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Comparative Study

Use of Cone Beam Computed Tomography for identification and evaluation of Medication-Related Osteonecrosis of the Jaws: a dosimetric and multimodal imaging comparison

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ABSTRACT

The aim of this study was to compare Orthopantomograms (OPT) and Computed Tomography (CT) with Cone Beam Computed Tomography (CBCT) in patients with Medication-Related OsteoNecrosis of the Jaws (MRONJ). The study included 25 patients (6 males and 19 females) with MRONJ who had a history of long-term bisphosphonate therapy or one of the recently re-entered MRONJ drugs and underwent OPT, CT and/or CBCT for determination of the extent of disease. We excluded patients with maxillary neoplasia. Considering the presence of early and late signs, OPT was diagnostic in 6 out of 17 cases (35%), while CT and CBCT were diagnostic in 25 out of 25 cases (100%). Analysing the different radiant doses delivered by the selected radiological methods on a phantom, it was found that a more significant effective dose was spread by CT (2.6 mSv) than CBCT (0.164 mSv) or OPT (0.02 mSv). CBCT, from our experience, is a candidate to replace OPT in the first diagnostic step in patients with suspected MRONJ, generating less effective doses and artefacts from metal components than CT.

INTRODUCTION

Medication-Related Osteonecrosis of the Jaws (MRONJ) is defined by the consensus of the American Association of Oral and Maxillofacial Surgeons (AAOMS) as exposed bone or bone that is palpable by probing an intra- or extra-oral fistula, which is persistent for more than 8 weeks in the maxillofacial region (1). This definition has been replacing the previous acronyms "BRONJ" (2-4) in order to emphasise the aetiology of this pathological condition that is ascribed not only to the administration of bisphosphonates but can also be induced by the intake of other drugs (4-6) like monoclonal antibody with anti-resorptive activity (Denosumab), anti-angiogenic drugs or anti-VEGF (Bevacizumab and Aflibercept), tyrosine-kinase inhibitor drugs (TKIs) (Sunitinib, Sorafenib and Cabozantinib), mammalian target of rapamycin (mTOR) inhibitor drugs (Everolimus and Temsirolimus).

The inclusion criteria for MRONJ are: previous or current therapy with bisphosphonates or other drugs falling into the MRONJ category and clinical and radiological diagnosis of progressive bone destruction and necrosis; the exclusion criteria are previous or current radiotherapy of the head and neck area.

Bisphosphonates are used to reduce pain, improve quality of life, and reduce bone complications such as fractures in patients with metastatic lytic lesions, malignant disease-related hypercalcemia, severe osteoporosis, multiple myeloma, Paget's disease, and symptomatic fibrous dysplasia (4-6).

According to the literature, the incidence and prevalence of MRONJ are relatively low. Still, they can change with different types of patients (cancer patients or osteoporosis patients) and anti-resorptive drugs (sequential or single therapy) (2, 3).

The most common events associated with the disease are dental extraction, implantology, mandibular exostosis, periodontal pathology, and trauma (4, 5).

Before the advent of Cone Beam Computed Tomography (CBCT), the main radiological technique available for studying facial bones was multislice Computed Tomography (CT). Its well-established advantages are high sensitivity and specificity even on soft tissues with or without contrast medium, but it exposes the patient to a considerable quantity of ionising radiation (7, 8). Although the Orthopantomogram (OPT) is demonstrated to be exhaustive and complete in numerous circumstances, and it is considered the first step in the study of MRONJ, it often proves to be insufficient in the study of faces with complex conditions (9). Second-level

methods like CT can, in most cases, detect early signs of a disease that are too small and nuanced to be identified by the first-level methods (9-12).

The aim of the study was to compare CBCT with CT and OPT and to suggest CBCT as an alternative in the case of MRONJ, even as a first-level examination; this is because CBCT can diagnose earlier than OPT, and it provides much more detailed information on the relationship between the lesion and the surrounding structures and on the presence of any complications. Moreover, it exposes the patient to a lower number of ionising radiations than CT, as already demonstrated in previous studies (13, 14). Only in evaluating the soft tissues adjacent to the lesion CBCT proves to be lacking, making it necessary to perform either a conventional CT or a Magnetic Resonance (MR) scan before and after administering the contrast medium.

MATERIALS AND METHODS

This study assesses all patients referred to the Department of Radiology G.B. Rossi Hospital between 2006 and December 2020 who were affected by MRONJ and presenting a long-term bisphosphonate therapy or one of the recently re-entered MRONJ drugs. We examined 25 patients (6 males and 19 females) from 48 to 92 years, excluding patients with maxillary neoplasia.

AAOMS inclusion criteria were applied (1): 1. Current or previous BP treatment; 2. Exposed necrotic bone in the maxillofacial region for more than 8 weeks; 3. No radiotherapy to the jaws.

Patients were affected respectively by breast cancer (8 pts), severe osteoporosis (6 pts), renal cancer (3 pts), rheumatoid arthritis (2 pts), multiple myeloma (2 pts), breast cancer associated with osteoporosis (2 pts), prostate cancer (1 pt) and severe osteoporosis associated with rheumatoid arthritis (1 pt). Among the population considered, 13 performed both CT and OPT, 6 only CT, 4 both CBCT, CT and OPT, 1 both CBCT and CT, and 1 only CBCT (Table I).

Table I. *Distribution of patients who underwent different types of radiological exams (CBCT, CT and/or OPT).*

n° patients/exams	CBCT	CT	OPT
13		x	x
6		x	
4	x	x	x
1	x	x	
1	x		

The ability of the radiological tests to make a diagnosis was assessed by considering respectively the 4 early signs (thickness of the alveolar ridge and hard lamina, non-healing post-extraction socket persistence, bone sequestrum, enlargement of the periodontal space) and the 5 late signs (pathological fracture, thickening of the canal of the inferior alveolar nerve, diffuse osteosclerosis, radiopacity of the maxillary sinus, periosteal reaction) that could be present on the OPT and then the 7 early signs (focal medullary osteosclerosis, cortical erosion, trabecular thickening, post-extraction socket persistence, bone sequestrum, periodontal space

enlargement, thickening of the alveolar ridge and hard lamina) and the 8 late signs (diffuse osteosclerosis, oro-antral fistula, bucco-nasal fistula, mucocutaneous fistula, sinusitis, inferior alveolar nerve canal thickening, periosteal reaction, extended osteolysis to the maxillary sinus, osteosclerosis of cheekbone and /or hard palate) that could be present on CT or CBCT (9, 15).

The scanners used in the study were a CBCT Vgi (NewTom, Verona, Italy), a multislice Brilliance CT 64 (Philips, Eindhoven, The Netherlands) and an Orthopantomograph ProMax 2D (Planmeca, Helsinki, Finland). CBCT and CT used their respective protocols with FOVs to acquire the maxillo-facial district while the equipment pre-set mode was used in the OPT for acquiring both jaws.

The three devices were also subjected to dosimetric analysis using an adult male tissue-equivalent Rando Anthropomorphic Phantom (Alderson Research Laboratories, Stanford, CN, USA) (Fig. 1).

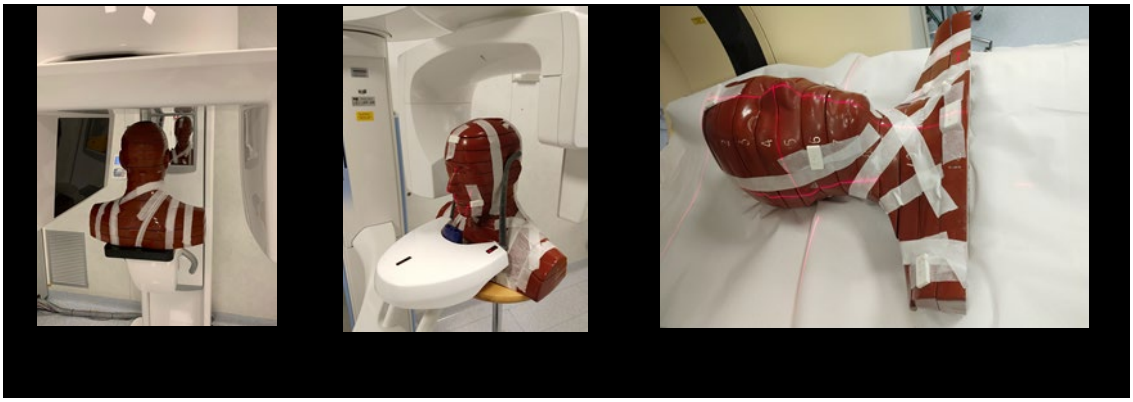

Fig. 1. *From left to right: phamtom under examination at CBCT, OPT and CT.*

Inside the phantom, sixty ThermoLuminescent Dosimeter chips (TLD-GR200A, Harshaw Chemical Co, Solon, USA) were inserted in areas of interest to measure the dose absorbed by specific organs and in other positions to be able to evaluate more generally the distribution of the dose. The examinations were performed using the manufacturer's protocols for the specific area, positioning the phantom similarly to the patient. The TLD readings were used to obtain the air kerma values. Tissue dose was obtained by multiplying the air kerma values by the ratio of air–muscle mass-energy absorption coefficients. The calculation was performed according to the latest International Commission on Radiological Protection (ICRP) guidelines (16). Equivalent doses delivered to different organs (Ht, measured in millisievert (mSv)) were calculated by multiplying the dose obtained with TLDs by the volume fraction of the irradiated organ (Dt, measured in mGy) and by the weight coefficient of ionising radiation (WR): the weight coefficient of radiation is considered equal to 1. The contribution of a single organ/tissue in determining overall patient risk during radiation exposure was obtained by multiplying the equivalent dose (Ht) by the tissue-weight coefficient (WT). The summation of the weighted products of single organs gives the value of effective dose (E, measured in mSv), which is the dose magnitude related to the stochastic, somatic and genetic risk ($E=Ht\times Wt$).

RESULTS

All patients were analysed by verifying the ability of OPT, CT and CBCT to diagnose MRONJ; in 8 cases (32%), the pathology was present only on the upper jaw, in 12 cases (48%) on the mandible alone, in 5 cases (20%) both on the maxilla and mandible.

The presence of early and late signs for OPT, CT, and CBCT was considered. OPT was diagnosed in 6 out of 17 cases (35%), and CT and CBCT were diagnostic in 25 out of 25 cases (100%).

In the 6 cases where OPT was diagnostic, the frequency of early and late signs presence is summarised in Table II.

Table II. *Early and late signs presence and percentage in OPT.*

OPT Early Signs	OPT Late Signs
• thickness of the alveolar ridge and hard lamina 2/6 (33%) • non-healing post-extraction socket persistence (33%) • bone sequestrum 2/6 (33%) • enlargement of the periodontal space 1/6 (16%)	• pathological fracture 0/6 (0%) • thickening of the canal of the inferior alveolar nerve 1/6 (16%) • diffuse osteosclerosis 5/6 (83%) • radiopacity of the maxillary sinus 0/6 (0%) • periosteal reaction 1/6 (16%)

In the 25 cases in which CT and CBCT were diagnostic, the frequency of early and late signs presence is summarised in Table III.

Table III. *Early and Late Signs were found in CBCT and CT.*

Early signs of CBCT and CT	Late signs of CBCT and CT
• focal medullary osteosclerosis 17/25 (68%) • cortical erosion 11/25 (44%) • trabecular thickening 11/25 (44%) • post-extraction socket persistence 9/25(36%) • bone sequestrum 9/25 (36%) • periodontal space enlargement 7/25 (28%) • thickening of the alveolar ridge and hard lamina 4/25 (16%)	• diffuse osteosclerosis 14/25 (56%) • oro-antral fistula, bucco-nasal fistula, mucocutaneous fistula 9/25 (36%) • sinusitis 9/25 (36%) • inferior alveolar nerve canal thickening 8/25 (32%) • periosteal reaction 7/25 (28%) • extended osteolysis to the maxillary sinus 5/25 (20%) • osteosclerosis of cheekbone and/or hard palate 5/25 (20%) • pathological fracture 2/25 (8%)

Our data analysis revealed that CBCT and CT could diagnose and provide comprehensive information on MRONJ in all cases (100%). Only 35% of the total cases were OPT diagnostic. Compared with OPT, it emerges that CBCT provides much more detailed information even in full-blown cases and when the upper jaw is involved (Fig. 2-4). CBCT is the only one capable of making an early diagnosis; however, it provides a higher quantity of ionising radiation to patients. Reconstructions with CBCT also include panoramic-like images similar to OPT, which is particularly useful for a preliminary global evaluation. In comparison with conventional CT, it emerges that the ability of CBCT to diagnose MRONJ is superimposable; the latter, however, thanks to the greater definition of the bone tissues and the lower susceptibility of the artefacts to

hardening of the radiant beam, proves to be preferable to obtain even more precise images, it also exposes the patient to a lower quantity of ionising radiation. From the analysis on the phantom, all the equivalent doses delivered to different organs were obtained (Table IV). Finally, it was found that the effective dose in mSv is 0,164 for CBCT, 2,6 for CT and 0,02 for OPT, respectively (Fig. 5).

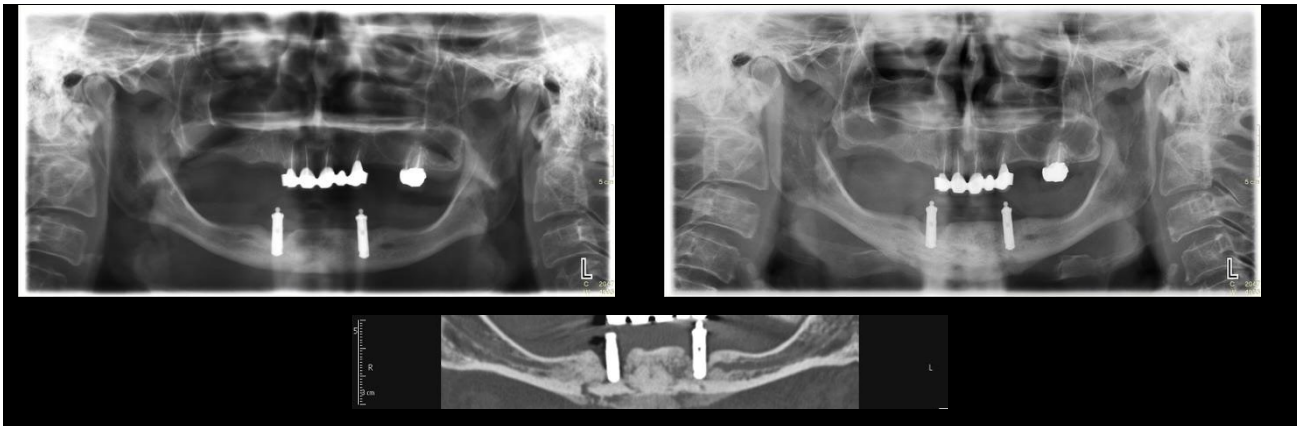

Fig. 2. *From top left clockwise: initial OPT shows no signs of MRONJ, only nonspecific signs of peri-implantitis and a very thin periosteal reaction area at the base of the mandible; OPT at the next check shows a clear picture of MRONJ; CT is the only method capable of providing important details of the lesion such as fistoulous routes.*

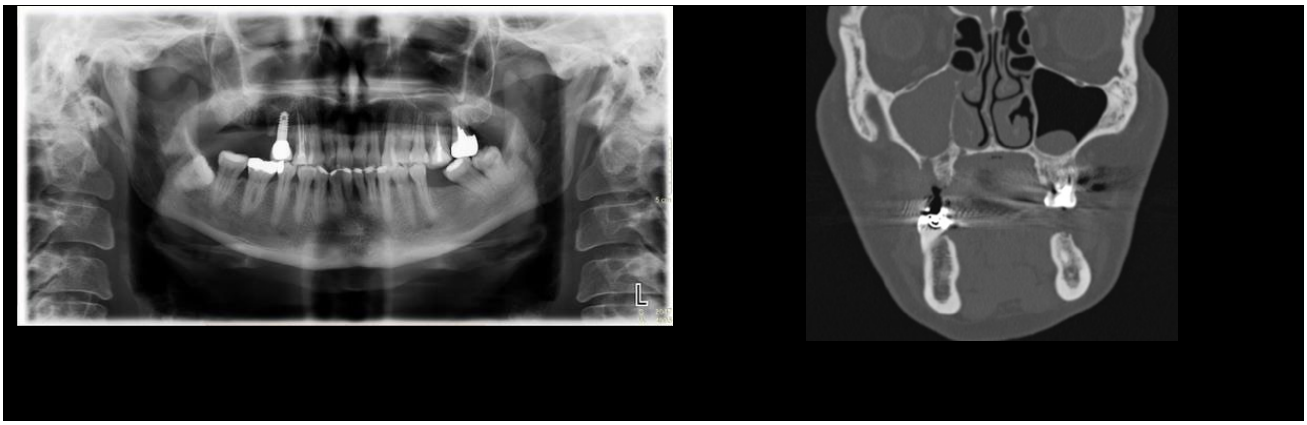

Fig. 3. *Left: OPT performed after an extraction procedure in the upper jaw shows no sign of MRONJ. Right: CT shows a clear imaging of MRONJ as well as the communication with the maxillary sinus fully occupied.*

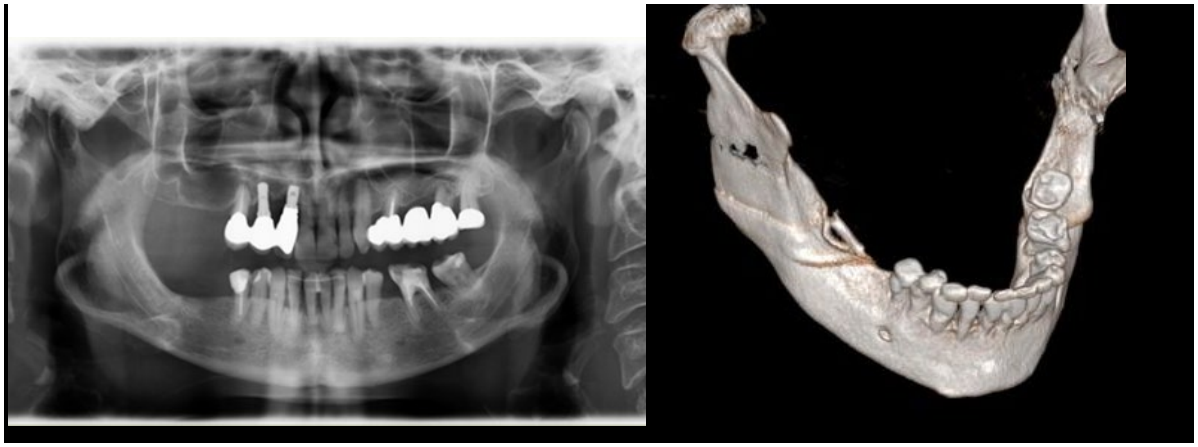

Fig. 4. *Left: OPT in correspondence of the right mandible highlights only an osteo-thickening area. Right: on CT an area of bone detachment is highlighted.*

Table IV. *Example of dosimetric values of various organs/tissues evaluated on the phantom with an equivalent weighted dose expressed in µSv.*

	OPT	CBCT	CT
Organ/tissue	µSv	µSv	µSv
Bone marrow	4,856828	48,627417	749,648077
Esophagus	0,864072	2,049687	66,066957
Bone surface	0,404735	4,052284	62,470673
Brain	1,556679	22,964369	274,426440
Salivary glands	2,328707	7,341881	297,543381
Lung	0,522564	2,283972	6,491628
Bladder	0,174188	0,761324	2,163876
Bowel	0,522564	2,283972	6,491628
Gonads	0,348376	1,522648	4,327752
Thyroid	2,818524	14,569028	536,47098
Breast	0,522564	2,283972	6,491628
Liver	0,174188	0,761324	2,163876
Stomach	0,522564	2,283972	6,491628
Skin	0,131673	3,244105	41,512678
Remainder	2,131755	40,556470	412,938025

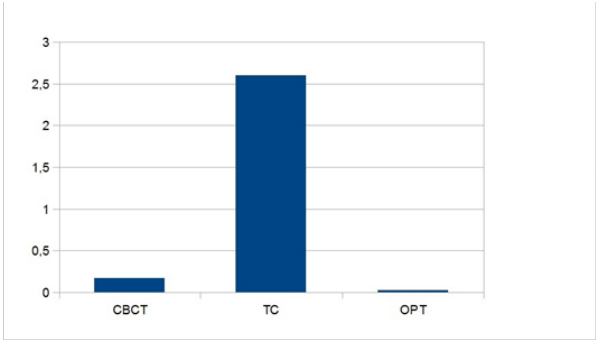

Fig. 5. *Summary graph of the effective dose according to the different radiographic systems.*

DISCUSSION

AAOMS defines the disease presentation and the stages of MRONJ (1), but the literature lacks quantitative studies and standardised imaging protocols to be followed (17).

A common clinical practice is still performing an OPT as a preliminary examination and then a conventional CT later to deepen the case study. In this way, patients are initially exposed to low ionising radiation. However, given the high number of false negatives, in the persistence of symptoms, it will be necessary to investigate further, exploiting another radiological examination with a greater amount of radiation administered. With the advent of new EURATOM guidelines (18), a clear understanding of the amount of radiation dose to which the patient is subjected has gained increasing importance in choosing the correct device an*d personam*. The ALARA principle ("As Low as Reasonably Achievable") is a starting point for physicians and radiologists to solve the diagnostic question. In our study, conventional CT can define the pathology in detail but exposes the patient to a greater quantity of ionising radiation than CBCT with the same diagnostic potential, also considering sometimes the necessity to perform follow-up examinations (8). Therefore, CBCT is found to be an extremely suitable method for defining the picture of osteonecrosis of the jaws, both for its ability to make an early diagnosis and for the definition of the disease (9). The ability to make an early diagnosis is crucial as it allows one to immediately proceed with a therapeutic approach that involves the suspension of the drug, the use of the antibiotic and targeted oral hygiene (4). In the most advanced cases, the therapy involves the surgical approach that can lead to mandibulectomy in the most serious cases. Osteonecrosis of the jaws, as seen from the name of the pathology itself, is a condition that mainly affects bone tissue, and CBCT is even more precise than CT in defining it. Furthermore, the mouth is often the site of non-removable metal components used in dental practice, which are responsible for the creation of artefacts, capable of decreasing the diagnostic capacity of the tissues adjacent to them. This type of artefact is less important in CBCT and OPT exams than in multislice CT.

CONCLUSIONS

In MRONJ advanced cases with clear clinical suspicion, OPT proves to be a sufficient method to diagnose osteonecrosis. However, it provides less information in terms of fine details and extent of the disease compared to CBCT; moreover, it appears to be strongly limited in the early stage of the disease and in those cases in which bone involvement is confined to the upper jaw. CBCT exposes the patient to a higher amount of ionising radiation than OPT but provides much more information about the size and stage of the disease.

OPT is still considered the first-level test in assessing oral status in asymptomatic patient candidates for medical therapy with bisphosphonates or other drugs at risk of MRONJ. Conversely, the use of OPT as a first-level exam in the early diagnosis of MRONJ in symptomatic or paucisymptomatic patients is deficient and can be burdened by false negative cases, resulting in a delay and greater invasiveness of the treatment. CBCT, thanks to its intrinsic characteristics (volumetric acquisition, high resolution at high contrast for the study of the bone, and low radiation exposure), is an optimal candidate to replace OPT in these cases with suspected MRONJ. The possibility of reconstructing the 2D "panoramic-like" images also facilitates the dentist or maxillofacial specialist's conventional evaluation of the two arches. In cases with an extra-osseous extension of the disease suspect and, therefore, soft tissue involvement, the first CBCT evaluation can be followed by a multislice CT scan after infusion of intravenous iodinated contrast medium or even better by an MR, also in the post-contrast phase.

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