Maxillary osteoradionecrosis – review of published literature: incidence, classification, risk factors, physiopathology and prevention

Osteorradionecrose dos maxilares – revisão da bibliografia publicada: incidência, classificação, fatores de risco, fisiopatologia e prevenção

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Abstract

Introduction: osteoradionecrosis (ORN) of facial bones is a serious complication of radiotherapy. Objective: this literature review was performed to study maxillary osteoradionecrosis, its incidence, classification, risk factors, physiopathology, prevention, and current treatment. Literature review: literature search using Medline was performed for all relevant articles with specific keywords from January 2000 to November 2011 aiming to find current data available on ORN and the paradigm change in physiopathology and prevention of the disease. The literature reviewed showed lack of either controlled or randomized trials, a few prospective studies, and a great amount of retrospective studies. Final considerations: adjunctive hyperbaric oxygen (HBO) therapy may be applied for osteoradionecrosis prevention, before and after dental procedures, with satisfying results. Nonetheless, several studies indicated that HBO therapy is not beneficial.

Keywords: Osteoradionecrosis. Radiotherapy. Head and neck neoplasm.

Introduction

Radiotherapy is an extremely effective treatment for head and neck cancer, as a primary mode, and as an auxiliary treatment following surgery. Osteoradionecrosis (ORN) of facial bones is a well-known serious complication of radiotherapy. Regaud first described ORN, in 1922 and it still represents a clinical challenge[1]. Wong best defines it, in 1997 as a slow-healing radiation-induced ischemic necrosis of variable extent occurring in the absence of local primary tumor necrosis, recurrence, or metastatic disease[2]. Clinically ORN starts with an asymptomatic small mucosal breakdown exposing the overlying bone, but it may evolve to a very painful, debilitating situation[3,4]. The management of ORN is controversial varying from the more conservative to the more aggressive treatment[5-8].

The aim of the present article was to review the current database available regarding ORN.

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Methods

A computerized electronic literature search was performed using Medline, for articles published from January 2000 to November 2011 on ORN and its incidence, classification, risk factors, physiopathology, and prevention. The keywords used were osteoradionecrosis, osteoradionecrosis hyperbaric oxygen, ORN dental extractions. The authors selected 37 relevant articles, which included prospective and retrospective cohort studies, randomized clinical trials, systematic reviews, and technical notes. Case reports and abstracts were not included.

Incidence

Most cancers of the head and neck are squamous cell carcinomas and are generally considered to be radiosensitive lesions[9]. There is a well-established relationship between the radiation dose delivered to the tumor and the probability of tumor control[9]. With refinements in radiation techniques and increased attention to oral hygiene, the incidence of ORN has declined, but the risk has not been totally eliminated. Although ORN can occur in any period after radiotherapy, the majority appears within 3 year after RT[10].

The incidence of ORN in literature ranges from 0.9 to 35%[11-13]. This variability is probably due to differences of study populations, in observation periods, and the existence of pretreatment dental assessment and dental management of the cohort[11-13]. Reuther et al.[13] (2003), in a retrospective study of 830 patients demonstrated 8.2% of ORN, and 3 fold higher incidence for men than women.

Classification

The characteristics of ORN are widely recognized, and several staging or scoring systems have been proposed[3-5,14]. These systems were based on clinical features, response to treatment, combined clinical and radiological features, and treatment need.

In 1983, Marx proposed the Wilford Hall protocol, which later became known as Marx´s protocol, and was based on the combination of Hyperbaric Oxygen (HBO) therapy and surgical treatment[5]. He categorized ORN in three stages based on the response to treatment. In Stage I, there are 30 dives, after ORN is re-examined, and additional 30 dives for achievement of mucosal coverage. If there is no clinical improvement, the patient is classified as non-responder and advances to Stage II. In Stage II, a transoral alveolar sequestrectomy is accomplished with a primary closure followed by additional HBO dives. If the wound presented dehiscence the patient is consider a non-responder to Stage II, and advances to Stage III. In patients whose initial presentation includes either pathological fracture, orocutaneos fistula, an initial course of 30 dives is given and the patient directly enters Stage III. In Stage III the patient undergoes a resection and stabilization of the segments, with primary closure if fistula is present. Than ten weeks after resection the patient enters Stage III-R and is given additional 20 dives in preparation for bone grafting. Reconstruction is accomplished from strictly transcutaneous approach. Then ten more dives are given to the patient. If a quantitative soft tissue deficiency exists, it is corrected by a myocutaneos or myomucosal flap prior to reconstruction[5].

Epstein, in 1987, proposed a classification system based in the clinical behavior of ORN. In stage I, ORN is resolved, in Stage II, ORN is chronic persistent, and in Stage III ORN is active progressive[14]. The staging is followed with the letters A and B, where A represents no pathological fracture, and B represents pathological fracture[14].

In a review of clinical and radiological data of 73 patients, Store and Boysen established four distinct stages of ORN[4]. Stage 0: mucosal defect only; Stage I: radiological evidence of necrotic bone with intact mucosa; Stage II: positive radiographic findings with denuded bone intra-orally; Stage III: clinically exposed radionecrotic bone, verified by imaging techniques along with skin fistulas and infection[4].

Notani in 2003 used a new classification of ORN to improve study methods[3]. It was based according to the extent of ORN lesion and divided in three grades. Grade I was defined as ORN confined to the alveolar bone. Grade II was ORN limited to alveolar bone and mandible above the mandibular canal. Grade III was ORN that extended to the mandible under the level of mandibular canal with a skin fistula and/or pathological fracture. This classification is simple and easy to use, but is limited to mandible[3].

Risk and predisposing factors

In the attempt to prevent ORN because of its difficult management, several risk factors were established over the years. Undoubtedly, the radiation dose contributes to the development of ORN, although there is no consensus in literature concerning safe maximum dosing. Goldwaser et al.[15] (2007) concluded that patients receiving a radiation dose above 66Gy increased the risk of developing ORN by almost 11-fold. However, because some ORN patients received doses significantly lower than 66Gy and some non-ORN patients received doses of 66Gy or higher, it seems clear that the dose alone does not predict absolute risk[15].

Reuther et al.[13] (2003) found an association between the radiation dose and the size of ORN, so higher the dose the greater the size of ORN. The study also found that RT prior to surgery significantly reduced the time interval between RT and ORN in comparison to RT after surgery. The field of irradiation was found to be associated to the appearance of ORN by Thorn et al.[16] (2000) The mandible is more affected than the maxilla, and the posterior molar region of the mandible is more affected than the anterior region. The possible explanation is vascular limitations in the mandible and the fact that it is more often inside of the field of irradiation due to head and neck cancer type[13].

Trauma was recognized to be part of physiopathology of ORN in the theory developed by Meyer[15] (1970), however it is not currently considered because many ORN occurs spontaneously, although it corresponds to a very important risk factor to ORN[17-19]. Among the several types of trauma that can affect bone, teeth extraction is the most associated to ORN especially in the post-irradiation period[13]. Extraction is a very common procedure in irradiated patients because they present alterations in salivary glands, which initiate or aggravate periodontal disease, caries, and infection[20]. The dental management of patients receiving radiotherapy is discussed later in this article.

Other source of trauma is the resection surgery, which includes the field of irradiation, and certainly reduces the blood supply to the area[21]. Reuther et al.[13] (2003) demonstrated that segmental resections with a discontinuity of mandible caused a significant earlier occurrence of ORN compared to a en-bloc resection and resection with preservation of the lower border of the mandible, or no resection at all.

Some authors found alcohol and tobacco abuse as risk factors. Katsura et al.[22] (2008) hypothesized that smoke causes a vasoconstriction that may enhance the occurrence of mandibular hypovascularisation after radiotherapy.

Goldwaser et al.[15] (2008) showed that the body mass index (BMI) of patients who developed ORN averaged 23.02 while the BMI of those who did not averaged 25.13; On multivariate analysis, for every point increase in BMI, ORN risk decreased by 27%. This association between increased BMI and lower incidence of ORN is important because the effects of surgery, radiation, and chemotherapy often compromise the nutritional status of these patients. Another important finding of this study was that 54% of non-ORN patients compared to 28% of ORN patients took steroids before and after radiation therapy; on multivariate analysis, steroid use before and after radiation reduced the risk of ORN by 96%. These results support the "radiation-induced fibrosis" theory that will be discussed further in this article. The anti-inflammatory effects of steroids may inhibit the initial inflammatory phase of ORN, thereby preventing progression to thrombosis, atrophy, and necrosis[15].

Physiopathology

In the seventies Meyer proposed the classic triad of ORN as radiation, trauma, and infection. This study suggested that trauma permitted the entry of bacterial flora into the irradiated bone, which had lost its resistance to bacteria[17].

In 1983 Marx contested this model and introduced the theory that radiation causes a hypoxic, hipocelular, and hipovascular environment that leads to a tendency of tissue breakdown, exposure of underling bone, and formation of a chronic non-healing wound because the metabolic demands excess supply[23]. In this study he cultivated resected specimens of ORN for microorganisms. The microorganisms varied widely suggesting saprophytic contaminants. The study concluded that ORN is not a primary infection and microorganisms play only a contaminant role in its physiopathology, and proposed the sequence: radiation, Hypoxic-hipovascular-hipocelular tissue, tissue breakdown, non-healing wound.

In 2004, Delanian and Lefaix[24] hypothesized that the radiation-induced fibroatrophic mechanism contributed for ORN. Radiation Induced fibroatrophy (RIF) is an occasional irreversible damage, which is unavoidable and may last for years after RT; it affects any part of the body exposed to RT[24]. The histopathology of RIF development varies from inflammation to sclerosis and three phases are observed. The first phase is the initial pre-fibrotic phase in witch chemokine - released in response for injury, attracts leukocytes to the site of injury, contributing to a chronic non-specific inflammation. This inflammation is characterized by increased vascular permeability with edema formation. The subsequent destruction of endothelial cells (EC) and associated vascular thrombosis may lead to necrosis of microvessels and local ischemia, leading to fibroblastic activation. The second phase is the constitutive organized phase in which the RIF tissue is essentially composed of fibroblasts and extracellular matrix (ECM). Constitutive RIF is characterized by a patchwork of myofibroblasts, which are differentiated fibroblast, in a dense sclerotic ECM. Myofibroblast is a phenotype that is temporary in normal wound healing and appears during the initial inflammatory phase. However, combined damage to EC and connective tissue cells, amplified by action of cytokines generate the permanent state of RIF and the permanence of myofibroblasts. Lastly in the late fibroatrophic phase RIF tissue is progressively densified by successive remodeling of

ECM deposits. At this stage of lesions constituted decades after RT, the tissues are friable and develop poorly vascularized and cellularized fibroatrophy, with a few fibroblasts and a dense ECM.

Prevention

Patients with oral cancer usually present a poor dental status, even in developed countries, and require dental treatment before and after RT[25]. RT affects the salivary glands, changes dental structure, predisposing the patient to rampant caries and severe periodontitis aggravating the oral condition[26]. Even patients who regularly visit dental offices need specific dental care during RT. The aggravation of oral condition can lead to infection, raising the risks to ORN. Extractions prior to RT were recommended for teeth with poor condition or dubious prognosis[26]. Criteria for extraction of teeth before RT include: moderate to advanced periodontal disease, extensive periapical root lesions, extensive decays, partially impacted teeth, and residual root tips not fully covered by bone[26,27]. A consensus report from the National Cancer Institute in 1990 recommended a minimum time of 2 weeks between extractions to the onset of RT[28]. However Chang et al.[29] in 2007 evaluated, in a retrospective study of 413 patients submitted to dental extractions before and after radiotherapy and found that 37 patients developed ORN, and the majority (81%) within 3 years. The authors found that pre-RT extractions do not seem to reduce the risk of ORN, and teeth with good condition do not require prophylactic extraction for the sole purpose of preventing ORN in the future[29].

Bonan et al.[30] (2006) in a study with a much smaller cohort of 40 patients with head and neck cancer and poor oral hygiene received dental treatment before radiotherapy. The most common treatment performed was dental extractions with an average of 8.6 extracted teeth per patient; five of them developed ORN later. The author concluded that dental treatment did not prevent ORN.

Atraumatic extraction technique must be preconized in the irradiated patient because it significantly reduces complications postoperatively[27,31]. Sulaimen et al.[27] in 2003 reported a retrospective analysis of 1194 patients as only 187 of them needed dental extractions, in the Memorial Sloan-Kettering Cancer Center. The authors found a very low incidence of ORN (2%) when using atraumatic technique of pre and post-RT extraction, as the majority did not achieve primary closure (54%)[27]. Patients should be adequately advised on the risk and benefits of having teeth in place versus undergoing extractions[29]. Patients must understand the proper application of daily fluoride and the need for routine dental care to reduce post-RT complications[29].

HBO therapy in prevention

HBO therapy has been used to prevent ORN since 1973 and nowadays its use has been questioned[27,29,31]. HBO therapy can be applied to patients who underwent RT and require extractions[32,33]. Marx in 1985 established a protocol consisting of 20 dives of HBO before extraction and 10 dives after, advocating that HBO increases tension and diffusion of oxygen, collagen synthesis, and vascular network consequently healing the tissue[33]. This study is the only randomized clinical trial concerning HBO for the prevention of ORN after post irradiation extraction[33,34].

Fritz et al.[34] (2010) in a systematic literature review evaluated the efficacy of pre and post irradiation HBO in the prevention of post extraction ORN. They selected 14 articles and only one was a randomized clinical trial. Seven studies had HBO, and in 4 studies Marx's protocol was used. In the cohort and observational studies, the occurrence rate of ORN in prophylactic HBO patients was 4.1%, whereas in non-HBO patients the average was 7.1%[34]. The authors concluded that the systematic review failed to identify any reliable evidence to support or refute the efficacy of HBO in prevention of post extraction ORN[34]. However, another systematic review with meta-analysis by Nabil and Samman[35] (2011) found a 7% incidence of ORN after tooth extraction. When extractions were performed along with HBO the incidence was 4%, while extraction in conjunction with antibiotics presented an incidence of 6%. The authors concluded that based on weak evidence prophylactic HBO is effective in reducing the risk of developing ORN after post-radiation dental extractions.

Kanatas et al.[36] (2002) demonstrated that only 22 out of 65 surgeons who answered a questionnaire would prescribe HBO in a hypothetic clinical case of second molar root removal in a patient previously irradiated, and just 10 out of 65 surgeons would prescribe HBO in another hypothetic clinical case of a previous irradiated patient requiring the extraction of 3 mobile and periodontally-involved lower central incisors. The authors concluded that surgeons were reluctant to substitute the use of antibiotics for HBO, probably for reasons such as geographical location, costs, and the lack of perceived necessity[36].

Final considerations

ORN is a serious complication of head and neck RT. It is a disease of difficult treatment and most cases appear within 3 years after RT[10]. Trauma is the most important risk factor to the development of ORN, however some ORN occur spontaneously[20].

The use of HBO for ORN prevention is controversial[33]. Adjunctive HBO therapy can be applied in prevention, before and after dental procedures, with satisfying results. Nonetheless, several studies indicated that HBO is not beneficial.

The literature reviewed showed lack of randomized control trials, a few prospective studies, and a great amount of retrospective studies. Systematic review is a very relevant method to guide evidence--based practice. However, it depends on the quality of the studies reviewed. There are systematic reviews regarding the incidence and prevention of ORN[32,34,35,37]. However, most studies included are retrospective analysis and represent weak evidence. Randomized clinical trials are considered to be one of the most reliable forms of scientific evidence, but there is only one randomized clinical trial regarding ORN, which was conducted by Marx et al.[33] (1985).

Resumo

Introdução: a osteorradionecrose (ORN) dos ossos faciais é uma complicação séria da radioterapia. Objetivo: esta revisão da literatura foi realizada com o objetivo de estudar a osteorradionecrose dos maxilares, sua incidência, classificação, fatores de risco, fisiopatologia, prevenção e tratamento atual. Revisão da literatura: uma pesquisa bibliográfica foi realizada por meio do Medline para todos os artigos relevantes com palavras--chave específicas de janeiro de 2000 a novembro de 2011, no intuito de achar dados atuais disponíveis sobre ORN e a mudança de paradigma na fisiopatologia e prevenção da doença. A literatura revisada mostrou falta de estudos controlados e randomizados, alguns estudos prospectivos e uma grande quantidade de estudos retrospectivos. Considerações finais: a terapia adjuvante com oxigênio hiperbárico pode ser aplicada na prevenção da osteorradionecrose, antes e depois dos procedimentos dentários, com bons resultados. No entanto, alguns estudos apontaram que essa terapia não é benéfica.

Palavras-chave: Osteorradionecrose. Radioterapia. Neoplasia de cabeça e pescoço.

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