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Intraindividual comparison of preoperative ^{99m}Tc-MDP SPECT/CT and intraoperative and histopathological findings in patients with bisphosphonate- or denosumab-related osteonecrosis of the jaw

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ABSTRACT

Purpose: Bisphosphonate- or denosumab-related osteonecrosis of the jaw (BRONJ/DRONJ) requires reliable preoperative assessment of the extent of disease for surgical planning. The aim of this study was to compare the extent of BRONJ/DRONJ as detected by Tc-99m-methylene diphosphonate (MDP) bone scintigraphy with intraoperative and histopathological findings, and to assess the additional value of hybrid single photon emission computed tomography/computed tomography (SPECT/CT) for evaluation of disease.

Material and methods: Twenty-one patients with BRONJ/DRONJ underwent three-phase bone scintigraphy including SPECT/CT. The diagnostic certainty using conventional SPECT or fused SPECT/CT imaging was compared. Location and extent of disease on scintigraphic imaging and pre- and intra-operative clinical assessment were compared. Intraoperative and histopathological findings served as reference standard.

Results: A total of 29 sites of BRONJ/DRONJ were histopathologically confirmed in 21 patients. Bone scintigraphy demonstrated increased perfusion in 57.1% of patients, increased blood pool in 76.2%, and increased tracer accumulation at the metabolic phase in all patients. The intensity of tracer accumulation at the metabolic phase correlated significantly with clinical stage of disease ($r_s = 0.47$, $p = 0.03$). Clinical examination ($p < 0.0001$), but not SPECT ($p = 0.19$), underestimated the extent of disease as determined by surgical evaluation. SPECT/CT offered a significantly higher diagnostic certainty ($p < 0.0001$).

Conclusion: In patients with BRONJ/DRONJ, the true extent of osseous lesions as determined by surgery is significantly underestimated by clinical examination. Tc-99m-MDP bone scintigraphy can reliably predict the extent of disease. Hybrid SPECT/CT may significantly increase the diagnostic certainty of anatomical localization.

1. Introduction

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a newly recognized disease (Marx, 2003; Arce et al., 2009; Ruggiero et al., 2014). It has been linked to administration of bisphosphonates, as well as nuclear factor−κB ligand (RANKL) antibody administration (denosumab). In most cases, bisphosphonates are administered intravenously at high doses for treatment of malignant lytic osseous lesions (Marx, 2003; Assaf et al., 2013). Oral bisphosphonates are typically used in patients with osteoporosis (Otto et al., 2011; Wysowski and Greene, 2013; Paiva-Fonseca et al., 2014; Assaf et al., 2014). The clinical presentation and the course of

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BRONJ is very similar to that of osteoradionecrosis (ORN) (Ficarra et al., 2005; Hansen et al., 2006; Bertoldo et al., 2007; Assaf et al., 2013). BRONJ prevalence in osteoporosis patients taking oral bisphosphonates has been reported to be about 0.02%–0.05%. In cancer patients taking intravenous bisphosphonates, it may be encountered more frequently in about 1.7%–6.7% of cases (Bamias et al., 2005; Dimopoulos et al., 2006; Coleman et al., 2011a, 2011b). That markedly different ONJ incidence is at least partially explained by the administered dose (Lewiecki et al., 2007; Palaska et al., 2009; Grbic et al., 2010; Coleman et al., 2011a, 2011b; Rathbone et al., 2013). The mechanism of action of bisphosphonates affecting bone metabolism has been described in detail elsewhere (Russell, 2006; Ruza et al., 2013). Denosumab shows inhibition of bone resorption similar to that of bisphosphonates, but the pharmacological profile is different (Gibiansky et al., 2012; Pourvasei et al., 2013). In comparison to bisphosphonates, the frequency of ONJ in cancer patients treated with denosumab has been reported to be similar in most studies (Henry et al., 2011).

Precise preoperative assessment of the extent of disease is crucial for surgical planning. Besides clinical evaluation, a variety of different diagnostic procedures are applied to visualize different structural and physiologic aspects of BRONJ or DRONJ, and to reveal disease-related complications (Table 1). Radiographs, computed tomography (CT), magnetic resonance imaging (MRI), and bone scans are available for assessment of BRONJ (Dore et al., 2009; Hutchinson et al., 2010; Stockmann et al., 2010; Wilde et al., 2012; Assaf et al., 2013; Farias et al., 2013; Ohbayashi et al., 2013; Joshi et al., 2013). Nuclear medicine bone scanning using Tc-99m-methylene diphosphonate (MDP) is widely used for visualization of bone metabolism in a variety of diseases including ONJ (Joshi et al., 2013; Ohbayashi et al., 2013). To obtain a maximum of information, three-phase bone scanning is often performed. Each phase detects different types of pathology in the bone. The first-phase image, also known as the nuclear angiogram, is obtained directly after injection and typically shows perfusion to a lesion. The second-phase image, also known as the blood pool image, is obtained some minutes after injection. It demonstrates the relative vascularity to the area. The third phase, or delayed phase, image is obtained several hours after the injection. It shows the amount of bone turnover associated with a lesion (Schauwecker, 1992). In addition to planar imaging, tomographic imaging (i.e.), single photon emission computed tomography [SPECT] may be used to improve detectability. Newer hybrid SPECT/CT systems combining tomographic bone scanning with low-dose CT have been introduced for better anatomic characterization of skeletal lesions, and significantly improve the specificity over standard planar or tomographic bone scanning. Bone scintigraphy has been described as a useful tool to visualize necrotic bone areas in patients with BRONJ, and may be able to predict clinical outcomes of BRONJ and DRONJ therapy (Joshi et al., 2013; Ohbayashi et al., 2013). However, data on the value of bone scanning in that context are limited. SPECT/CT may provide a comprehensive evaluation of BRONJ by simultaneously assessing morphologic changes on CT and functional changes of bone turnover on SPECT.

Surgical intervention in patients with BRONJ is usually performed in patients with stage II and III disease, and rarely also in patients with stage I (Pautke et al., 2011a; Assaf et al., 2014). In most cases, partial bone resection of the affected regions may be sufficient, performing cautious necrectomy or sequestrectomy. In other cases, total resections are necessary, with subsequent microsurgical reconstruction of the resected area (Mücke et al., 2009; Pautke et al., 2011b). New surgical strategies have been evaluated, using fluorescence-guided bone resections after administration of tetracycline, for more precise demonstration of the affected necrotic areas (Pautke et al., 2010; Pautke et al., 2011a, Otto et al., 2013; Assaf et al., 2014).

The aim of this study was to compare imaging findings on Tc-99m-MDP scintigraphy with intraoperative and histopathological findings to assess whether preoperatively performed bone scintigraphy may be used to precisely predict intraoperative findings, including the size of necrotic areas in patients with BRONJ. To our knowledge, intraindividual comparison of clinical findings, fluorescence-guided bone resection with histology, and SPECT/CT have not been studied in this manner before.

2. Material and methods

2.1. Study population

The study population consisted of 21 patients (15 women and 6 men; mean age, 66.7 ± 14.0 years, range, 29.5–84.2 years) who were referred to the Department of Oral and Maxillofacial Surgery at our University Medical Center with a suspected diagnosis of BRONJ/DRONJ between August 2011 and October 2013.

The study protocol was approved by the local institutional review board (PV3806) and complied with the Declaration of Helsinki. All patients provided written informed consent.

2.2. Nuclear medicine imaging

Imaging was performed using a hybrid camera (Symbia T2; Siemens Medical Solutions, Germany) combining a dual-head γ-camera (low-energy high-resolution [LEHR] collimators) with a dual-slice spiral CT scanner. Three-phase bone scintigraphy was performed after intravenous administration of about 500 MBq of Tc-99m-methylene diphosphonate (Rotop-MDP; Rotop Pharmaka). Whole-body emission data were in a 256 × 1024 matrix in anterior and posterior projections, with perfusion images being obtained with a speed of 200 cm/min immediately after tracer injection, blood pool data with a speed of 40 cm/min 4 min after tracer administration, and delayed images with a speed of 10 cm/min 3 h after tracer injection. In addition, static lateral blood pool and delayed

Table 1
Overview of selected imaging studies for assessment of BRONJ.

Author	Year	n	Imaging modality	Sensitivity	Key point
Dore et al.	2009	15	Tc-99m diphosphonate SPECT/CT	100%	Precise definition of extent of disease
Hutchinson et al.	2010	10	CT or CBCT or radiographs	100%	Stage 0 disease only
O'Ryan et al.	2009	51	Tc-99m diphosphonate bone scan	67.5%	Prediction of areas that subsequently developed BRONJ.
Phal et al.	2007	15	Radiographs and/or CT	100%	Osseous sclerosis was most common finding
Stockmann et al.	2010	24	Radiographs	54%	Limited relevance of MRI and CT for the preoperative assessment of the extent of BRONJ.
			CE MRI	92%	
			CT	96%	
Wilde et al.	2012	27	CBCT	92.6%	Cancellous bone destruction, cortical bone erosion, sequestration, and osteosclerosis across all stages

CB, cone beam; CE, contrast-enhanced; CT, computed tomography; MRI, magnetic resonance imaging; SPECT, single photon emission computed tomography.