

# Endodontic Treatment and Prevention of Osteonecrosis in Patients undergoing Radiation and/or Bisphosphonate Therapy: A review of the Literature and Recommended Treatment Protocol

Review Article

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## Abstract

The annual incidence of head and neck cancers worldwide is more than half a million cases. 85% of these patients are to receive radiation treatment. Bisphosphonates (BP) are nowadays a common choice of therapy for osteoporosis and other skeletal related conditions. Of the most severe oral complications of radiotherapy and BP therapy is osteonecrosis of the jaw (ONJ). ONJ is an alarming medical condition, that can be very painful, deteriorate patients' everyday life and, if not timely diagnosed, may demand extended surgical treatment, as both radiation and BP affects the activity of osteoclasts and osteoblasts and also damages blood vessels.

Endodontic therapy has an important role in these patients' dental management. At the pretreatment phase, root canal treatment is needed to be performed to teeth with pulpal inflammation or necrosis, or apical periodontitis, in order to prevent the complication of flare-up of periapical lesions. At the post-treatment phase, endodontic therapy is the treatment of choice for inflammation of odontogenic origin, especially when extraction poses a high risk of osteonecrosis. Additionally, the clinician should be aware of the precautions needed to be addressed, in order to perform endodontic treatment safely to these patients. A recommended protocol is presented and discussed herein, concerning these cases, based on individualized manifestation of complications.

**Keywords:** Endodontic Treatment, Osteonecrosis, Osseonecrosis, Prevention, Treatment Protocol, Radiation Therapy, Bisphosphonates

## Introduction:

The annual incidence of head and neck cancers worldwide is more than 550.000 cases [Web Reference 1]. According to Cancer Research UK, up to 85% of these patients receive radiation treatment. Oral complications of radiotherapy can compromise patients' health and quality of life or even affect and postpone their cancer treatment. The most severe complication is osteoradionecrosis, or most commonly referred as osseonecrosis or osteonecrosis. Osteonecrosis of the jaw (ONJ) is an alarming medical condition, that can be very painful, deteriorate patients' everyday life and, if not timely diagnosed, may demand extended surgical treatment.

ONJ is also associated with antiresorptive medications including bisphosphonates such as alendronate, risedronate, ibandronate, zoledronic acid and denosumab [1]. Bisphosphonates (BP)

are the drugs of choice for patients suffering from osteopenia, osteoporosis, Paget's disease, multiple myeloma and bone metastases. Since their appearance more than 50 years ago, their use has been increased exponentially [2].

Malignant-suffering patients have started to become a more frequent encounter in everyday dental practice. Thorough medical and dental history is essential in these cases [Web Reference 2]. The clinician should be aware of the details of the disease, along with the type, time and duration of treatment (and medication administered), in order to prepare the appropriate treatment plan [3].

Unfortunately, not all patients are informed that dental evaluation (and possible treatment) is mandatory before this kind of treatments, while about 80% of patients who are about to receive radiation need some kind of dental care [4]. After

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radiation and BP medication, invasive dental treatments or even oral infections alone can cause osteonecrosis.

Endodontic therapy has an important role in these patients' dental management. At the pretreatment phase, root canal treatment is needed to be performed to teeth with pulpal inflammation or necrosis, or apical periodontitis, in order to prevent the complication of flare-up of periapical lesions. At the post-treatment phase, endodontic therapy is the treatment of choice for inflammation of odontogenic origin, especially when extraction poses a high risk of osteonecrosis [5]. Additionally, the clinician should be aware of the precautions needed to be addressed, in order to perform endodontic treatment safely to these patients. A recommended protocol is presented and discussed herein, concerning these cases, based on individualized manifestation of complications.

### **Osteoradionecrosis**

Oral complications occur in all patients receiving head and neck radiation and include oral mucositis, xerostomia, taste alterations and functional disabilities (Web Reference 2). Radiation can also cause radiation caries, trismus, osteoradionecrosis (ORN) and affect the pulpal microcirculation. The changes of pulpal microcirculation can lead to negative response to pulp tests but this is temporary. The circulation can be normal about 5 months after radiation and thus the clinician should take that into consideration before making any decisions for treatment [6,7]. From the above complications, xerostomia and ORN have the worse impact in patients' quality of life [8]. Xerostomia is caused from salivary gland dysfunction, a common side effect of radiotherapy [8]. Patients usually recover from xerostomia but it can last up to 2 years [9]. Severe xerostomia, combined with the susceptibility of hard tissues to demineralization after radiation, causes rapidly progressing post-radiation caries [10]. This type of caries often starts from labial cervical areas and soon it extends and encircles the tooth. It can also affect smooth surfaces like anterior teeth which is not common for typical caries thanks to continuous flow of saliva [10].

In 1983, Marx defined Osteoradionecrosis (ORN) as "an area larger than 1 cm of exposed bone in a field of irradiation that failed to show any evidence of healing for at least 6 months" [11]. Radiation affects the activity of osteoclasts and osteoblasts and also damages blood vessels. These two aforementioned actions combined have a negative impact in repairing and healing ability of the bone. Marx Staging system of ORN is the most common today. The risk of ORN depends on many factors such as radiation dose, radiation technique, tumor location and oral hygiene [12]. The prevalence varies in the literature and ranges from 0,4% to 56% [13].

A group of drugs, the family of bisphosphonates, can also cause osteonecrosis, as they suppress the metabolism rate of bone modelling/remodelling. Those drugs are prescribed for treatment of osteoporosis and specific types of cancer that cause bone damage. For patients who receive this medication, bisphosphonate – related osteonecrosis of the jaw (BRONJ) is an uncommon but serious oral complication [14]. According to American Society for Bone and Mineral Research, BRONJ is defined as an exposed area of the bone in the upper or lower jaw, in the maxillofacial region, which does not recover within 8 weeks after diagnosis in a patient taking a BP, who has not received radiation therapy in the maxillofacial region. In 2014, American

Association of Oral and Maxillofacial Surgeons proposed the term medication-related osteonecrosis of the jaw (MRONJ) in order to accommodate the growing number of osteonecrosis cases involving the maxilla and mandible associated with other antiresorptive (denosumab) and antiangiogenic therapies. MRONJ is highly associated with intra venous (IV) bisphosphonates whereas oral BP cause BRONJ in about 4% of the cases [15]. The prevalence of this complication varies from 0-28% [16]. The risk of BRONJ depends on several factors such as type of BP, frequency of use and therapy duration. 64% of BRONJ are triggered from extractions and trauma. Moreover, periodontitis accompanies 84% of BRONJ cases [17]. BRONJ can be asymptomatic for a long time or cause symptoms like tooth mobility, ulcer, swelling and paresthesia [17].

The above symptoms can appear before the alveolar bone gets exposed [16]. The appearance of symptoms before BRONJ diagnosis can lead the clinician to false diagnosis of odontogenic pain and thus extractions. In those cases, healing will not occur after normal healing period.

### **Preventive Treatment:**

The time period between diagnosis and starting of therapy or medication is usually short. Ideally, the preventive dental treatment should start at least one month before the beginning of radiation or BP treatment because that time period is enough for oral evaluation and recovery after invasive dental treatment [Web Reference 3]. The healing period of periapical lesions can last from 6 months to 4 years [18]. Periapical healing cannot be confirmed one-month post-op and as it is discussed below, extraction is recommended in cases of periapical disease. Apart from the recommended dental treatments, it cannot be highlighted enough that this effort will lead to desirable results only when combined with proper education of oral hygiene.

The clinician should form a treatment plan before radiation or BP treatment starts. A common dilemma is whether to endodontically treat or extract teeth with severe caries. According to Schiodt's model [19], prior to radiation therapy, teeth with deep caries (nonreparable), root caries > ½ of root circumference, internal or external resorption and pulpal combined with periapical disease should be extracted because of their high dental risk factor (DRF). According to Bruins, DRF is defined as "dental disease unrelated to cancer therapy that directly and/or indirectly increases the risk for oral complications of cancer therapy" [20]. Schiodt also takes into consideration for the treatment plan conditions associated with a high malignancy-related risk factor. The clinician's goal should always be to prevent the appearance of oral inflammation after radiation or BP treatment. At the pretreatment period it is also important for the dentist to combine recommended protocols with clinical judgement. For example, in a case of severely poor oral hygiene, the treatment plan may be more aggressive.

In the pretreatment phase, it is essential to check the vitality of all teeth but also be able to differentiate the necrotic pulp from the stressed pulp syndrome in order to avoid unnecessary root canal treatments. According to Abou-Rass, "the term "stressed pulp" describes a vital dental pulp that has been subjected to repeated damage, including operative trauma, accidents, or other pathologic changes" [21]. The clinician should keep in mind that the stressed pulp condition may be asymptomatic but after crown preparation or failed restorations, it can lead to diseased and necrotic pulp [21].

The clinician should also be able to evaluate the existing endodontic treatments. Endodontically treated teeth without periapical lesion should be followed-up every 6 months. In cases of periapical lesion, the clinician should evaluate the quality of treatment and previous radiographs. If the quality of treatment is adequate and it is apparent from previous radiographs that the lesion is healing or healed with scar tissue, there is no need for retreatment or extraction as these cases are not considered dental conditions with high DRF [19].

In any other case, when the treatment is inadequate and unsuccessful, retreatment or extraction should be considered. The final treatment plan is affected by remaining time until radiation or BP treatment begins. Unfortunately, in most cases patients seek dental evaluation just before their treatment starts and so root canal retreatment and waiting for healing is not an option.

### **Recommended Protocol for Endodontic Therapy**

#### **Before Endodontic Treatment:**

Communication with patient's physician is essential before any treatment plan. Medical history should include type, time and duration of medication with details and sometimes this information cannot be provided by the patient. Informed consent is also necessary. Diagnostic periapical x-rays may be challenging in cases of severe trismus. Smaller sizes of films which are usually used for children can be useful.

#### **Antibiotic Prophylaxis:**

According to a 2017 position statement of AAE, clinician should decide whether or not to prescribe antibiotic prophylaxis prior to surgical procedures in patients at a significant risk for medication-related osteonecrosis of the jaw depending on his judgement and consultation of patient's physician [22]. Similarly, in an ESE position statement, prophylaxis is proposed for patients who receive IV bisphosphonates prior to endodontic surgery and for irradiated patients prior to nonsurgical endodontic treatment [23]. Although it is clear that all patients after radiation of head and neck should receive antibiotic prophylaxis before endodontic treatment, guidelines for patients receiving BP medication are unclear. Several authors propose antibiotic prophylaxis in the following cases: necrotic infected pulps in patients receiving IV BP treatment and in patients treated with oral BP medication for more than 3 years [14,24].

#### **Preparation for Treatment:**

Mouthwash rinse with chlorhexidine for one minute can reduce the number of microorganisms of the oral cavity and thus the possibility of bacteremia in case of soft tissue trauma [25,26]. Anesthetics without vasoconstrictors are the indicated choice because the blood circulation of the area is impaired [27,28]. Aseptic conditions are mandatory and thus rubber dam is necessary. Even though it is not proven that traumatic clamp placement can cause osteonecrosis, the clinician should be cautious and avoid the contact with soft tissues if possible. In a case report, ONJ occurred 5 months following root canal treatment, and the placement of clamp was considered as the cause of the complication [29]. A proper and atraumatic isolation can be challenging in cases of irradiated patients with excessive and deep caries at the cervical area. Complete removal of caries and pre-endo built up is indicated. Disinfection of the rubber dam and isolated tooth with iodine solution is recommended.

In extreme cases of heavily inflamed gingiva, ISOLITE may be considered as an alternative for safe perform of endodontic treatment.

#### **Chemomechanical Preparation:**

Occlusal reduction of teeth or even buccal access combined with short files or modified files can be helpful in cases of severe trismus [30,31]. The main principles of chemomechanical preparation remain the same under all situations. However, in cases with risk of osteonecrosis, mechanical trauma of the periapical tissues and extrusion of microorganisms should be strictly avoided. Determination of working length should be performed with electronic apex locator but patency of the apical foramen should be avoided. Every file should be restricted to the working length (which is desired to be distinctly short of the apical foramen), and thus the continuous use of apex locator is recommended during the whole preparation. Nowadays, endodontic headpieces come with intergraded apex locators.

It is also important to irrigate with caution using safe ended needles and light pressure. Using low concentration of NaOCl can also be considered. Extrusion of debris is considered unavoidable during nonsurgical endodontic treatment, but there are techniques which can reduce it [32]. According to research, Ni-Ti rotary files lead to less extrusion than hand files [33]. Among rotary systems, statistically significant differences in extrusion of debris are not evident [33,34,35]. The self-adjusting file system (SAF) should be seriously considered for adaptation in such cases, as it results in significantly less apically extruded debris, compared to other rotary systems [36,37].

#### **Obturation:**

The main goal of obturation for these cases should be to avoid mechanical (overfilling and overextension of the filling material) and thermal damage of the PDL during obturation. It is proven that cold lateral condensation (CLC) leads to less overfilling than warm techniques [38]. In patients with high risk of osteonecrosis, warm vertical techniques should be avoided.

It has been shown that the use of ill-fitting master cone is one of the causes of extrusion [39]. Precautions can be taken to prevent this iatrogenic event such as obturate 1mm shorter than the working length or customize the master cone with GP softener. In a study of Eastman Dental Institute in 2005, it was shown that CLC and customization of master cone reduces significantly the root filling extrusion [40]. According to Keane and Harrington, one dip of GP end in chloroform is enough and leads to the best results. A short description of the technique is the following: a non-standardized GP cone is selected to fit 1-1.5mm short of working length with tugback, the apical 4mm of the cone dips into chloroform for maximum of 1sec and then the cone is seated in the canal with firm apical pressure to the canal terminus [41]. The cone should stay there for at least 10sec in order to resolidify and prevent undercuts.

#### **Restoration:**

Coronal restoration should completely seal the pulp chamber and prevent microleakage. Composite resin fillings and direct inlays and onlays are recommended for permanent restoration. According to London Eastman study, teeth with satisfactory coronal restorations were found to have significantly better periapical healing compared to those with unsatisfactory restorations. However, in the same study, it was shown that endodontically

treated teeth with cast posts or functioning as abutment for fixed prosthesis have worse survival rates [42]. If the clinician decides that crown or other indirect restoration is needed, it is suggested to postpone it until the risk of osteonecrosis is minimized. If the tooth cannot be restored and the goal of endodontic treatment is to avoid extraction, the crown should be reduced to sub-occlusal level [43]. An alternative for non-restorable teeth is, after chemomechanical preparation and intra canal medication for the management of symptoms, restore the tooth temporarily with IRM or glass ionomer cement.

#### Follow-up:

Follow-ups including clinical and radiographical examination should be performed as in any other endodontic treatment. The effect of BPs on bone metabolism and remodeling could potentially interfere with healing of periradicular lesions. However, this is not proved and in one related study comparing healing between BP recipients and control group, statistically significant difference was not found [44]. Similarly, for irradiated patients the rate of success seems to be comparable to non-irradiated patients [45].

#### Discussion:

To prevent osteonecrosis followed by the compromised healing potential of the jaws, preventive extractions, undertaken before radiation therapy, was recommended for several decades. Additional complications of radiation, such as limited mouth opening, mucositis, severe caries, fractured tooth crowns and limited rubber dam application in such patients, probably supported an attitude that rejected maintenance of teeth. The same aggressive treatment plan was also considered before the initiation of IV BP medication. However, extracting functional teeth is a harsh and difficult decision. For this reason, endodontic therapy, if accomplished with utmost care and maximum regard for the fragility of the periapical tissues, is the preferred treatment [24].

Important considerations should be the patient's general condition and level of compliance, two factors that often contribute to problems during instrumentation and restorative techniques.

In patients with high risk of osteonecrosis, endodontic treatment can lead to healing or stabilization of periapical lesion even if the tooth is unrestorable [44,45]. There are case reports that present incidents of ONJ in some period after root canal treatment but in these cases a cause-and-effect relation cannot be proved. It is not wise based on these cases to jump to conclusions and blame endodontic treatment in general because: a) the treatment protocol applied in these cases is unknown, and b) it is quite possible that the pain related with spontaneous ONJ was mistakenly considered of odontogenic origin and endodontic treatment was performed in an area with established ONJ [46,47]. Even if endodontic treatment is followed by crown amputation, that solution is easier, cheaper and safer than extraction combined with hyperbaric oxygen.

For more than a decade, LLLT (Low Level Laser Therapy Or Low Level Laser Therapy) is used for treatment of BRONJ and cancer therapy-induced oral mucositis [48,49,50]. LLLT has also been used successfully after extractions in patients with high risk of osteonecrosis in order to eliminate this risk [51]. It is proved that LLLT has antibacterial effects on soft and hard tissue and

that it can fasten and improve wound healing [49,52]. Taking the above into consideration, LLLT can be suggested as an adjunct to isolation clamp placement, even though, as it is already mentioned, correlation between isolation and osteonecrosis has not been proved.

#### Conclusion:

The clinician should be very careful when case-selecting teeth for endodontic therapy, undergoing radiation of head and neck and BP medication; as long as he/she follows the recommended protocols for such patients and stay on the safe side, risks are minimal. Apart from the elimination of symptoms, the dentist can offer a functional, aesthetic and safe alternative to extraction and thus improve patient's quality of life.

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