-frequency laser therapy in patients with oral cancer who are going to undergo radiotherapy or radiotherapy and chemotherapy simultaneously is effective in preventing oral mucositis **(Grade of Recommendation A)**. In patients undergoing radiotherapy with a dose lower than 50Gy, benzydamine rinses are recommended for the prevention of oral mucositis (0.15%, 15 ml every 3 to 6 hours, from the start of RT until two weeks after its completion) **(Grade of Recommendation A).** Benzydamine rinses are suggested for preventing oral mucositis in patients undergoing radiotherapy and chemotherapy or chemotherapy alone **(Grade of Recommendation B)**. Food supplements have shown very limited evidence in improving the occurrence of oral mucositis in patients undergoing radiotherapy and chemotherapy **(Grade of Recommendation D)**. The results obtained regarding the use of systemic or topical glutamine are controversial and do not allow recommendations to be made on its use. The use of topical or systemic honey does not seem to have a clear influence on the occurrence or degree of mucositis **(Grade of Recommendation B**). A dental check-up is recommended for patients undergoing radiotherapy and/or chemotherapy, as well as oral hygiene instructions **(Grade of Recommendation D)**. The use of saline and/or sodium bicarbonate rinses is suggested, as they could help oral hygiene and improve discomfort caused by oral mucositis **(Grade of Recommendation D)**. The use of chlorhexidine rinses is not recommended for the prevention of oral mucositis **(Grade of Recommendation B)**. During the design of the area to be irradiated, it is recommended to minimise the impact on the oral mucosa in order to avoid a higher occurrence and degree of oral mucositis **(Grade of Recommendation B)**. It is not possible to systematically recommend the use of intraoral devices to avoid the impact of radiation on the oral mucosa, although it is true that in some particular cases, depending on the location of the tumour, it could provide clinical benefit **(Grade of Recommendation D)**.

Prospective, well-designed studies are needed to compare the different treatments proposed or even a combination of them, as many of them are not mutually exclusive. It seems sensible to suggest from an ethical point of view that, given the results obtained, it is not appropriate at this time to conduct clinical studies with patients in a placebo control group, but rather that the control group should be the therapy that has demonstrated the greatest effectiveness, such as low-frequency laser therapy.

4. What actions in the pre-treatment period can reduce the occurrence of xerostomia and/or candidiasis in adult oral cancer patients?

Oral cancer is a challenge for the dentist, as its early diagnosis is directly related to the survival of the patients who develop it (1). The treatment of oral cancer is eminently surgical, sometimes accompanied by radiotherapy and chemotherapy, especially in advanced stages. These treatments give rise to a series of adverse effects, including mucositis, taste alterations, salivary gland hypofunction, which will manifest itself in the form of xerostomia, trismus, osteoradionecrosis, candidiasis, dysphagia, intraoral viral infections or dental caries (2). One of the main adverse effects of these cancer treatments, mainly radiotherapy, is salivary gland hypofunction, which will manifest itself in the form of xerostomia (3). The occurrence of xerostomia in patients who have received conventional radiotherapy to the head and neck is estimated at over 80% (4). This condition is caused by a direct impact of radiotherapy on the salivary glandular structures, with 2 types of xerostomia being described; acute xerostomia, associated with the inflammatory reaction caused by the radiation, and delayed xerostomia, which occurs months later or even permanently, associated with the destruction of the glandular parenchyma and its subsequent fibrosis (5). In addition to the discomfort and loss of quality of life of these patients, xerostomia is also associated with other oral complications, such as a yeast infection, the presence of rampant caries or swallowing problems. It should be noted that this adverse effect of radiotherapy is dose-dependent, so the higher the dose received in the glandular structures, the higher the damage. In this regard, in recent years, technical improvements in radiotherapy, such as intensity-modulated radiation, have reduced the impact of glandular damage (6). An interesting aspect is the primary prevention of these adverse effects associated with the treatment of oral cancer patients. This approach (before the treatment itself) would seek to reduce the comorbidity of these, leading to a better quality of life for patients.

Several treatments have been described before, during and after radiotherapy for the prevention and management of this adverse effect. (Table Question 4 Appendix Evidence Table) (1-30).

EVALUATION AND SUMMARY OF THE EVIDENCE

• Preventive treatments for the onset of xerostomia in oral cancer patients.

A total of 64 references were obtained and nine were selected for the answer to this question (7,8,10,16).

1. Intensity modulated radiotherapy.

The systematic review conducted by Jensen *et al. in 2010, which has served as a document for publishing the recommendations by the MASCC/ISOO Group, concludes that intensity-modulated radiotherapy causes a lower occurrence and severity of xerostomia, with more pronounced long-term effects (from 6 months post-RT, up to 2 years), recommending its use with parotid gland preservation in the prevention of salivary gland hypofunction and xerostomia associated with head and neck cancer.* **(Level of Evidence II, Grade of Recommendation A). In the systematic review conducted by Blugione** *et al. in 2016 (13), which is accompanied by the preparation of an expert consensus document following the Delphi Method, they recommend the intensity-modulated technique, excluding the major salivary glands from the radiation field and indicating that the exclusion of the minor salivary glands could also be beneficial.*

2. Amifostine.

In the review by Jensen *et al. (12), the authors argue that it is not possible to establish clear recommendations on the interpretation of the existing evidence, although it is true that the results show that the use of amifostine reduces the occurrence of xerostomia in patients who are going to undergo RT. In 2017 (11), Riley et al. conducted a systematic review, following the Cochrane methodology, with the aim of evaluating the effects of drugs in preventing radiotherapy-induced salivary gland dysfunction. With regard to amifostine, it is indicated that it could be an effective drug in reducing severe xerostomia (grade ≥2) at the end of RT. These data are repeated in the systematic review of randomised clinical trials published by Gu et al. in 2014 (14). These data contradict those presented in the consensus document and systematic review prepared by Buglione et al. in 2016 (13), where they do not recommend the use of amifostine in patients who are going to receive head and neck radiotherapy, given its high cost and the adverse effects it can produce.*

3. Surgical transfer of the submaxillary gland:

Data obtained from the systematic review by Jensen *et al. in 2010 suggest that preservation of the submaxillary gland by transfer to the submental space in selected patients could be of clinical importance. This is a surgical technique that is still under study. In the clinical trial conducted by Zhang et al. (15), patients who underwent a submaxillary gland transfer to the submental space demonstrated a salivary flow rate at 6 months similar to that obtained before surgery. After 2 years of follow-up, it was observed that 92.3% of patients had no or minimal xerostomia, these differences being statistically significant.*

4. Acupuncture:

In the randomised clinical trial conducted by Braga *et al. in 2011 (10), subjective improvements were found in the test group versus the control group in relation to xerostomia at the end of RT using a visual analogue scale, as well as improvements in the rates of stimulated and unstimulated saliva.*

• Preventive treatments for the onset of candidiasis in oral cancer patients.

On analysing the bibliography (17-30), we have found that there are no studies providing a specific answer to the clinical question posed. While it is true that several of these studies address the treatment simultaneously with cancer treatment, none of them analyse specific treatments before starting cancer treatment that reduce its occurrence.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

There is sufficient evidence to recommend the use of intensity-modulated radiotherapy for the prevention of acute and delayed xerostomia **(Grade of recommendation A).** The use of amifostine before radiotherapy sessions reduces the occurrence of acute and delayed xerostomia **(Grade of Recommendation A).** Submaxillary gland transfer surgery appears to be effective in reducing radiotherapy-associated xerostomia in selected patients **(Grade of Recommendation B).** Acupuncture as a preventive treatment for xerostomia in patients with oral cancer who are going to receive head and neck radiotherapy requires further evidence that it may be beneficial in the short-term **(Grade of Recommendation B)**. There is no evidence for preventive treatment of candidiasis in cancer patients **(Grade of Recommendation D).**

Studies comparing the different treatments proposed to prevent xerostomia with each other are needed in order to evaluate the comparative efficacy of each of them. It would also be interesting to evaluate the combined effect of these treatments, as they are not mutually exclusive. Specific studies are needed to assess prophylactic treatments for oral candidiasis in oral cancer patients. Economic evaluation and resource management studies are also needed to assess which treatment is more cost-effective within health systems.

5. What actions in the preoperative period can reduce the occurrence of caries or periodontal disease in adult oral cancer patients?

Radiotherapy is highly important in the management of patients with head and neck cancer. However, it has been associated with serious undesirable complications. Depending on the area receiving radiation (salivary glands, oral mucosa, jaws), secondary complications such as hyposalivation, xerostomia, mucositis and even loss of taste may occur (7). These patients are also more susceptible to a type of rampant caries known as radiation caries. These lesions usually appear four weeks after the start of radiotherapy treatment and affect atypical areas of the teeth (tongue surface, incisal area or cusps of molars). Clinically, this type of caries can be classified by different patterns of presentation. The

most common of all is type I, which affects the cervical area of the teeth and extends through the amelocemental junction, resulting in circumferential damage. Type II is characterised by areas of demineralisation in all areas of the tooth, resulting in widespread erosions in the occlusal and incisal areas relatively frequently. Finally, type III presents colour changes in the dentine, resulting in a dark (black or brown) discolouration of the crown area (7). Although radiation caries has a multifactorial aetiology, the main causative factor is the reduction of salivary flow. Initially, the use of sugar-free chewing gum was considered to stimulate this salivary flow; however, it has been shown that it is not a recommendable product for these patients, as this mechanical stimulation of the saliva is insufficient. Another technique that was also used was the use of acidic substances, which are no longer recommended due to the stimulation of demineralisation. Some of the ways to compensate for this lost salivary flow in many of the radiated patients are the use of salivary substitutes, which are capable of increasing tissue lubrication, hydration and pH neutralisation (3,7).

EVALUATION AND SUMMARY OF THE EVIDENCE

After analysing the 28 articles found in this systematic search, a total of eight were selected to answer the proposed clinical question.

Aguiar *et al.* (7) conducted a literature review in which they highlighted radiation-induced hyposalivation as the ideal method for preventing the development of radiation caries. To this end, they proposed protecting the major and minor salivary glands from radiation in order to prevent damage to them. They also recommended the use of fluoride in different presentations and concentrations, which should be applied during radiotherapy treatment. Despite all the measures proposed, the authors concluded that patient motivation, adequate plaque control, as well as salivary stimulation, the use of fluoride and adequate nutritional guidance represented the basis for prevention (7). Frydrych AM *et al.* conducted a study that aimed to observe whether patients previously diagnosed with head and neck cancer complied with anti-caries protocols. Among their findings was the relationship between the occurrence of caries after treatment and poor protocol compliance. It was also shown that the presence of caries at the base appointment (prior to cancer treatment) was related to poorer compliance with the established anti-caries protocol (4). Sim *et al.* developed two studies. In the first, they sought to determine the effect of the application of amorphous calcium phosphate (CPP-ACP) on the progression of caries in irradiated patients with nasopharyngeal carcinoma. They concluded that no statistically significant results were obtained between the two experimental groups (6). In the study published four years later, they aimed to compare the effect of the same concentration of the cream (10% CPP-ACP), but this time in combination with a 0.4% Stannous Fluoride (SnF2) gel and a 0.32% Sodium Fluoride-NaF toothpaste (experimental group) compared to a placebo group without CPP-ACP, where they concluded that the combination of these products gave a lower progression of coronal caries in the experimental group (8). Gupta N *et al.* published a systematic review based on 57 articles, where they aimed to review the mechanisms involved in the development of radiation caries, as well as their prevention and management. After analysing all the information, they concluded that the main cause of this type of caries is hyposalivation, which can be prevented by avoiding radiation in the area of the salivary glands, thus agreeing with Aguiar GP *et al.* These authors also stressed the importance of dental check-ups before, during and after RT to reduce the occurrence of caries and improve the quality of life of patients diagnosed with head and neck cancer. On the other hand, Sohn HO *et al.* developed a clinical trial to evaluate the effect of professional oral hygiene on patients diagnosed with head and neck cancer undergoing radiotherapy, concluding that regular check-ups and professional oral hygiene in these patients resulted in improved oral health, which confirmed their initial hypothesis (2). Finally, the narrative review by Deng J *et al.* focused on describing the critical factors related to head and neck cancer patients and caries. Some of the preventive measures highlighted include the use of fluoride, salivary stimulants and the use of calcium phosphate supplements (3).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

After analysing the articles selected for this section, we have found that in general, head and neck cancer patients are more prone to developing caries and periodontal disease. For this reason, a general dental check-up before starting cancer treatment is extremely important. Extractions are recommended at least two weeks before starting cancer treatment.

To reduce the occurrence of caries, the application of fluorides and calcium phosphate is recommended, although there is no consensus on the form, concentration and frequency of application **(Grade of recommendation D)**.

It would be advisable to supplement the existing data with well-designed randomised clinical trials.

6. Is there a standard for measuring quality of life in adult oral cancer patients? How does it relate to therapeutic decisions?

The main goal of cancer therapies is to increase the time the patient is disease-free, thereby increasing survival. Logically, a therapeutic decision based solely or mainly on quality of life would not be valid from a clinical point of view if it sacrifices the patient's survival time, except in certain situations.

Therefore, the situations in which quality of life is a factor to be taken into account in the choice of treatment to be applied are reduced to those situations where the different therapeutic options have a similar result or those clinical situations in which the patient is doomed to exitus and aspects relating to dignified death or quality of life in the final moments of the patient's life take precedence over positive clinical results that we know will not occur.

EVALUATION AND SUMMARY OF THE EVIDENCE

With regard to the published evidence of the quality of life tools most commonly used in the case of adult cancer patients (1-39), an extensive search was carried out and a systematic review published by Ojo *et al. in 2012 (2) was identified, in which a study was conducted with* level of evidence 2++ and grade of recommendation B on quality of life assessment instruments in head and neck cancer, selecting those that meet the most suitable criteria for both their clinical use and for their course of management research. The most widely used quality of life assessment tool is the EORTC QLQ-H&N 35, with 284 items, 46.48 % of the sample of 611 studies evaluated. The next most frequently used questionnaires are the UWQOL, with 172 studies (28.15%), the FACTHN, with 99 studies (16.2%) and the HNQOL with 27 studies (4.41%). There are 14 quality of life assessment tools in our search. However, the four we have indicated above account for 95.25% of the studies we have identified, and one of them accounts for almost half of the studies.

With regard to the articles that study how the different therapeutic options affect the patient's quality of life, we have found a total of five articles that we are going to review below. Silveira *et al. (3) evaluated the quality of life related to inflammation in patients who had undergone radiotherapy or chemotherapy for head and neck cancer, where it was found that the quality of life of all patients decreased, especially those whose primary cancer site was the oral cavity in relation to the fatigue domain. Bilal et al. (4) studied factors associated with health-related quality of life. The factors of treatment status, tumour stage and tumour location had the greatest negative impact on the quality of life of patients. Maciejewski et al. (5) conducted a quality-of-life study on 54 patients who had undergone surgical resection, demonstrating that emotional quality of life tended to be more negative among women, whereas men had a more negative evaluation of social function. Tumour size influenced decreased bodily function in the case of a large tumour, while a small tumour was significantly associated with lower cognitive function. In 2017, Breeze et al. (6) presented research where they found a significant reduction in quality of life in patients who suffered from tumours on the floor of the mouth. Laser excision, when possible, was associated with an improvement in quality of life compared to other excisional techniques. Melo et al. (7) found that quality of life decreased significantly when associated with clinical stage, patient gender and treatment approach. Specifically, women with advanced head and neck cancer, treated with radiotherapy or chemotherapy, were the patients with the lowest quality of life values.*

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Currently, there is no consensus questionnaire model for the assessment of quality of life in adult cancer patients with head and neck cancer, although we have identified three tools that account for 90% (EORTC QLQ H&N-35, UW-QOL and FACT-H&N) **(Grade of Recommendation B)**. In this regard, it is recommended that, when evaluating the specific quality of life of adult cancer patients with head and neck cancer, one of these three tools should be used. Quality of life may be an important prognostic factor related to the clinical result obtained by the patient, and therefore may be likely to be included in hypothetical clinical decision-making, at least in certain situations **(Grade of Recommendation B)**. However, the data available are scattered, taken with a significant diversity (there is no specific tool for this purpose) of health-related quality of life assessment tools, which makes it difficult to integrate this idea into clinical practice **(Grade of Recommendation C)**.

The scientific community should identify the common points of at least the three or four tools that have been the most successful in research on quality of life in adult head and neck cancer patients and, to the extent possible, generate a consensus model that can be used in all future research. The generation of a specific tool for incorporating the quality-of-life assessment in decision-making, specifically designed for these situations and easily individualised, should be further developed.

7. What actions in the preoperative period can improve quality of life in adult oral cancer patients?

The results of the clinical activity should generally be evaluated in two major areas: the reduction of morbidity and mortality as one of the first objectives, but without forgetting that the centre of healthcare is the patient, so improving their quality of life is established as the second of these major areas.

With regard to oral cancer, there are countless studies and trials that focus on reducing mortality in this disease, and there are also many studies that seek the best way to reduce morbidity during and after cancer treatment.

However, studies focusing on the patient's quality of life both during and after treatment, as well as the factors that actually have a decisive influence on improving quality of life, are much less frequent.

It is true that international initiatives (1) have been developed, as well as standardised quality of life assessment tools for several languages by international organisations (2) including the World Health Organisation (3) among others, but these instruments are far from being used regularly and consistently by quality of life studies focused on oral and head and neck cancer.

EVALUATION AND SUMMARY OF THE EVIDENCE

A trial by Funk *et al. (4) compared a basic treatment consisting of oral examination and treatment of emergencies with a protocol for dental treatment prior to oncology and oral hygiene education. After experimentation, the CAO, EORTC and WOHQOL-BRE index results were similar. Only improvements related to candidiasis and mucositis were found. Clough et al. (7) attempted to identify the influence of tooth extractions on the patient's quality of life, as this extractionist approach is supported by several studies on the basis of reduced complications during and after cancer treatment. The result, not too surprisingly, is that patients found that tooth loss was experienced in a traumatic way and negatively affected their quality of life. Therefore, and returning to the initial question, we are faced with a question on which we have very little evidence to answer. And in addition to being scarce, the approaches are very varied and fundamentally far from international standardisation and randomised clinical trial methodology. Kufta et al. (8) indicate that the level of motivation to obtain oral care in these patients is important in order for their dental treatment to be performed. They indicate that there is a low rate of compliance with this dental care obligation and that this may lead to an increase in tooth extractions. Moore et al. (11) indicate that loss of taste or taste disturbance is one of the most influential aspects in the loss of quality of life of these patients. This aspect is also highlighted by Epstein et al. (12).*

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

There is no clear evidence that regular dental treatment improves quality of life **(Grade of Recommendation B)**. However, those measures aimed at avoiding tooth loss would have a direct influence on improving the quality of life of oral cancer patients, given that this treatment has been shown to be perceived as traumatic by patients and would greatly reduce their quality of life **(Grade of Recommendation C)**.

The following lines of future research are proposed: 1) A greater number of clinical trials should be conducted; 2) with large sample sizes, 3) using internationally accepted and validated tools, 4) as well as comparing different dental treatment protocols (as far as possible, moving away from extraction-based treatment, which although currently the most widespread, has been proven to reduce the patient's quality of life).

8. What actions in the preoperative period can reduce the occurrence of medication-related osteonecrosis or chemonecrosis in adult oral cancer patients?

Osteonecrosis of the jaw (ONJ) is described as an intraoral complication and is defined as an unexpected development of necrotic bone in the oral cavity, which is commonly associated with the administration of anti-resorptive drugs, which include bisphosphonates (pamidronate, zoledronate, etc.) and Denosumab, which is a monoclonal antibody very commonly used in osteoporosis. On the other hand, medicines that inhibit angiogenesis also cause this pathology (1). In order to distinguish MRONJ (medication-related osteonecrosis of the jaw) from other pathologies and to address evolving clinical observations and concerns about the disease, patients may be considered to have MRONJ if all of the following features are present:

- Current or previous treatment with anti-resorptive or anti-angiogenic agents.
- Exposed bone or palpable bone through an intraoral or extraoral fistula from probing in the maxillofacial region that has persisted for more than 8 weeks.
- There is no history of radiotherapy to the jaw or metastatic disease of the jaw. Commonly misdiagnosed conditions may include the following: alveolar osteitis, sinusitis, fibro-osseous lesion, sarcoma, osteomyelitis (2).

Among the related medications, two major groups stand out: anti-resorptive agents and anti-angiogenic agents.

EVALUATION AND SUMMARY OF THE EVIDENCE

From a total of 69 articles, 15 were finally selected and included in the bibliography to answer this question (1-15).

Nicolatou Galitis *et al.* (3) report in their study that the risk of developing MRONJ is reduced if prophylactic measures are used prior to taking medication, although these vary depending on whether the patient is low risk (low-dose treatment for less than 3 years or no treatment) or high risk (high-dose medication or low-dose treatment for over 3 years). In low-risk patients, an oral and radiological examination is sufficient for prevention, while in high-risk patients, moreover, they should be encouraged to have proper daily hygiene, previously extract teeth with a poor prognosis, stop smoking, adjust their prostheses to avoid trauma and detect sources of future infection. Fedele *et al.* (7) describe in their study that restorative, endodontic, prosthodontic and orthodontic treatments have proven to be completely safe. In contrast, surgical and periodontal procedures should be performed at least 4-8 weeks prior to the start of medication treatment for proper soft tissue healing, as it serves to prevent bone infection and bone exposure. These treatments are also described and supported by the following study teams: Owosho *et al.* (8), Bonacina *et al.* (9) and Goodday *et al.* (10). In 2013, Sciannameo *et al.* (11) published a study comparing prophylactic measures before, during and after the start of medication, concluding that preventive measures are very effective in preventing JRONB and that it is essential to take them as soon as possible, especially before starting medication, results that coincide with those of Cossío *et al.* (13). In the systematic review and meta-analysis conducted by Harry Karna *et al.* (1), they point out that the dental preventive measures to reduce the occurrence of MRONJ are the following: complete oral examination with photographs and radiographs; oral hygiene instructions and maintenance of good oral health; completion of necessary dental treatment before starting anti-resorptive therapy; use of anti-

microbial mouth rinses and antibiotics before and after surgical procedures (1 gram of amoxicillin 48 hours before surgery and two weeks after surgery, if allergic, 600 mg of clindamycin with the same regimen). It is advisable to perform all surgical procedures before starting intravenous drug treatment in order to avoid having to perform them once the treatment has started due to the high risk of osteonecrosis associated with the jaw. Soutome *et al.* (14) conclude in their study that there is a higher risk of developing MRONJ in patients who undergo dental treatment during or 180 days after the start of bisphosphonate therapy than in patients who have undergone preventive dental treatment 180 days before the start of therapy, therefore, this anticipation is very important in order to avoid the pathology derived from anti-resorptive medication. The study also reveals that the cause of developing MRONJ is not related to the extraction of the tooth, but rather to the underlying infection following the extraction. An alternative to extraction according to the American Association of Endodontics is root canal therapy in patients who should not have an extraction due to the high risk rate of developing MRONJ (15).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Preventive and prophylactic dental measures in the preoperative period are able to decrease the occurrence of medication-related osteonecrosis, although not completely prevent it in all cases **(Grade of Recommendation D)**. Prior to starting drug therapy (oral or systemic bisphosphonates or denosumab) in adult oral cancer patients, patients can safely undergo any dental treatment (endodontic, restorative, prosthetic, orthodontic, etc.) with the exception of surgical and periodontal procedures, which should be performed at least 4-8 weeks prior to the start of medication. It is important to perform all possible treatments so that once treatment with bisphosphonates has started, the patient does not have to undergo traumatic treatments such as extractions. It is highly recommended to sanitise the oral cavity and educate and motivate the patient by explaining the risks involved in developing MRONJ **(Grade of Recommendation D)**.

With regard to future lines of research, prospective and randomised clinical studies should be conducted with large samples to provide us with clear and convincing scientific evidence on which techniques or dental treatments should or should not be carried out preventively to reduce the occurrence of medication-related osteonecrosis of the upper or lower jaw.

9. What actions in the pre-treatment period can reduce the occurrence of osteoradionecrosis in adult oral cancer patients?

Osteoradionecrosis (ORN) of the jaw is one of the most serious complications of radiotherapy (RT) treatment for malignant tumours of the head and neck. It is defined as exposure of irradiated bone that devitalises through the skin and mucosa, which ulcerates or necroses, and persists for a period of more than 3 months, not caused by neoplastic recurrence (1). When ORN of the jaw progresses, patients develop trismus, neuropathic pain and chronic drainage, resulting in a severely reduced quality of life. Although there are numerous reports on the medical management of ORN of the jaw, including surgical and conservative interventions, preventing ORN is the most important therapeutic approach for healthcare professionals (2).

To minimise the risk of patients developing ORN, it is necessary to implement oral management strategies before starting radiotherapy in patients with head and neck cancer, and multidisciplinary treatment between the maxillofacial surgeon, dentist and oncologist is essential. Once these patients have been diagnosed by their oncologist, they should be referred to the maxillofacial surgeon and the dentist for follow-up and to perform the treatments and preventive measures they deem appropriate so that the occurrence of ORN during and after radiotherapy is as low as possible (6).

The aim is to know and analyse which dental treatments in the preoperative period reduce the occurrence of ORN in adult oral cancer patients.

EVALUATION AND SUMMARY OF THE EVIDENCE

From a total of 53 articles reviewed in the literature, 15 were finally selected and included in the bibliography to answer this question.

Hans. P *et al.* (7) suggest that prior to making decisions about which treatments to perform, the patient should stop smoking, the glycaemic control value should be monitored and the dental assessment by the dentist should be at least one month before the start of radiotherapy, so that when dental procedures are performed, including surgical procedures, there is a margin of healing of the soft tissues before the start of cancer treatment, thus leading to a decrease in the occurrence of ORN. At the first visit, the patient will undergo a clinical and radiological dental assessment to plan the treatment to be performed. The main objective should be to optimise the condition of the dentition to confirm that high-risk procedures (surgical procedures) will not have to be performed in the post-irradiation period. Treatment will vary depending on whether the dental problem is in the >40 Gy or <40 Gy irradiation zone. In cases of deep caries, periapical pathology, periodontal pathology (periodontal pocket of more than 6 mm, grade 1 mobility, gingival recession of more than 6 mm, etc.), cysts, impacted teeth or internal reabsorptions, the treatment to be performed when irradiation is greater than 40 Gy will be tooth extraction, except when the periapical pathology is asymptomatic, in which case a root canal treatment will be performed. On the other hand, when irradiation is less than 40 Gy or when treatment is performed outside the irradiation field, the procedures to be carried out will be more atraumatic and conservative, performing restorations with root canal treatment whenever necessary, in addition to periodontal treatment to save teeth that have a favourable prognosis, performing surgical procedures such as cystectomies when indicated (2,3,9). With regard to definitive restorations, N Beech *et al.* (10) point out that they should be done before the start of RT, and that if this is not possible, temporary restorations with a glass ionomer should be made, silver amalgams should be avoided.

Tooth extraction prior to radiotherapy is a controversial issue. In 2017, Ti Hao Wang *et al.* (11) presented a study in which they support the idea that performing pre-treatment extractions reduces the risk of ORN, as it avoids performing extractions after RT, which have a higher risk of developing ORN. In contrast, other authors confirm that the risk factors for the occurrence of ORN include pre-RT extractions (4). Beech *et al.* (13) report that tooth extractions prior to cancer treatment significantly increase the risk of ORN. Fang Huang *et al.* (14) advocate that 2 weeks before radiotherapy and 1-3 months after radiotherapy, extractions should be avoided to reduce the occurrence of ORN. Oral surgery is best avoided to reduce the risk of ORN from 3 months before radiotherapy to 6 months after the end of radiotherapy.

Batstone *et al.* (15) conducted a randomised double-blind clinical trial to observe and analyse the importance of platelet-rich plasma (PRP) in the post-extraction sockets of 22 patients who required extractions and were to undergo bilateral radiotherapy. It was concluded that there is no scientific evidence to support that PRP is better in post-extraction sockets that are to be subsequently irradiated to reduce the occurrence of ORN.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Endodontic, conservative, prosthetic and orthodontic treatments of teeth with a favourable prognosis should be performed before the start of therapy, whereas teeth with a questionable or unfavourable pathology and prognosis, and if the patient is subjected to an increased risk (high dose of RT > 55 Gy, mandibular molar, tooth close to the tumour, etc.), should be extracted.

The use of platelet-rich plasma does not have a beneficial effect on the occurrence of osteonecrosis. It is highly recommended to sanitise the oral cavity and educate and motivate the patient by explaining the risks involved in developing MRONJ **(Grade of Recommendation D).**

With regard to future lines, it would be interesting to conduct in-depth research (with well-developed randomised clinical trials with large samples) on the ideal time to perform tooth extractions, before or after treatment with RT, since, as we have mentioned above, there is no clear and conclusive consensus, with ambiguous thinking and clinical judgements. It would be important to carry out a proposal for well-controlled prospective studies with large samples on the use of platelet concentrates in post-extraction sockets prior to the start of RT, as they are highly successful when used in other surgical procedures (PRP, PRGF, PRF, etc.).

10. What actions during cancer treatment can reduce taste impairment in adult oral cancer patients?

Eating habits are governed, in part, by the sensory detection of taste. The sense of taste is essential in life because it regulates food intake, as well as providing hedonic pleasure from eating. Taste perception also activates neurochemical signalling pathways that enable the preparation for digestion, absorption and transportation of nutrients (1). There are five basic tastes: sweet, bitter, sour, salty and umami. The perception of these tastes is mediated through the taste buds, which are distributed over the tongue (goblet or circumvallate, fungiform and foliated papillae) and the palate. Taste buds are also found in the epithelium of the pharynx and on some of the laryngeal surfaces of the upper aerodigestive tract. Although primary tumours in the head and neck (H&N) region rarely directly affect the sense of taste, its alteration is a frequent complication of conventional cancer treatments (2,3). Changes in taste are mainly due to damage to taste cells located in the radiation field. The pattern of taste alteration is strongly influenced by the distribution of taste buds damaged during radiotherapy. Radiation and chemotherapy induce apoptosis of taste receptor cells and inhibit the proliferation of taste stem/progenitor cells. Additionally, the role of xerostomia, which results from radiotherapy damage to the salivary glands and ultimately alters the amount and composition of saliva, is also a factor involved in taste distortion (1). Patients with H&N cancer treated with radiotherapy and/or chemotherapy, such as cisplatin, carboplatin, 5-fluorouracil and taxanes, frequently experience a complete (ageusia) or partial (hypogeusia) loss of taste, or a distortion in taste perception, known as dysgeusia (4). Typically, impairment is observed in all five tastes (3). The lack of a significant relationship between tumour location and taste disorders obtained in numerous studies demonstrates the widespread nature of taste dysfunction in patients with H&N cancer. As multiple nerves transmit taste sensations, treatment in any area from the mid-facial third to the base of the neck may result in an impaired taste sensory function (5,6).

In this paper, we performed a meticulous search and critical evaluation of the existing evidence on the different interventions during cancer treatment that can reduce taste impairment in adult oral cancer patients.

EVALUATION AND SUMMARY OF THE EVIDENCE

To answer the PICO question, a total of 8 studies were included that evaluated the efficacy of different strategies in preventing taste impairment in oral cancer patients undergoing cancer treatment, including: zinc sulphate (19-21), bethanechol (22), pentoxifylline and vitamin E (23), amifostine (24,25) and dietary advice and education (26).

- **Zinc sulphate supplements**

  Chemotherapy can be associated with changes in zinc metabolism and could potentially cause carbonic anhydrase deficiency in some patients (1). This is why the therapeutic administration of zinc has been proposed for various taste dysfunctions and has been studied in numerous studies. According to a recent Cochrane review there is evidence, albeit of very low quality, that zinc supplements improve taste acuity in patients with idiopathic/zinc deficiency taste disorders (29). Three randomised clinical trials (RCTs) investigating the use of zinc in preventing taste impairment in patients with H&N cancer undergoing cancer treatment have been included in this paper. Two of them found that zinc has no preventive effect against changes in taste perception (20,30). On the contrary, the remaining study by Najafizade et al. concluded that zinc does prevent radiation-induced taste impairment (21).

- **Bethanechol**

  The effect of bethanechol, a sialogogue and acetylcholine analogue, on salivary gland dysfunction has been studied (32). The authors concluded that bethanechol did not prevent taste loss, mucositis or candidiasis associated with RT.

- **Amifostine**

  Amifostine, as a cytoprotective agent, protects normal organs and tissues from oxidative damage induced by cancer treatment by removing the free radicals produced by chemotherapy or radiotherapy. Its role in taste maintenance may be possible either directly through taste bud protection or indirectly through salivary gland protection. Buntzel et al. found that the use of amifostine was significantly effective in protecting against various radiochemotherapy-induced toxicities (primary or adjuvant), including loss of taste. On the contrary, in their previously published study, the results were not as satisfactory, especially with regard to taste impairment, with a slight decrease in its severity.

- **Pentoxifylline and vitamin E**

  Its inhibitory effect on transforming growth factor beta (TGFβ1), an inflammatory mediator, is very useful in protection against radiation. Sayed et al. evaluated the effect of this combination in patients with H&N cancer and found that pentoxifylline and vitamin E significantly reduced the occurrence of dysgeusia.

- **Nutritional advice and education**

  One RCT investigated the influence of individualised dietary advice on the occurrence of oral side effects of cancer treatment, including dysgeusia. Among its results, it showed that dietary advice has a smaller impact on early-onset dysgeusia but a more significant effect on long-term dysgeusia.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Although zinc supplements have shown beneficial effects in non-cancer patients with idiopathic or zinc deficiency taste disorders, their use would not be recommended in head and neck cancer patients undergoing radiotherapy, with or without chemotherapy **(Grade of Recommendation A)**. On the other hand, the combination of pentoxifylline and vitamin E, as well as bethanechol, have shown promising results in reducing taste alterations in these patients. **(Grade of Recommendation D)**.

In the absence of a clear protocol for action, it is recommended that patients be referred to a dietician for dietary advice, especially in cases of malnutrition or those at risk of malnutrition. **(Grade of Recommendation D)**.

The insufficient scientific evidence in the published studies makes it necessary to have more randomised clinical trials, of better quality than those included in this PICO question, in order to know the real effect of pharmacological and nutritional strategies in preventing or treating taste alterations during cancer treatment in patients with oral cancer.

11. What actions during cancer treatment can reduce xerostomia and candidiasis in adult oral cancer patients?

In recent decades, research has been conducted into the use of a wide range of drugs to treat or prevent side effects during radiotherapy, with the aim of increasing the amount of radiation that can be safely administered to patients (8). These include:

1. Drugs used in the treatment/prophylaxis of xerostomia:

1.1. Parasympathomimetic or sialogogue drugs: Pilocarpine, Bethanechol, Cevimeline.

1.2. Cytoprotective agents: Amifostine.

1.3. Others: Palifermin (KGF, keratinocyte growth factor), Vitamin C/E complex.

2. Drugs used in the treatment/prophylaxis of candidiasis (Cochrane Library classification)

2.1. Absorbed in the digestive tract: Fluconazole, Ketoconazole, Itraconazole.

2.2. Partially absorbed in the digestive tract: Miconazole, Clotrimazole.

2.3. Not absorbed in the digestive tract: Amphotericin B, Nystatin, Chlorhexidine.

EVALUATION AND SUMMARY OF THE EVIDENCE

To answer the PICO question, a total of 14 studies evaluating the efficacy of different therapeutic and preventive pharmacological measures in reducing xerostomia and candidiasis in patients undergoing radiotherapy/chemotherapy of the head and neck have been included.

Xerostomia

1. Preventive pharmacological measures:

- **Pilocarpine**: According to the most recent Cochrane systematic review and meta-analysis (9), the evidence is not sufficient enough to determine whether or not it is effective compared to placebo.
- **Amifostine**: In the Cochrane review with meta-analysis (9), there is low quality evidence showing that amifostine, compared to placebo, may reduce the risk of moderate to severe xerostomia, results that are consistent with those of another study (13).
- **Palifermin**: According to the Cochrane review, there is insufficient evidence to determine

whether or not it is beneficial, both in the prevention of xerostomia and in the occurrence of adverse effects (9).

- **Vitamin C/E complex:** Evaluated in an RCT that reveals a promising effect of this vitamin complex, with a highly significant reduction in xerostomia compared to placebo (18).

2. Therapeutic pharmacological measures:

- **Pilocarpine:** Three meta-analyses find a benefit in its use versus placebo in reducing the symptoms of xerostomia (10-11,17).
- **Cevimeline:** A review with meta-analysis (10) suggests a benefit from its use, however, these same studies were considered by the Cochrane review as inadequate due to the inconsistent data they provide on xerostomia (17).

Candidiasis

1. Preventive pharmacological measures:

- **Drugs absorbed in the gastrointestinal (GI) tract:** In a Cochrane review, the meta-analysis showed that these drugs prevent oral candidiasis (16), with fluconazole having the most predictable effect. One RCT finds that fluconazole (100 mg/day, from the 6th to the last day of RT) significantly reduces the occurrence of oral candidiasis (22).
- **Drugs partially absorbed in the GI tract:** In the same Cochrane review, they compared drugs partially absorbed in the GI tract (miconazole and clotrimazole) with placebo and found that these drugs also prevent oral candidiasis (16).
- **Drugs not absorbed in the GI tract:** No significant benefits were observed for drugs not absorbed in the GI tract (nystatin, amphotericin B, chlorhexidine and thymostimulin) (16).

2. Therapeutic pharmacological measures:

- **Drugs absorbed in the GI tract:** There is evidence that these drugs are more effective than those not absorbed in the GI tract. Specifically, the use of ketoconazole in patients with candidiasis demonstrated an especially significant benefit over placebo (15). However, the oral formulation is currently contraindicated due to the high risk of hepatotoxicity.
- **Drugs partially absorbed in the GI tract:** Clotrimazole was included in the same Cochrane review, but its effectiveness was not demonstrated. However, another study found that 50 mg of clotrimazole did eradicate more cases than the lower dose of 10 mg (15).
- **Drugs not absorbed in the GI tract:** No significant benefits were observed for non-absorbed drugs in the GI tract in the Cochrane review compared to absorbable drugs (15).

However, the Cochrane review does conclude that there is insufficient evidence to claim or refute a benefit associated with any antifungal agent in treating candidiasis.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

In the case of xerostomia, the evidence supports the therapeutic role of pilocarpine, with small doses (5 mg/3/day) being more appropriate as adverse effects are minimised. **(Grade of Recommendation B).** On the preventive side, however, there is insufficient evidence to confirm the long-term beneficial effect of a given drug, although the evidence is encouraging for amifostine or vitamin C/E complex. **(Grade of Recommendation B).**

For candidiasis, there is strong evidence to support the efficacy of drugs absorbed (completely or partially) in the digestive tract in its prevention. **(Grade of Recommendation A).** For their part, there is inconclusive evidence that drugs that are completely absorbed in the digestive tract (fluconazole, ketoconazole and itraconazole) are effective in reducing the occurrence of candidiasis in oral cancer patients. **(Grade of Recommendation B)**. As a systemic agent, fluconazole is a good choice due to its proven benefit as well as its safety. For topical treatment, both miconazole and clotrimazole may be good options. **(Grade of Recommendation B)**.

Future well-designed randomised clinical trials are needed to investigate the long-term efficacy of drugs for which the current evidence is promising but insufficient, and to determine or confirm the most appropriate and safe doses to be used in each case. Subsequently, it would also be interesting to compare the drugs with each other and verify which is more beneficial. Furthermore, the studies to be conducted must be similar in terms of clinical measurement scales and must include the adverse effects produced by the drug.

12. What actions during cancer treatment can reduce mucositis in oral cancer patients?

Given the need to prevent OM or reduce it as much as possible, extensive research has been carried out to determine the effectiveness of a large number of different interventions for preventing or treating OM in cancer patients. Although many interventions used for treating or preventing mucositis have some evidence to support their use, no intervention has been conclusively validated by the scientific community to date, making it necessary to supplement the opinion of clinical experts to answer this question.

Currently, the treatments available for OM are mostly palliative and include extensive oral care, use of anti-inflammatory drugs, local anaesthetics, antiseptics and antimicrobial agents. No effective prophylactic or curative agents for OM are currently available (4).

EVALUATION AND SUMMARY OF THE EVIDENCE

Oral care protocol. Kawashita *et al.* (6) evaluated a protocol where infected teeth were prophylactically extracted before starting radiotherapy, patients took pilocarpine hydrochloride, together with topical steroids (dexamethasone) and received check-ups and professional oral care at least once a week. The results showed that oral cleaning and hygiene together with topical dexamethasone treatment prevented severe oral mucositis caused by radiotherapy alone, but not that caused by chemoradiotherapy. This suggests that therapy with strong or very strong topical steroids may prevent severe oral mucositis caused by chemoradiotherapy (6).

Drugs that decrease mucosal toxicity caused by chemoradiotherapy.

Patil *et al.* reported that curcumin 0.4% mouthwash is safe and effective in controlling the signs and symptoms of OM (22). Curcumin nanamicelle appears to be an effective agent in preventing OM or reducing its severity during radiotherapy (1, 20-22).

Mucosal cell stimulants. According to authors such as Lins, laser therapy does not have a direct curative effect, but seems to promote tissue repair of the injured region through cellular biostimulation (23). Marín-Conde *et al.* report that low-frequency laser photobiomodulation reduces the occurrence and severity of mucositis in patients treated with radiotherapy and/or chemotherapy (3). Today, there are numerous nutritional supplements containing L-glutamine that are prescribed to cancer patients because of their ability to stimulate protein synthesis and reduce inflammation (7,31). The study by Chattopadhyyay *et al.* analysed the role of glutamine in the occurrence of radiation-induced mucositis with or without chemotherapy for head and neck cancer. Oral glutamine was shown to delay the development of mucositis, as well as the average time of onset (8).

Mixed-action mouthwashes. Einstein *et al.* indicate that the use of benzydamine in patients treated with moderate doses of radiation reduces the occurrence of erythema and ulceration, as well as the use of analgesics for pain relief (32). Benzydamine hydrochloride mouthwash has been confirmed to decrease the severity of oral mucositis in patients receiving radiotherapy less than 50 Gy (15). On the other hand, Rastogi *et al.* through their study conducted on patients with doses between 50 Gy and 70 Gy, treated with benzydamine hydrochloride rinses together with saline rinses experienced a significant decrease in OM rates (9), so the positive effect of benzydamine in decreasing the occurrence of OM in patients subjected to radiation seems to be confirmed. The study by Hussain *et al.* showed that Nigella sativa oil mouthwash has potential anti-inflammatory activity that may be beneficial in minimising or preventing radiation- or chemoradiation-induced OM in patients with head and neck cancer, and future research is needed to corroborate this finding (4). The pilot study by Sio *et al.* shows promising results that N-acetylcysteine may benefit patients with RT-related mucositis toxicity, including thick secretions and xerostomia (5). The study by Baharvand *et al.* analysed the influence of phenytoin on the occurrence of OM. Phenytoin mouthwash (at 1% concentration) produced significant pain relief and improved quality of life in patients with cancer therapy-induced OM, and although it reduced the severity of mucositis, it was not considered statistically significant (12). In the clinical trial conducted by Onseng *et al.* , patients undergoing simultaneous chemoradiation were randomised to receive 20 mg melatonin to gargle before radiation and 20 mg melatonin capsules taken nightly for 7 weeks. The results showed a lower occurrence of OM (18).

Mucosal barriers and protective agents. The study

by Watanabe *et al.* described Polaprezic as very effective in reducing the incidence of OM, pain, xerostomia and taste alterations without reducing tumour response to radiochemotherapy. It also prevented altered oral intake and reduced food quantity, indicating an improvement in quality of life (11). In the trial by Allison *et al.* , MuGard was shown to cause symptom mitigation as well as delayed progression of OM in patients with oral cancer (17).

Cytoprotection. The study by Henke *et al.* used a weekly palifermin dose of 120 µg/kg, which reduced severe OM in patients with head and neck cancer undergoing radiochemotherapy, however, they did not observe a decrease in xerostomia (13). In the pilot study conducted by Chaitanya *et al.* , they concluded that oral vitamin C supplements, particularly when consumed at high concentrations, that is, 4 g/day, can significantly decrease the intensity of mucositis in patients with oropharyngeal cancers undergoing radiotherapy and chemotherapy (10).

Natural drugs. From a nutritional point of view, OM reduces the ability to eat and drink due to xerostomia, pain and ulcers, which leads to malnutrition, dehydration and impaired overall condition. Harada K *et al.* analysed the effects of a diet rich in amino acids through a food supplement called Elental® in patients with oral squamous cell carcinoma undergoing chemoradiotherapy. These authors report that Elental® could be an attractive agent (7,31). They conclude that Elental® is beneficial in treating OM (7).

- **Honey:** Honey applied topically to the oral mucosa in patients undergoing radiotherapy acts effectively as a barrier in a protective manner, thus limiting the severity and occurrence of OM according to the results obtained in the trial conducted by Khanal *et al.* (14). This is confirmed in the meta-analysis conducted by Cho HK *et al.* in 2015 (16).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The systematic reviews, meta-analyses and clinical trials analysed have shown that, of all the measures adopted for treating oral mucositis resulting from cancer treatment, benzydamine mouthwash, low frequency laser with or without oral care protocol and 2% morphine mouthwash for pain have statistically significant effects, reducing the occurrence of OM in patients treated for oral cancer. Although oral care is essential for chemoradiotherapy-induced oral mucositis, it alone cannot prevent severe oral mucositis. It is nevertheless an adjuvant to the aforementioned previous treatments. **(Grade of Recommendation A).**

Low-frequency laser photobiomodulation reduces the occurrence and severity of mucositis in patients treated with radiotherapy and/or chemotherapy. **(Grade of Recommendation A).**

Using benzidine hydrochloride as a rinse serves as an anti-inflammatory agent, significantly reducing both erythema and ulceration. Benzydamine significantly reduces MO even at doses > 50 Gy in patients with oral cancer. Its role in patients receiving concomitant chemotherapy needs further evaluation. **(Grade of Recommendation B).**

Future multi-centre studies are needed, by using standardised scales, the description of data specifying standard deviation and degree of OM together with a pain assessment.

13. In which situations is it justified to perform dental treatment during the period of cancer treatment?

The main dental treatments performed on cancer patients are tooth extractions, implants, periodontal treatment, orthodontic extrusion and coronary lengthening.

EVALUATION AND SUMMARY OF THE EVIDENCE

To answer PICO question 13, 11 studies were selected that analysed dental treatment on head and neck cancer patients undergoing radiotherapy, chemotherapy or ablative surgery.

Extractions. Kojima *et al.* conclude that teeth with an apical focus that cannot be preserved should be extracted prior to radiotherapy to avoid the risk of ORN, and extraction a posteriori is not recommended (2,11,13). On the other hand, Nabil S. *et al.* analysed the occurrence of ORN after post-radiation extraction and concluded that the occurrence of ORN after post-radiation extraction is 7% if post-radiation extraction is without prophylaxis, 4% if post-radiation extraction is with prophylactic hyperbaric oxygen, 6% if post-radiation extraction is with antibiotic (3). Wanifuchi *et al.* analysed patients with ORN and found that 21% were caused by extractions. The time of occurrence of ORN did not depend on the time interval between the tooth extraction and the end of RT. The irradiation field is certainly related to the site of ORN; therefore, prophylactic tooth extraction should be performed considering the radiation field and dose (4).

Implants. Schoen *et al.* developed a list of advantages of implant placement during ablative tumour surgery, including (1): 1. Avoid implant surgery in an area compromised by radiotherapy, 2. Initial healing of the implant (osseointegration) will take place before irradiation, 3. The patient can benefit from implant support prior to radiotherapy and rehabilitate speech and swallowing functions, 4. No need for adjuvant prophylaxis, such as the long-term use of antibiotics or hyperbaric oxygen therapy. Korfage *et al.* show a high percentage of rehabilitated patients with lower jaw overdentures with five years of follow-up. 92% one year after overdenture placement and, after five years, 83% of patients maintained a functional prosthesis (1). Sammartino *et al.* showed a slightly more favourable success rate for mandibular implants (98.4%) compared to maxillary implants (57.1%) and a clearly better success rate for a radiation dose lower than 50 Gy. In the literature, an irradiation level higher than 60 Gy is considered the main cause of failure in the field of implantology (8). An ideal time period for implant placement has not yet been defined. Some authors accept a period of 6 months, while others recommend a period between 13 and 24 months from RT. The failure rate decreases with a period of 24 months or more. It seems that less time cannot guarantee bone quality and vascularisation, compromising osseointegration (8,12,14).

Periodontal treatment. Periodontal scientific evidence to date supports only conservative periodontal treatment for head and neck cancer patients treated with radiotherapy. Several authors recommend conservative periodontal treatment for patients who received radiotherapy, which included scaling and root planing, curettage, long-term tetracycline therapy and oral hygiene instructions (5,10). As far as surgical periodontal treatment is concerned, there is little evidence so far. The scientific community recommends that no surgical periodontal therapy should be performed in combination with high doses of radiation.

Orthodontic extrusion and coronary lengthening. Bisphosphonate medication may increase the risk of complications with normal lateral orthodontic tooth movement, which involves bone remodelling by osteoblasts and osteoclasts, making movement 40% less effective.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Extraction in the lower jaw within the radiation field in patients with a radiation dose higher than 60 Gy represents an increased risk of developing ORN. If a post-radiation extraction is performed, a series of prophylactic measures such as alveoloplasty, primary closure and limited periosteal trauma during extraction should be taken intraoperatively. The number of teeth to be extracted in one session should be limited and low adrenaline local anaesthesia should be used. **(Grade of Recommendation: B).**

Patients treated with doses lower than 50 Gy have a similar risk of implant loss as non-irradiated patients. Therefore, an exposure of 50-65 Gy should not be considered as a limit for implant treatment. **(Grade of Recommendation: B).**

Periodontal surgery can be performed on patients after radiotherapy, although further research is needed in this area. **(Grade of Recommendation: B).**

Bisphosphonate medication may affect orthodontic movements, affecting osteoblastic and especially osteoclastic activity. Even so, an extrusion in an irradiated patient medicated with bisphosphonates is possible, avoiding an extraction and an increased risk of osteoradionecrosis. **(Grade of Recommendation: D).**

More systematic reviews, meta-analyses and prospective cohort studies on the occurrence of ORN following extraction are needed, as the exact occurrence is currently unknown. Moreover, further research should be carried out on individual surgical treatments, such as periodontal surgery or bone distraction in irradiated patients, as there is little quality evidence so far.

14. What actions during cancer treatment can reduce the appearance of caries and periodontal lesions in adult oral cancer patients?

Post-treatment hyposalivation is the main cause of numerous conditions such as dry mouth sensation or xerostomia (1). Knowing this situation, it is essential that there is a collaboration between professionals, as a dry mouth can make it especially difficult to keep teeth free of caries. This situation, together with a possible cariogenic diet, is often the cause of radiation caries (1). It has also been shown that radiation treatment results in a reduced blood supply to the irradiated tissues, which is evident during treatment. Even the redox potential is diminished, which leads to impaired healing and local immunity. This situation may even lead to the proliferation of anaerobic bacteria, a group that includes many of the bacteria associated with caries and periodontal disease (3).

EVALUATION AND SUMMARY OF THE EVIDENCE

Sennhenn-Kirchner *et al.* (4) conducted a clinical trial in patients who had been diagnosed with some form of head and neck cancer where they were able to conclude that a relationship between dental and oncological professionals is essential for the patient's well-being (4). Meca *et al.* (5) published a randomised clinical trial to evaluate the influence of chlorhexidine gluconate, sodium fluoride and sodium iodide on the concentration of S. mutans found in the saliva of irradiated patients, where they demonstrate the importance of maintaining a proper dental control not only prior to the start of radiotherapy, but also during and even at the end of it. Dholam *et al.* (7) published a randomised clinical trial to evaluate the effectiveness of applying fluoride varnish for 3 months in irradiated patients with caries and tooth sensitivity. They concluded that the application of fluoride varnish was effective in these patients, reducing radiation caries and tooth sensitivity. Gupta *et al.* (2) published a systematic review where they concluded that the main cause of this type of caries is hyposalivation, which can be prevented by avoiding radiation in the area of the salivary glands. These authors also stressed the importance of dental check-ups before, during and after RT. They refer to the importance of good patient motivation, as well as the application of fluoride (agreeing with Dholam *et al.*) and salivary flow simulators (2). The group of Sim *et al.* (8) developed two randomised, double-blind, placebo-controlled studies in 2015 and 2019. In the first, they sought to determine the effect of the application of CPP-ACP on the progression of caries in irradiated patients with nasopharyngeal carcinoma. After a follow-up period of up to three months after completion of cancer treatment, they concluded that no statistically significant results were obtained between the two experimental groups (8). In the study published four years later, they aimed to compare the effect of the same concentration of the cream (10% CPP-ACP), but this time in combination with a 0.4% SnF2 gel and a 0.32% NaF toothpaste (experimental group) compared to a placebo group without CPP-ACP, where they were able to conclude that the combination of these products gave a lower progression of coronal caries in the experimental group (9). Frydrych *et al.* (1), in reviewing the compliance of cancer patients with the anti-caries protocols proposed by professionals, showed that the presence of caries prior to starting cancer treatment was associated with a lower compliance with the established anti-caries protocol (1). Gaetti-Jardim *et al.* (3) found that radiotherapy can induce microbiological changes in the oral flora, mainly affecting the supragingival flora. They also found that micro-organisms of the genus Candida and of the family Enterobacteriaceae were increased in those cases where oral hygiene had been poor, where there was tobacco use and/or where there were cases of severe mucositis (3).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Regular check-ups of these patients before, during and after treatment are recommended. During these appointments, radiographs should be taken to help diagnose early disease, as well as clinical examinations and topical fluoride application. Various formats of fluoride application have been proposed, including combined with other substances such as chlorhexidine, as well as varnish type and others. The researchers have evaluated the number of pathogenic bacteria present in the oral cavity throughout the duration of the follow-up in order to be able to discern which of the formats and presentations are the most appropriate at any given time. (Grade of Recommendation D).

In future research it would be advisable to conduct studies with a systematic review or meta-analysis structure.

15. What information is needed in an oncological discharge summary to ensure good postoperative dental treatment?

EVALUATION AND SUMMARY OF THE EVIDENCE

The advancement and development of new techniques in the treatment of oral cancer such as surgery, chemotherapy, radiotherapy, haematopoietic cell transplantation and medical oncology have allowed the survival rate of patients to increase. However, as the number of survivors increases, the need for management of oral complications to ensure the optimal oral health and well-being of patients is becoming increasingly apparent (12). Poor or absent dental care is associated with a higher occurrence of oral cancer and a worse stage at diagnosis compared to patients who attend dental visits at least once a year. Furthermore, the risk of complications increases with the extent of oral or dental disease, comorbidities and oral hygiene (10). Therefore, the oncologist must recognise the importance of dental care before, during and after treatment. Oncologists and dentists should collaborate not only to improve patient care, as follow-up should be rigorous, multidisciplinary and coordinated, but also to maintain continuous communication to increase their knowledge of preventive and therapeutic options (8, 10-12). Patients diagnosed with oral cancer often have poor oral hygiene and oral care. Around 58 to 97% of patients have some form of dental care at the time of diagnosis, and although 94% of patients had a dental consultation prior to their radiotherapy treatment, only 53% had a dental consultation after radiation. This is of great concern because, as stated in the literature, patients who have received oral surgery, radiotherapy and/or chemotherapy treatment should have lifelong dental follow-up and rehabilitation (11), which should also be individualised according to the patient's condition (10). Some authors recommend check-ups and prophylaxis at least once a year (2) and others every 6 months (3, 10), although sometimes it may be recommended every 2-3 months (10). In any case, oral cavity care plays a crucial role in the multidisciplinary approach of the cancer survivor. To ensure proper dental care after cancer treatment, it is ideal to have a Survivorship Care Plan that not only includes useful information for the patient, on whom it has a very positive impact (4), but also for all primary care providers, where dentists should be included. The type of treatment that the patient has received is crucial in order to know the type of complications that may occur as a consequence of these, as well as the type of dental treatment that the patient may receive, especially in the case of osteoradionecrosis where, for example, it is essential to know the total dose of radiation received in order to determine the likelihood of the complication occurring.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The Survivorship Care Plan should include diagnosis of the primary cancer, TNM staging and treatment. In terms of treatment, it should include:

1. Surgical:

type of surgical approach (conventional, robotic surgery, transoral laser microsurgery) and type of reconstructive surgery (if performed).

2. Chemoradiation therapy:

Type of radiotherapy fractionation: altered fractionation, hyperfractionation or normofractionation. In this way, the likelihood of acute or late toxicities can be known. Radiation dose: amount of radiation the patient has received, as well as the duration of treatment, time elapsed since the end of treatment, whether or not it has been combined with chemotherapy, and radiation area.

- Concomitant booster radiotherapy
- Intensity modulated radiotherapy

Other: volumetric modulated arc therapy, stereotactic radiotherapy, hypofractionated stereotactic body radiotherapy.

3. Haematopoietic cell transplantation therapy.

4. Medical oncology:

treatment and symptom management of acute or chronic oral complications.

The Survivorship Care Plan should also include information on guidelines for detecting recurrence or other tumours, sequelae, and type of

follow-up care. (Grade of Recommendation D)
Future research could focus on possible barriers to regular dental check-ups by patients diagnosed with oral cancer.

16. What are the appropriate post-treatment periods after cancer treatment for different dental procedures?

In order to provide information to professionals and patients about the prognosis and associated risks of dental treatments deemed necessary to maintain oral health and quality of life in patients treated with RT to the head and neck, a question has been asked about the safest time frames for their implementation, taking into account the start and end of RT sessions.

EVALUATION AND SUMMARY OF THE EVIDENCE

Tooth extraction. The frequency of occurrence of ORN in irradiated patients is 15.3% (4), 7% according to the systematic review by Nabil *et al.* (5), 2.68% according to Yi-Fang Huang *et al.* (6), 2.6% (7) or 2.2% according to Kuo *et al.* (8), with tooth extraction being considered one of the most frequent risk factors. In cases where extractions are indicated, these should be performed prior to RT, with the recommended waiting time between extraction and the start of RT being between 10 days and 3 weeks, depending on the total dose received (10)(4). If post-RT tooth extractions are unavoidable, they should be performed under anaesthesia with low adrenaline concentration, with minimal trauma, with alveoloplasty to facilitate primary mucosal closure and under antibiotic prophylaxis (4)(8). Recommendations regarding the time that should be respected before a tooth extraction after RT treatment range from 2 to 5 years, assuming a risk of ORN of 8% and 16% respectively (5). Stratifying this period, it has been reported that extractions performed 1-3 months post-RT increase the prevalence of ORN (HR=2.63 (95% CI=1.35-2.52)) (6), although this is inconsistent with that reported by Kuo *et al.* (8), who observed a decreased risk of ORN if extractions were performed within a period less than or equal to 0.5 years (p= 0.0315) post-RT, or even during RT compared to the group of patients on whom extractions were performed pre-RT. The recommended follow-up to re-evaluate the status of the dentition in the irradiated patient and prevent risky treatments varies between 6–8-week intervals in the first year, every 2-4 months in the second year, every 6 months for the 4th and 5th year and annually thereafter (16) (14).

Oral surgery. Oral surgery increases the prevalence of ORN (31.8% versus 18.2%). Performing oral surgery from 3 months before RT to 6 months after increases the risk of ORN by 1.85 times (95% CI=1.35-2.52) (17). Chemotherapy combined with oral surgery increases the prevalence of ORN by 2.55 times (6).

Other dental treatments. The risk of different oral treatments was analysed by periods (15 days, 15 days -1 month, 1-3 months before RT, during RT and at 1 month, 1-3 months and 3-6 months post-RT) (17). Caries filling was not related to the risk of ORN regardless of whether RT is instituted before or after dental treatment (6). RT induces changes in dental tissues that compromise the adhesion of materials, and it is therefore advisable to consider modified glass ionomers (18). With regard to periodontal treatments, supra- or subgingival curettage increases the prevalence of ORN by 1.77 times, and if started between 3-6 months post-RT it increases by 2.2 times (6). Post-RT endodontic treatment increases the prevalence of ORN, especially if performed between 2 weeks and 1 month pre-RT, where the risk of ORN is 5.82 times. However, it has been suggested to perform endodontic treatment on teeth with irreparable caries in order to avoid their extraction (6). This result is contradictory to the study by Lilly *et al.* , which reports no cases of ORN in pre-RT endodontic patients, although the treated group is small, with a mean follow-up of 19 months (20). Prosthetic rehabilitation should be planned from the start of treatment. It is advisable not to use the removable prostheses usually worn by the patient during RT treatment to prevent the risk of mucosal injury. It is advisable not to rehabilitate until one year after RT and to take into account that removable prostheses favour plaque retention and mucosal injury. However, Gerngross et al. (21) observed that patients who were fitted with a removable prosthesis within 6 months post-RT had fewer mucosal complications compared to longer periods of time. With regard to fixed prostheses, there is an increased risk of caries at the crown margin, so it is advisable that the preparations be supragingival, to maintain the patient's motivation to maintain a

meticulous hygiene habit and to practise local fluoridation to prevent cervical caries (4)(7).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The results regarding the timing of post-RT extractions are contradictory. Extractions are not recommended for 2 and 5 years post-RT, and especially in the first 3 months post-RT (**Grade of Recommendation B)**. Tooth extractions performed in a period of less than or equal to 6 months post-RT decrease the risk of ORN compared to those performed after a longer time **(Grade of Recommendation B)**. Doses higher than 50-60 Gy are determinant in increasing the risk of ORN. Systemic diseases such as diabetes and chemotherapy associated with RT increase the risk of ORN **(Grade of Recommendation C).** The number of extractions performed in a single session >5, increases the risk of ORN, therefore, it is recommended to limit the number of total extractions as well as the number of simultaneous extractions **(Grade of Recommendation B)**. Oral surgery within 6 months after RT has a high risk and increases if combined with chemotherapy **(Grade of Recommendation B)**. Endodontic treatment to avoid a post-RT extraction may decrease the risk of ORN **(Grade of Recommendation D)**. The success rate is high if endodontic treatment is performed prior to RT **(Grade of Recommendation D)**. Caries fillings do not pose any increased risk relative to ORN **(Grade of Recommendation D)**. The prognosis of fillings decreases depending on the number of sides that are filled in a tooth (**Grade of Recommendation D)**. Removable prostheses should be avoided in the first year post-RT **(Grade of Recommendation D)**. Fixed prostheses increase the risk of plaque accumulation at the coronary margin associated with difficulty of hygiene and xerostomia, which is why they are discouraged, and if marginal preparations are performed, they should be supragingival to facilitate hygiene and the control of cervical caries **(Grade of Recommendation D)**. Post-RT supra- and subgingival curettage is a risk factor for ORN **(Grade of Recommendation D)**.
Prospective cohort studies of patients treated with head and neck RT are needed to determine the risk factors of dental treatments (endodontics, fillings with different adhesive materials and fixed or removable prostheses). Comparative cohort studies are needed to determine risk factors for pre- and post-RT extractions given the conflicting results found. Cohort studies are needed to determine the type and timing of prostheses in irradiated patients.

17. In which situations is palliative dental treatment justified?

There is very little literature on palliative dental treatments aimed solely at achieving the greatest possible well-being in patients with a short life expectancy in order to maintain and improve function. Wiseman (2) proposes a treatment strategy in this scenario that he calls CARE: (C) care measures to maintain or improve function, (A) throughout the changing prognosis of the disease and (RE) realistic.

EVALUATION AND SUMMARY OF THE EVIDENCE

Dental treatments

Prevention of caries.
In addition to oral hygiene at least twice daily with a soft, small-headed brush, it is proposed to incorporate fluoridation into the palliative care routine in the form of rinses, varnish or gel. Dental check-ups on an outpatient or inpatient basis should be implemented in short periods of time in order to anticipate more serious and complex complications (2)(5)(6).

Filling of cavities.
The prevalence of xerostomia and dry mouth increases in the terminal stages of the disease and, as these are factors that contribute to increased susceptibility to caries and periodontal disease, along with chronic vomiting, these patients present a high prevalence of these conditions.
It is proposed to treat them if life expectancy is reasonable and always in agreement with the patient and their relatives. Sandwich fillings with a fluoride-containing ionomer base covered with composite have been proposed. If the patient cannot withstand a long treatment session, fillings with temporary materials should be suggested (2).

Extractions.
These will be suggested when they involve an emergency due to pain or active infection, in order to ensure the patient's quality of life and to reduce potential complications (2)(5).

Fitting and maintenance of dental prostheses

The fitting of implant-supported prostheses is discouraged if life expectancy is estimated to be less than one year on the grounds that it is ethically questionable (2). Newly fitted removable prostheses must have the minimum surface area in contact with the mucosa, bearing in mind that they can cause great discomfort and mucosal injury due to dry mouth. Consideration should be given to the need to rebase existing prostheses to improve masticatory ability (2). The care of removable prostheses must be paramount. Vigorous brushing with benzalkonium chloride detergent, followed by immersion in 0.12% chlorhexidine or antifungals (2) such as 100,000 IU/CC nystatin suspension (5) is advised. It is advisable to maintain the complete upper prosthesis, when possible, to preserve the patient's image (2).

Management of mucositis, xerostomia and dry mouth

Cocks *et al.* (8) in the multidisciplinary clinical practice guideline on palliative and supportive care treatment of head and neck cancer patients, suggest topical agents such as sulcralfate, benzydamine, carbenoxolone disodium, chlorhexidine, corticosteroids or, preferably, bioadhesive gel anaesthetic preparations for the treatment of painful mucositis. Topical anaesthetics such as lidocaine can also be used to alleviate pain and hypersensitivity of the oral mucosa (6). Keratinocyte growth factor in mouthwash as a preventive treatment for mucositis in irradiated head and neck patients reduces its occurrence and pain (6).

In palliative care patients with xerostomia, different alternatives have been proposed depending on the cause, the patient's abilities, the contraindications derived from the systemic pathology and the patient's degree of dependence. Firstly, saliva substitutes such as carboxymethylcellulose, hydroxyethylcellulose or mucin can be effective in RT or pharmacological dysfunctions (10,11,12). Among the salivary production stimulants, the consumption of soft chewing gum seems to be more effective than acidic products or artificial saliva, although it may cause disorders such as headache, flatulence, allergy to additives, etc. (13). Pilocarpine and other parasympathomimetic anticholinergics have also been shown to be effective, although they should be used with caution in patients with chronic obstructive pulmonary or uncontrolled cardiovascular pathology (13). Cevimeline and amifostine also promote increased salivary flow, although they do not have a clear outcome in terms of patient perception and also have multiple contraindications (6). Acupuncture could be considered as a complementary therapy (13, 16, 17).

Treatment of candidiasis or other fungal infections

Fungal lesions are very common in patients requiring palliative care. Fluconazole is an antifungal drug with very good results in these cases. A single dose of 150 mg appears to be a good treatment in terminally ill patients with symptomatic oral fungal lesions (18).

Management of trismus

Physical treatment to increase range of motion as well as muscle and joint stretching techniques are proposed for these patients. Botulinum toxin or pentoxifylline may also improve established trismus (6).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

With regard to conservative palliative dental treatments, there is no scientific evidence on their efficacy, prognosis or on the different techniques comparing their results, although it should be kept in mind that their design might be unethical. **(Grade of Recommendation D)**. Oral hygiene care and disinfection of the prosthesis are absolutely necessary for palliative care patients as they improve their quality of life and help to preserve nutrition and hydration. This care should be provided by the patient themselves if they are able to do so or by their caregivers, whether relatives or healthcare personnel **(Grade of Recommendation C)**. The management of mucositis, xerostomia and dry mouth is widely tested. Palliative treatment aimed at improving this condition must be undertaken given its high prevalence **(Grade of Recommendation C)**. In the treatment of oral candidiasis in terminally ill patients, a single dose of 150 mg of fluconazole orally has been shown to be effective, although if they do not have a good therapeutic response or show resistance, treatment should be prolonged, or a resistance study should be conducted. **(Grade of Recommendation C)**. Complementary palliative treatment with acupuncture or electroacupuncture can be effective in reducing pain and increasing salivary flow and do not present adverse reactions, although the studies supporting these therapies are very heterogeneous **(Grade of Recommendation C)**.

Well-designed studies with a homogeneous population are needed to selectively compare palliative dental treatments in head and neck cancer patients. It is essential to incorporate the figure of a palliative dentist in hospitals and care centres for chronic and terminal patients. It is essential, given the demographic growth of the elderly population and cancer patients, to incorporate additional content into the subjects comprising the training courses for general dentistry in order to teach students about palliative dental care.

18. Following cancer treatment, what is the treatment of choice for osteoradionecrosis depending on its stage?

There are various classifications that attempt to unify diagnostic and therefore therapeutic criteria for ORN, with these four classifications being the most commonly used in published studies:

- **Marx classification (1983) [Based on response to 30 sessions of HBO]**
  Stage I: cases with exposed alveolar bone with no pathological fracture that respond to 30 immersions in HBO to achieve healing of the mucosa.
  Stage II: cases that do not respond to the HBO treatment and require alveolar sequestration.
  Stage III: cases with full-thickness bone damage or pathological fracture usually requiring total resection and soft tissue reconstruction with free graft.

- **Epstein *et al.* classification (1987) [Based on clinical and radiological findings]**
  Stage I: ORN resolved or cured.
  Stage II: Chronic (> 3 months duration), persistent, non-progressive ORN; with or without pathological fracture.
  Stage III: Progressive and active ORN, with or without pathological fracture.

- **Notani *et al.* classification (2003) [Based on clinical and radiological findings]**
  Stage I: ORN limited to the alveolar bone.
  Stage II: ORN limited to the alveolar bone and/or the upper area of the mandibular inferior dental canal.
  Stage III: ORN encompassing the mandible below the mandibular inferior dental canal and/or dermal fistula and/or pathological fracture.

- **Lyon *et al.* classification (2014) [Based on clinical and radiological findings]**
  Stage I: < 2.5 cm length of affected, damaged or exposed bone.
  Stage II: > 2.5 cm of bone, including pathological fracture and/or involvement of the inferior dental nerve.
  Stage III: > 2.5 cm length of bone, symptomatic, but without other features.
  Stage IV: > 2.5 cm length of bone, bone fracture involving the inferior dental nerve or fistula.

EVALUATION AND SUMMARY OF THE EVIDENCE

Conservative treatment

Hyperbaric oxygen (HBO) therapy is a widely used treatment, but its use is controversial, not only because of the adverse effects mentioned above, but also because of the different results obtained depending on the study. The use of HBO is recommended as a complement to surgical debridement in stage I (54% cured or improved cases) and II (25% cured or improved cases) patients, but not for stage III, according to Marx and Notani's classifications (6,7,21,22). There is no consensus on its benefits, although it is clear that it cannot be considered as the sole therapy for ORN, but rather as a complementary therapy to debridement and sequestration surgery. A systematic review conducted by Cochrane showed that HBO could prevent the development of ORN after tooth extraction in patients who have undergone previous radiotherapy (25).

With regard to hormone therapy, a study in which teriparatide hormone was administered subcutaneously in cases of ORN, after a treatment period of 4-6 months, achieved the healing of the fistula and partial bone filling of the mandibular defect,

although the cases were not staged. However, this study does not provide sufficient evidence (20).

With regard to pharmacological therapy, given that the origin of ORN is known to be non-infectious, the use of antibiotics is complementary in ORN. Furthermore, they are usually prescribed after an antibiogram has been performed and the causative bacteria are known. The most commonly prescribed antibiotics are amoxicillin-clavulanic acid, clindamycin, metronidazole and ciprofloxacin (1,5,14). Antibiotic therapy is often accompanied by a corticosteroid regimen aimed at achieving an anti-inflammatory effect. Some studies also add an antifungal regimen with fluconazole, all aimed at subsequently achieving a greater absorption of the treatment with pentoxifylline, tocopherol and clodronate (14,19). This pre-treatment regimen with PENTO or PENTOCLO usually lasts 2-4 weeks in studies (17). Studies on the pharmacological treatment of ORN are divided into two groups: those using pentoxifylline and tocopherol and those adding clodronate to the regimen. The cases included in this type of study correspond to stages II and III according to the classification of Marx, Epstein and Notani, in which orocutaneous fistula and/or pathological fracture were found in the most advanced cases (5,9,14,19,26). The treatment regimen accepted to date is that proposed by Delanian, combining 800 mg/day of pentoxifylline + 1000 mg/day of tocopherol + 1600 mg/day of clodronate (5 times/week). The addition of clodronate is based on the improvement experienced in cases of recurrent ORN after the use of pentoxifylline and tocopherol, as clodronate promotes osteoblastic differentiation and osteogenesis; although not all studies use it, as bisphosphonates can lead to osteochemonecrosis (9,26). The recommended and most widespread duration of treatment in the studies analysed is 6 months (5,14,19), although some authors recommend a period of 12 months to avoid recurrence (5,9).

Surgical treatment

Surgical treatment of ORN begins with the debridement of necrotic tissue and sequestrations in early stages. More aggressive techniques such as mandibular decortication or mandibulectomy are combined with hard and soft tissue reconstruction techniques in more advanced stages and/or in recurrent cases. Two of the compiled studies analysed surgical treatment in advanced stages (18,23).

Lee *et al.* conducted a systematic review of the use of free grafts for maxillary reconstruction to determine the failure rate, revealing that the free fibula graft was the most commonly used graft in the literature, followed by iliac crest and scapula grafts. This is because the fibula graft had the highest success rate (95.3%), and the iliac crest graft had the highest failure rate (16.3%). They concluded that the free fibula graft is considered the gold standard in the reconstruction of mandibular defects (18).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

It is important to opt for conservative therapy whenever possible as not all patients are candidates for resective surgery and not all patients wish to undergo surgery. Resective surgery and jaw reconstruction surgery should be reserved for the most severe cases **(Grade of Recommendation B).** In the early stages, conservative treatment based on antibiotics (in case of infection), analgesics, strict oral hygiene, saline irrigations, use of hyperbaric oxygen combined with debridement surgery and extraction of the affected teeth is recommended **(Grade of Recommendation D)**. In intermediate stages, two pharmacological guidelines are recommended: the first with antibiotics, anti-inflammatory and antifungal drugs as prior therapy and then pentoxifylline, tocopherol and clodronate, combined with the implementation of sequestrectomies or alveolar mandibulectomy when necessary, as this would accelerate healing **(Grade of Recommendation D)**. In advanced stages and in aggressive or recurrent cases, resective mandibular treatment and reconstruction with bone grafting is recommended, with free fibular grafting having the highest success rate **(Grade of Recommendation B)**.

Randomised clinical trials and more prospective cohort studies are needed to determine the best treatment option according to the patient's stage and comorbidity. Pharmacological therapy is the most promising and is where future research studies should be directed. They should also apply the same patient staging criteria, focusing on dose and duration of treatment. More standardised studies could lead to systematic reviews and meta-analyses.

19. Following cancer treatment, what is the treatment of choice for drug-induced osteochemonecrosis or osteonecrosis depending on its stage?

In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) established the stages of osteonecrosis caused by taking bisphosphonates. This classification is still used to stage osteonecrosis induced by any type of drug (6):

- **Stage 0:** No clinical evidence of necrotic bone, with non-specific but disease-related radiographic signs and presence of symptomatology.
- **Stage 1:** Exposure of necrotic bone or presence of fistula probing to bone in asymptomatic patients with no evidence of infection.
- **Stage 2:** Exposure of necrotic bone or presence of fistula probing to bone, associated with infection, pain and erythema in the region of the exposed bone with or without purulent drainage.
- **Stage 3:** Exposure of necrotic bone or fistula probing to bone in patients with pain, infection and at least 1 of the following: exposure of necrotic bone with extension beyond the alveolar bone (inferior border and mandibular ramus, maxillary sinus, maxillary zygoma) resulting in a pathological fracture, extraoral fistula, oronasal/orantral communication or osteolysis extending to the inferior border of the mandible or the base of the maxillary sinus.

The usual treatment for early-stage oral cancer (1 and 2) is surgery or radiotherapy.

In locally advanced stage (3), both treatments are combined, and a second tissue reconstruction surgery may be necessary. Chemotherapy is also another treatment option in stage 3/4 that can be combined with radiotherapy. Recently, a new generation of drugs has emerged as an alternative to traditional chemotherapy, called targeted therapy or molecular therapy. In the case of head and neck cancer, this therapy is based on monoclonal antibodies and immunotherapy.

Like with osteoradionecrosis, the treatment of osteochemonecrosis is also based on a combination of conservative and surgical treatment.

EVALUATION AND SUMMARY OF THE EVIDENCE

After an exhaustive search of the literature, no publications were found on osteonecrosis caused by taking chemotherapy drugs in oral cancer, therefore, an attempt has been made to extrapolate treatment guidelines and formulate recommendations according to the stage of osteonecrosis associated with chemotherapy drugs used in head and neck cancer that are also applied in oral cancer. Studies on osteonecrosis associated with non-antiresorptive drugs have also been included.

Conservative treatment

There is increasing evidence that "conservative-surgical" treatment based on the debridement of necrotic bone and subsequent suturing would be more effective than conservative treatment in stages 1 and 2, based on the clinical guideline described in 2014 by Ruggiero *et al.* (aimed at osteonecrosis caused by bisphosphonates and denosumab) for staged treatment in the case of osteochemonecrosis caused by non-antiresorptive drugs (2).

The conservative treatment of chemonecrosis is based on the use of antibiotics, mouth rinses, hyperbaric oxygen (HBO), low-power laser treatment, plasma rich in growth factors or treatment with pentoxifylline and tocopherol (18,21,24).

The use of hyperbaric oxygen as an adjunctive therapy in the treatment of osteochemonecrosis reduces the symptom resolution time and is associated with a higher rate of clinical improvement compared to the use of surgery and antibiotics alone. There is no consensus as to its benefits, although it is clear that it is considered an adjuvant therapy to debridement and sequestration surgery (22).

The low-power laser used for treating osteochemonecrosis is the Er:YAG laser, which is used in patients in early and advanced stages, with the highest prevalence of use in stages 2 and 3. However, there is insufficient evidence to be able to state that the laser is superior to the usual surgical interventions in terms of completely curing the lesions. Other publications estimate that its use would be more effective in conservative treatment combined with other therapies. On the other hand, the combination of surgical and laser treatment would not offer significant improvements in patients (21). In terms of its analgesic function, there is insufficient evidence to show superiority over other treatments, although it would be more effective in early stages with regard to the stimulation of bone for-

mation (24).
The effectiveness of treatment with platelet concentrate is controversial and there is little evidence on the subject. The three most commonly used platelet concentrates are growth factor-rich plasma, platelet-rich plasma and fibrin-rich plasma. It provides a higher cure rate in combination with surgical treatment, but the results are unclear (23).
With regard to the use of pentoxifylline and tocopherol in the treatment of antiresorptive osteochemonecrosis, the evidence is still very limited and, although the treatment is promising, the level of evidence and the quality of the articles published to date are insufficient (18).
Although the classification by Ruggiero *et al.* is commonly used in all publications, the type of treatment according to stage has changed since the publication of this classification. In this classification, conservative non-surgical treatment is recommended for stage 1, which causes asymptomatic bone exposure (6). However, a year later (2015), this same author conducted a cohort study in which it was observed that those patients who received stage 1 and 2 surgical treatments were 28 times more likely to improve or be cured than those who received conservative treatment. Moreover, stage 1 and 2 patients had better results after treatment than stage 3 cases. They concluded that patients who received surgical treatment at earlier stages were more likely to improve or completely cure the lesions (19). Ristow *et al.* wanted to analyse whether conservative treatment was effective in early stages, observing that 91.3% of patients not only did not improve, but that there was progression of the pathology to stages 2 and 3 in approximately 80% of cases and 68% of cases required surgical treatment. The authors concluded that conservative treatment should be reserved for patients who are reluctant to undergo surgery or whose overall medical condition discourages intervention (25), a conclusion also reached by ElRabbany *et al.* (12).
A European expert committee on the management of drug-induced osteonecrosis was held in 2019. The need to review the indicated treatment depending on the stage was highlighted in the consensus article by Ruggiero *et al.* in 2014. In this study, conservative treatment is recommended for stages 1 and 2 and surgical treatment for stage 3. The latest published studies reinforce the evidence that removal of necrotic bone could be curative (with mucosal closure, disappearance of symptoms and prevention of pathology progression) in all stages of osteochemonecrosis, with surgical treatment having the highest success rate (20,25,28).

Surgical treatment

The preferred surgical treatment in patients with osteochemonecrosis would be resective surgery with healthy margins and subsequent microvascularised grafting, which has been observed to have a total mucosal cure rate of 97% (17).
The therapeutic decisions outlined so far contradict the systematic review conducted by Nicolau-Gakitis in 2019, based on osteochemonecrosis caused by non-antiresorptive drugs (antiangiogenic and chemotherapy drugs, among others). The conclusion of the authors was that, because the half-life of non-antiresorptive drugs (5 hours-32 days) is much shorter than that of antiresorptive drugs (25-360 days), the prognosis of this type of osteonecrosis is better, with faster healing and a higher cure rate, which would justify the preferred use of conservative rather than surgical treatment in osteochemonecrosis related to non-antiresorptive drugs (15).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The following recommendations are adapted from the classification described by Ruggiero *et al.* in 2014 (6). Due to the lack of published articles on osteochemonecrosis in patients with oral cancer, the recommendations have been formulated based on evidence extrapolated from other studies that are also not directly applicable to the target population (Grade of Recommendation D). In at-risk patients, only patient education about the problem should be incorporated, no treatment is necessary. In stage 0, it is recommended that treatment be systemic and based on pain control (analgesics) and the occurrence of possible infections (antibiotics). This treatment modality is also recommended for elderly patients, patients who are not candidates for surgery or cancer patients with palliative treatment (Grade of Recommendation D). In stages 1 and 2, conservative-surgical treatment is recommended based on debridement with removal of possible sequestrations and in combination with adjuvant conservative treatment: 0.12% chlorhexidine rinses, microbial culture to guide the antibiotic regimen, analgesic regimen and/or hyperbaric oxygen

(Grade of Recommendation D). In stage 3, surgical treatment combined with antibiotic and analgesic treatment is recommended. Surgical treatment will vary depending on the size of the lesion: surgical debridement, alveolectomy, marginal or segmental mandibulectomy, and may be accompanied by reconstructive surgery (microvascularised free graft) (Grade of Recommendation D).
Due to the limited existing literature, prospective cohort studies are needed to establish the frequency and origin of osteonecrosis due to drugs used in oral cancer, as well as randomised clinical studies to determine the best treatment depending on the stage of the pathology. It would be important to know what the effect of this type of drug is on the patient's immunological, angiogenic and bone remodelling levels and to what extent it would be associated with the development of subsequent osteonecrosis.

20. Following cancer treatment, what is the treatment of choice for xerostomia depending on its stage?

The stages of xerostomia have been assessed by different scales based on the patient's subjective feelings. It has also been objectively quantified by measuring total salivary flow under basal conditions or stimulated with different substances or physical means. Among the most frequently used subjective scales that can be used as a reference for the classification of xerostomia and the assessment of treatment results, the 4-point Likert Scale, the Quality of Life Assessment (QoL), the Visual Analogue Scale (VAS), CTC 3.0 (5,6), CTCAE v5.0 (7), LENT-SOMA Analytical Scale (8), RTOG-EORTC, and EORTC-QLQN&H (9) are proposed. Knowledge of different grading scales will allow for the interpretation of the results of the treatments that have been tested in order to improve this life-limiting situation of patients suffering from xerostomia, although it has been shown that the concordance between the degree of xerostomia given by professionals is lower than that perceived by patients (10,11). Changes in protocols make it necessary to re-evaluate the indications for the different treatments of xerostomia in the context of a patient who has undergone head and neck irradiation and to reconsider these indications, the efficacy level of the proposed therapies and the described adverse effects, as well as new possibilities.

EVALUATION AND SUMMARY OF THE EVIDENCE

1. Pharmacological, chemical and phytotherapy treatments.

Pilocarpine and cevimeline, when compared with placebo, showed equal benefit in terms of increased salivary flow in the short-term (12), although their adverse effects such as nausea, vomiting, sweating and polyuria should be taken into account and may be aggravated in elderly patients taking other drugs simultaneously, which may lead to high intolerance and a clear contraindication (13).
Amifostine has been shown to be effective in reducing the risk of developing grade 3-4 mucositis, acute grade 2-4 xerostomia, or delayed grade 2-4 or grade 3-4 dysphagia based on an assessment of treatment response (partial or complete resolution) evaluated at 6 weeks, as proposed by the World Health Organisation (WHO) (16). Amifostine significantly reduces mucositis, xerostomia and dysphagia without protecting the tumour in patients treated with RT, with acceptable toxicity (17). Other studies have reviewed different treatments according to the degree of intensity of xerostomia as measured by the 4-stage SOMA analytical scale. Depending on the degree of impact, different actions are proposed: in grade 1, no action; in grade 2, saliva substitutes, sugar-free sweets or chewing gum and sialogogues occasionally; in grade 3, the same measures used more frequently; and in grade 4, the use of saliva substitutes, water with meals, sugar-free sweets, chewing gum and sialogogues. The use of other substances such as benzydamine, aloe vera gel or honey products may also be advisable (8).
Malic acid has also been used as a sialogogue, achieving up to a 15-fold increase in salivary flow (18).
According to the NCI CTCAE v3.0 scale, bethanechol chloride improves xerostomia in grade 3 patients (21).
Another drug studied has been Visco-Ease® (LMS 611), but no improvement has been found (22).
Thyme and honey rinses have shown a statistically significant improvement in quality of life, pain support and dysphagia, with 0% Grade 3

and 4 xerostomia found after 7 weeks of use, and all symptoms evaluated at one month were downgraded to grades 3 and 4 on the Likert scale (3).

When analysing the effect of phytotherapy in the form of a mixture of multiple herbs used in traditional Chinese medicine on the VAS and QoL scales, there was an improvement in terms of speech, eating and perceived pain (23).

2. Treatments with physical agents

Laser phototherapy has been shown to be useful as an adjuvant to improve salivary gland hypofunction with a regimen of three sessions per day, even if patients are treated with concomitant CT (24).

When evaluating the use of hyperbaric oxygen (HBO) according to the [EORTC] QLQC30, EORTC QLQ Head and Neck Cancer Module (H&N35), Performance Status Scale, and a VAS scale for dry mouth and pain symptoms, a significant improvement is found in the parameters of "swallowing" from EORTC H&N35, "dry mouth" from EORTC H&N35, "sticky saliva" from EORTC H&N35, "eating in public" from PSS and "mouth pain" according to VAS, concluding that treated patients have a better quality of life. Other studies have also shown that the increase in salivary flow produced by HBO leads to an improvement in the VAS scale (11, 27, 28).

Transcutaneous nerve stimulation (TENS) has also been shown to be effective in the treatment of xerostomia as it improves salivary flow in a statistically significant way (29).

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

The indications and results regarding the use of pilocarpine and cevimeline for the treatment of xerostomia caused by radiotherapy cannot be related to the degree of glandular impact prior to their administration. Their effect is determined by the degree of glandular preservation. The adverse effects of pilocarpine may be a restriction of its indication **(Grade of Recommendation B)**. Amifostine was shown to be effective in reducing the risk of developing grade 3-4 mucositis, acute grade 2-4 xerostomia or delayed grade 2-4 or grade 3-4 dysphagia but was not effective in the subgroup of patients concomitantly treated with chemotherapy. Although it may be debatable, it has no tumour protective effect, but has adverse events **(Grade of Recommendation A)**. Depending on the degree of xerostomia, different actions are proposed: grade 1, no action; grade 2, saliva substitutes, sugar-free sweets or chewing gum and sialogogues occasionally; grade 3, the same measures used more frequently; and grade 4, the use of saliva substitutes, water with meals, sugar-free sweets, chewing gum and sialogogues **(Grade of Recommendation: A grade of recommendation cannot be established)**. Malic acid or acidic sweets with added calcium are effective and decrease the risk of caries development by dissolving hydroxyapatite **(Grade of Recommendation: A grade of recommendation cannot be established)**. Betanechol decreased the severe grade and increased the proportion of medium grade **(Grade of Recommendation C)**. Phytotherapy, thymol and honey are effective in the treatment of xerostomia. Rinsing with thymol and honey can reduce xerostomia in grade 3 and 4 patients **(Grade of Recommendation B)**. Visco-Ease® has not been shown to be effective **(Grade of Recommendation: A grade of recommendation cannot be established)**.

Hyperbaric oxygen may have beneficial effects on xerostomia related to grades of impact **(Grade of Recommendation B)**. Studies assessing the efficacy of TENS report significant differences in flow increase after application but do not relate them to the degree of pre- and post-xerostomia severity **(Grade of Recommendation D. The grade of recommendation for treatment depending on the degree of severity of xerostomia cannot be established).** Invasive treatments such as submaxillary gland reimplantation or ultrasound-guided infiltration of mesenchymal stem cells, although they offer good results, refer to studies with a small number of patients or with a short follow-up and do not compare their results according to the degree of severity of xerostomia **(Grade of recommendation B. A grade of recommendation for glandular reimplantation cannot be established. The grade of recommendation for treatment depending on the degree of severity of xerostomia cannot be established)**.

Although xerostomia grading scales are fairly equivalent, they are multiple and do not facilitate the comparison of results between published studies. The different degrees of xerostomia are not always related to the initial values and those obtained after the treatments proposed to improve the symptoms of xerostomia. For these reasons, it would be necessary to formalise the design and reporting of treatment results in future studies. Local treatments such as mesenchymal stem cell transplantation, TENS or topical treatments in the form of mouthwashes that do not cause adverse effects should prevail until systemic treatments without toxicity are found. The long-term effects of the proposed treatments should be investigated.

21. What are the indications and time frames for the prosthetic and implant rehabilitation of adult oral cancer patients?

The morbidity of therapies used for the treatment of oral cancer is very high and seriously affects the patient's functional (chewing and speech), aesthetic and psychosocial ability. The functional rehabilitation of these patients is a primary objective for their physical and psychological well-being and for the positive evolution of their disease. Studies examining the quality of life of patients with head and neck cancer after completing cancer treatment have reported that recovery of their oral function, through prosthetic rehabilitation, is of the utmost importance (1,3). In this regard, the sequelae of cancer surgery often include an altered oral anatomy, secondary to the loss of bone and soft tissue structures or tissue reconstructive techniques. This fact means that the use of conventional prostheses for the oral rehabilitation of these patients can in many cases be compromised or impeded, making their functional recovery a challenge. In these situations, dental implants are used as a valid alternative to achieve optimal rehabilitation in terms of chewing, speech and aesthetics. However, their use is not free of controversy in terms of their impact on the patient's quality of life, the ideal time for their placement with respect to surgery and/or radiotherapy (RT), the osseointegration time (OI) required, the factors that may influence implant survival such as RT, the nature of the bone bed (native versus grafted), the maxillary or mandibular location, the number of implants or the type of prosthesis to be designed and its complications.

EVALUATION AND SUMMARY OF THE EVIDENCE

The influence of oral rehabilitation on the patient's quality of life is analysed by 10 articles (4-7,11-16), three (8-10) study the influence of the timing of prosthetic treatment on results and 17 (17-33) assess the influence of different factors on implant and prosthetic survival.

1. IMPACT OF PROSTHETIC REHABILITATION ON THE PATIENT'S QUALITY OF LIFE

The studies include very heterogeneous groups of patients in terms of the stage of their disease, the treatment received and the post-surgical anatomical deficit, but they coincide in highlighting a significant improvement in quality of life and in the level of satisfaction and masticatory function after prosthetic rehabilitation. Rehabilitation with conventional prostheses resulted in an improvement in the quality of life of all patients analysed by Dholam *et al.* (4) one year after prosthetic rehabilitation, with patients adapting well to the prostheses. The studies (5-7,11,14) that compare satisfaction, prosthesis retention, masticatory performance and force between patients rehabilitated with conventional prostheses and implant-supported prostheses coincide in indicating better functional results (objective masticatory retention and force) with implant-supported prostheses, but disagree in confirming the existence of a significant difference in terms of the quality of life and satisfaction described by the patient themselves. Studies exclusively analysing patients rehabilitated with implant-supported prostheses agree that rehabilitation led to an improvement in both quality of life and functional satisfaction compared to before rehabilitation (12, 13, 15, 16).

Given that xerostomia and tissue fibrosis secondary to radiotherapy may hinder the use of prostheses, some authors have tried to analyse whether the improvement in quality of life and satisfaction provided by their prostheses varies between irradiated and non-irradiated patients. Thus, the only study that refers to conventional prostheses (4) reports that irradiated patients showed no difference in the perception of their quality of life compared to non-irradiated patients, one year after rehabilitation and use of their prostheses. With regard to implant-sup-

ported prostheses, patients who were irradiated at doses of 60-70 Gy showed lower satisfaction and lower subjective masticatory function with their prostheses than patients who were not irradiated, even though the objective bite force and masticatory efficacy were similar (5). In another study, patients who underwent radiotherapy had significantly worse results for the following parameters: masticatory function, pain, mouth opening and functional limitation, physical and social disability (11), although when the total radiation dose was less than 46 Gy, RT did not significantly influence the quality of life results of patients after implant-supported prosthetic rehabilitation (13).

2. IDEAL TIMING FOR REHABILITATION WITH RESPECT TO SURGERY AND/OR RADIOTHERAPY

2.1. Timing of implant placement in relation to cancer surgery:

The 3 studies (5,8,10) analysing this focus their interest on the suitability of their placement during cancer surgery, comparing the results with those placed later. With regard to the deferred technique, most of the studies analysed delay implant placement by 12 to 14 months, as the first year after the initial cancer treatment is the period in which the greatest number of recurrences occur. The studies analysed (5,8,10) coincide in pointing out that simultaneous or delayed implant placement did not influence the survival of the implants once they had been loaded. Woods *et al.* (8) report survival rates of 94.8% at one year and 77.55% after 4 years of loading with no differences between the two techniques. Wetzel *et al.* (5,10) report similar failure rates, with no significant differences between simultaneous and delayed implant placement. The authors also agree that the simultaneous technique resulted in a significant shortening of the time to final prosthesis placement, but also in a high percentage of implants that were not loaded. The authors suggest that when considering implant placement during ablative surgery, the oncological prognosis and overall life expectancy of each patient should be taken into account.

2.2. Timing of implant placement in relation to RT:

Implant survival appears to be significantly influenced by the total dose of radiation administered and the timing of implant insertion from the completion of radiotherapy, with better results reported for implants placed at least 14 months after completion of radiotherapy (9). On the contrary, another study found no difference between placement before or after 12 months post-radiotherapy (20).

2.3. Osseointegration time:

In all studies analysed (9,11,15,18,19,21,23,28), it is recognised that an osseointegration time equal to or greater than 6 months is associated with a higher success rate if we compare with lower osseointegration times and, moreover, most of them advocate performing the submerged technique and avoiding or contraindicating immediate loading. The two studies (9,28) that specifically analyse the influence of OI time on implant survival coincide in pointing out that OI periods of less than 6 months are significantly associated with implant loss.

3. FACTORS WITH A POSSIBLE INFLUENCE ON THE RESULTS

3.1 Radiotherapy:

Various studies (9-11,13,15-20,22,26-33) refer to the influence of radiotherapy on prosthetic rehabilitation, with most of them agreeing that radiotherapy has a negative influence on implant survival. In terms of the implant placement bed, worse results were observed among irradiated patients in whom implants were placed in bone grafts compared to those who were placed in native bone (22).

3.2 Nature of the implant bed:

Fibular grafting is the “gold standard” in those patients requiring hard and soft tissue reconstruction that restores anatomy, function and aesthetics. Various studies (17,19,22-24,27,29,32,33) analysed the influence of the nature (native/grafted) of the bed on the survival (SV) of implants, most of them finding worse results in implants placed in grafted bone.

3.3 Location:

Various studies (26-29,32) found no differences in implant survival in terms of maxillary or mandibular location, while in other cases significantly better results were observed for implants placed in the mandible than for those inserted in the maxilla (20,21,24). With regard to anterior or posterior location, more failures are observed in the posterior area of both the maxilla and the mandible (28, 29).

3.4 Number of implants:

When comparing the result of treatment in patients rehabilitated with implant-supported overdentures over 2 or 4 implants in patients reconstructed with vascularised fibula graft and in native bone respectively, no differences were found in terms of the number of implants or the type of attachment used (11, 23).

4. COMPLICATIONS DERIVED FROM IMPLANT-SUPPORTED REHABILITATIVE TREATMENT:

With regard to peri-implantitis, some of the studies analysed show results similar to those described in non-cancer patients, without mentioning the criteria adopted for its diagnosis (18, 23, 29), while in other cases percentages of 67% have been found, pointing to the absence of inserted mucosa as the risk factor most associated with it (27). Most authors describing complications (18, 23, 27, 31) agree that there is a higher occurrence of peri-implant hyperplastic lesions compared to conventional cases, describing them as lesions accompanied by marginal bone loss and associated with the emergence of implants in alveolar mucosa and skin grafts.

Few studies provide data on ORN in these patients and its occurrence varies between 0 and 7.7% (10, 19, 23). With regard to preventive treatment with hyperbaric oxygen and the administration of systemic proangiogenic medication for preventing ORN in oral cancer patients who are going to undergo implant placement, there are still no published clinical trials to support or discourage their use.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

Prosthetic rehabilitation, both conventional and implant-supported, of patients treated for oral cancer significantly improves their quality of life and masticatory function **(Grade of Recommendation B)**. Implant-supported prostheses provide the patient with better functional results than conventional prostheses, with no significant differences in terms of quality of life and patient satisfaction, therefore, their indication should be directed to cases in which a clear functional deficit is confirmed or expected with conventional prostheses **(Grade of Recommendation C)**. The studies analysed do not indicate that simultaneous or delayed implant placement influences implant survival after loading. Although the simultaneous technique resulted in a significant shortening of the time to final prosthesis placement, it resulted in a high percentage of implants that were not loaded **(Grade of Recommendation C)**. A time interval of 12-14 months from completion of cancer treatment to implant placement is considered necessary **(Grade of Recommendation D)**. Osseointegration periods of less than 6 months are significantly associated with implant loss **(Grade of Recommendation C).** Treatment with RT and the nature of the bone bed negatively influence implant survival, showing worse results for irradiated patients and for implants placed in grafted bone **(Grade of Recommendation B).** There are no differences in survival between implants located in the maxilla or mandible, but more failures are observed in the posterior area **(Grade of Recommendation D)**. The prevalence of peri-implantitis in these patients differs according to the authors, although they agree that the local and overall conditions in these patients are more conducive to peri-implantitis than in the general population **(Grade of Recommendation D)**. Patients treated for oral cancer show a higher occurrence of hyperplastic peri-implant lesions than the general population, associated with the absence of inserted keratinised mucosa, given their more frequent emergence in alveolar mucosa and skin grafts **(Grade of Recommendation C).** The few data reported on the occurrence of ORN in these patients reveal that it is not the main cause of implant failure, although it may be its cause. Smokers have a higher risk of developing ORN, with smoking being a predictive risk factor for its development **(Grade of Recommendation C)**.

Heterogeneity in the characteristics of the patients included in the various studies in terms of their overall condition, stage of disease and oral situation after cancer treatment make it difficult to extrapolate accurate results on the variables studied. Prospective studies are needed to describe the criteria for inclusion/exclusion of patients taking into account their comorbidities (dysphagia and/or xerostomia) and their prognosis. Data on the aetiology of non-loaded implants are needed, as well as a more accurate description of the complications of non-loaded implants.

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