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Osteoradionecrosis and intensity modulated radiation therapy: An overview

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ABSTRACT

Osteoradionecrosis (ORN) is an ongoing topic, especially about its definition, pathogenesis, staging system and management algorithm. But what about its real incidence in intensity modulated radiotherapy (IMRT) era?

This paper discusses the mandible in radiation therapy planning as organ at risk and reviews the literature for evidence of radiation damage, discussing likely dose constraints and the use of IMRT to reduce radiation dose to this structure. PubMed search was performed.

1. Introduction

Radiation therapy (RT) is an efficient treatment for head and neck cancer (HNC). However it may have severe late effects. Although infrequent, osteoradionecrosis (ORN) is a well documented late complication and it represents one of the worst toxicity. It is a slow process, not apt to heal spontaneously, characterized by chronic, painful necrosis associated with late sequestration and permanent bone deformity (Reuther et al., 2003a).

ORN of the mandible was reported since the 1950s, when RT of HNC became a well-established practice. In those years, the primary goals of most clinical trials were improvement in survival rate and local control (Argiris et al., 2008). By time, together with those important measures of success, other equally important end-points were taken into consideration, such as how to improve quality of life while reducing treatment-related toxicity. To achieve these purposes, different alterated fractionated RT and chemotherapy (CHT) regimens have been tested, as well as significant technical progress has been made in radiation techniques (Pignon et al., 2009; Withers et al., 1995a; Mohan et al., 2000). Refinement in intensity

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modulated radiation therapy (IMRT) has produced good results in treatment planning, especially for HNC, due to its potential to spare irradiation on organ at risk (OAR).

The aim of this review is to investigate the mandible tolerance after IMRT. PubMed search was performed using the following combinations of research criteria: "intensity modulated radiation therapy", "osteoradionecrosis", "mandible", "toxicity" and "late effects". Cited studies were ascertained from PubMed searches. Relevant references cited in those papers were also selected. An attempt was made to include all relevant studies and systematic reviews.

2. General concepts

The bone is a radio-resistant structure, able to sustain damage as long as it is not exposed to trauma and the overlying soft tissue remains intact (Ben-David et al., 2007).

Clinical manifestation of ORN is impacted not only by tumor location (proximity to bone), but also oral cavity related factors (poor oral hygiene and dentition status) and patients related factors (old age, bad habits and general health) (Mendenhall, 2004). A careful and complete dental and oral evaluation is recommended, because extraction of teeth in poor condition should be carried out before start treatment, to reduce the subsequent risk of oral cavity damage. Patients should be incited to change their "unnecessary" habits and advised to practice an excellent oral hygiene, to optimize the efficacy of the treatment (Zevallos et al., 2009).

ORN is characterized by hypoxic, hypocellular and hypovascular tissue, followed by tissue breakdown. Hypoxia and hypocellularity are secondary to radiation-induced activation and dysregulation of the fibroblastic activity that caused vascular fibrosis and thrombosis (Wong et al., 1997). The mandible is exclusively supplied by the inferior alveolar artery (IAA), a branch of the maxillary artery; therefore the obliteration of the IAA causes an ischemic necrosis in irradiated atrophic tissue (Bras et al., 1990; Thiel and Osteoradionecrosis, 1989). Due to this relatively poor vascularization and the absence of collateral blood supply, the mandible, especially buccal cortex of premolar, molar and retromolar regions, is at greater risk of symptomatic necrosis versus other bones of the head and neck region.

Since the first ORN description in 1922, the different radiographic and clinical appearance and the optimal utilization of new therapies has been largely elucidated and several scales have been proposed to provide an universal scoring system to classify it (Regaud, 1922; Marx, 1983; Epstein et al., 1987; Schwartz and Kagan, 2002; Støre and Boysen, 2000; Lyons et al., 2014). Although the severity of pain and the limitation to daily activities were difficult to capture properly from the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, there is a general consensus about this scale-system as grading system (Anon, 2016).

3. Basic clinical radiobiology and fractionation

Today a wide variety of dose-fractionation regimens have been developed and shorter regimens using fewer fractions are often used in radical treatment (Withers et al., 1995a). Clinical practice is based on the rational foundation provided by the 5 traditional Rs of radiobiology: repair, repopulation, redistribution, reoxygenation, radiosensitivity (Good and Harrington, 2013). Currently, the linear quadratic (LQ) model dominates the field of mathematical tumor radiobiology. It includes the parameter changes that occur during fractionated radiotherapy and thus it provides the rational basis for comparisons between different RT regimens (Jones and Dale, 1999). Detailed analysis of this biological model is beyond the aim of this review, thus we only briefly described it. LQ model admits that radiation-induced alterations are a linear-quadratic function of dose. At low doses, cell damages are directly proportional to dose (linear), whereas at high doses, they are proportional to the dose squared (quadratic). According to the LQ model, the surviving fraction (SF) is expressed by the equation $SF = Exp(-\alpha d - \beta d2)$, where d is the given single dose and α and β are irradiated cells parameters characteristics. α represents the linear component of cell killing, and β the quadratic one. Thus, the α/β ratio corresponds to the dose of radiation, in Gy, at which the total of cell killing directly proportional to dose is equal to the total of cell killing proportional to the dose squared. In other words, α expresses cells intrinsic radiosensitivity, β expresses the extent to which damage can be repaired.

The mandible, with an α/β ratio of 0.85 Gy, has radiobiological parameters similar to those for late responding normal tissues; thus a change in dose per fraction is a significant factor for bone complications (Withers et al., 1995b). With increasing fraction size, tissues react differently. When considering different schemes, one should assume that the different fractionations have equal biological effects on a given tissue. The biological equivalent dose (BED) refers to the effective total absorbed dose, in Gy, for a given fractionation scheme if it was given by conventional fractionation (1.8–2 Gy/day). In HNC, RT should be given using uninterrupted treatment. Fractionation was introduced to exaggerate survival differences between tumor cells and normal cells, as well as to minimize tumor cell repopulation and overall treatment time. The total dose that could be prescribed safely to the tumor is limited by the tolerance of surrounding normal tissues. Tissue radiation tolerance depends on its architecture and its reserve capacity, as well as the proportion of the organ treated, the dose received, fraction size, overall treatment time, and the length of follow-up. Conventionally, it is assumed that each organ is composed of basic structures, defined functional sub-units (FSUs), and their spatial rapport is essential to maintain organ integrity (Withers et al., 1988). The mandible bone has a mixed type of organization, and it can be classified into "parallel" and "serial" organ. The percentage of the entire organ volume exposed to a defined dose (i.e. V50) is essential to predict tissue complication (parallel organ), as well as the maximum absorbed dose in predicting tissue tolerance (serial organ) (De Luca et al., 2010). ORN is determined by the volume of irradiated mandible (parallel organ), and the maximum dose to the mandible (serial organ). Actually, as suggested by the International Commission on Radiation Units and Measurements 83 report, the near-maximum dose received by 2% of the volume (D2%) may be more dosimetrically reliable than punctual maximum dose (ICRU, 2010). ORN is dose dependent and relates to the V50 and V60 of mandible within the treatment field (Tsai et al., 2013; Ahmed et al., 2009).

4. Recommendation for mandible contouring and dose constrain

IMRT allows for steep dose gradients and, due to the variety of beams, it is crucial to contour the entire bone. Potentially, mandible segments, previously not irradiated, now could receive higher doses that result in clinical toxicity (Rosenthal et al., 2008).

Rosenthal et al. (2008) were able to demonstrate substantial dose reduction with IMRT to parotids, optic and central nervous system but a markedly mandible higher toxicity profile than 3-dimensional conformal (3D) RT. With the previous two lateral beam approaches, ORN arose frequently in the body of the mandible. At present it is most commonly located in the anterior segments of the mandible (Reuther et al., 2003b). In fact IMRT treatment typically requires at least nine radiation beams to achieve a satisfactory plan.