

Panoramic radiograph, computed tomography or magnetic resonance imaging. Which imaging technique should be preferred in bisphosphonate-associated osteonecrosis of the jaw? A prospective clinical study

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Abstract It was the aim of the present study to find out which radiological imaging techniques allow assessing the extent of bisphosphonate-associated osteonecrosis of the jaw (BONJ) in an adequate way. Twenty-four patients suffering from BONJ were included in the study. Before surgery, each patient was examined with panoramic radiograph, contrast-enhanced magnetic resonance imaging (MRI) and non-enhanced computed tomography. The detectability of BONJ was assessed for the three imaging techniques. The extent of the jaw region affected by BONJ was determined in MRI and CT scans and compared to the intra-operative situation. The detectability of BONJ lesions was 54% for panoramic radiographs, 92% for MRI scans and 96% for computed tomography (CT) scans. The intra-operatively assessed extent of BONJ correlated significantly with the measurements on CT scans ($p=0.0004$) but did not correlate significantly with the measurements in MRI scans ($p=0.241$). The intra-operatively measured extent of BONJ differed significantly from the CT measurements

($p=0.00003$) but not from the MRI data ($p=0.137$). Although MRI as well as CT have a high detectability for BONJ lesions that exceeds that of panoramic radiographs by far, both techniques show problems with the exact assessment of the extent of BONJ lesions in the individual patients. Therefore, the relevance of MRI and CT for the preoperative assessment of the extent of BONJ lesions is limited. Future research should focus on the identification of imaging techniques that allow assessing the extent of BONJ lesions with a higher accuracy.

Keywords Bisphosphonates · Computed tomography · Magnetic resonance imaging · Osteonecrosis · Panoramic radiograph

Introduction

Bisphosphonate-associated osteonecrosis of the jaw (BONJ) represents a growing concern for oral- and maxillofacial practice [9, 11, 12]. BONJ can severely affect quality of life and can even become the major concern of cancer patients because of pain, difficulties in performing oral hygiene and in eating. The characteristic symptoms of BONJ are a non-healing extraction sockets or exposed jaw bone with progression to sequestrum formation associated with localised swelling and infection. The American Association of Oral and Maxillofacial Surgeons defined BONJ as exposed bone without healing tendency over a period of minimum 8 weeks [1].

The pathogenesis of BONJ is barely understood, and the diagnosis of osteonecrosis is largely based on clinical criteria. Multifactorial cause is assumed, similarly to osteoradionec-

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rosis [7], and a time-dependent relationship in bisphosphonate administration is thought to exist [12, 13].

Although the current guidelines for the treatment of BONJ seem to favour conservative approaches, recent publications have shown that osteotomy of the affected jaw bone regions and primary wound closure can lead to success rates between 58% and 86% [1, 2, 14]. Before an adequate treatment option can be chosen, the extent of BONJ has to be assessed. Clinical examinations do not always allow determining the extent of bone affected by BONJ. Therefore, different radiological examination methods have been applied in cases of BONJ with these imaging techniques. However, previous studies focus on description of imaging findings in BONJ [3, 5, 6, 10]. To date, it is not clear which imaging modality should be preferred when the extent of BONJ has to be determined. A direct comparison between the clinical extent and the most often used imaging techniques, which are panoramic radiographs, computed tomography (CT), and magnetic resonance imaging (MRI), is not available in the current literature as far as the metric determination of the extent of BONJ is concerned.

Therefore, it has been the aim of the present study to find out which of the different imaging techniques showed the best correlation with the actual intra-operative extent of BONJ.

Materials and methods

The study was approved by the ethical committee of the University of Erlangen–Nuremberg. Patients suffering from BONJ were included in the study (Fig. 1). All patients gave their informed consent to participation in the study. Overall, 28 patients (16 women, mean age, 68 ± 10.1 years; 12 men, mean age, 71 ± 6.6 years) were included in the study.

Main inclusion criteria were:

1. Exposed bone in mandible or maxilla for longer than 8 weeks
2. Life expectancy of more than 1 year according to the assessment of the attending oncologist.

Patients were excluded from the study

1. If there was a history of radiation therapy in the head and neck region
2. If lost to follow-up during the observation period
3. If there were general medical contraindications for surgery under general anaesthesia or
4. If there was a recurrence of BONJ in the region operated on during the 6 month of follow-up
5. If there were contraindications to perform CT or MRI.

Gender, age, the administered bisphosphonate and region of occurrence of BONJ were assessed. The stages



Fig. 1 Bisphosphonate-associated osteonecrosis (BONJ) lesion exposed to oral cavity

of BONJ were categorised according to the guidelines of the AAOMS [1].

Radiological examination

Ten days before surgery, each patient was examined with panoramic radiograph, contrast-enhanced MRI and non-enhanced multislice computed tomography (MSCT).

Panoramic radiographs (OrthophosTM, Sirona, Bensheim, Germany, $\times 1.2$ magnification) were taken under gender specific settings (female patients, 69 kV and 15 mA; male patients, 66 kV and 8 mA; Fig. 2).

CT scans were obtained using a 64-slice MSCT-Scanner (Somatom Sensation 64TM, Siemens, Forchheim, Germany). Scan settings were 120 kV, 110 mAs eff., 64×0.6 slice acquisition, 0.9 pitch, 1 s rotation time, 1 mm reconstructed slice thickness, 0.8 mm reconstruction increment and sharp kernel (B70s). No contrast media was used for CT imaging. MRI scans were



Fig. 2 Panoramic radiograph of the patient affected by BONJ in the right mandible

obtained at 1.5 T (Magnetom Symphony™, Siemens, Erlangen, Germany). The following sequences were used for image evaluation in axial planes with 3-mm slice thickness: T1-weighted spin echo [repetition time (TR)=450 ms, echo time (TE)=17 ms], T2-weighted STIR [TR=4,470 ms, TE=105 ms, inversion time (TI)=140 ms], T1-weighted spin echo with fat saturation after contrast administration (TR=652 ms, TE=17 ms). Gadobutrol (Gadovist™, Bayer Schering Pharma AG, Berlin, Germany; 1 ml/kg body weight) served as a MR contrast agent.

All images were reviewed by two experienced radiologist blinded to the clinical findings. The panoramic radiographs were exclusively used to see if all jaw regions affected by BONJ could be identified on the image.

The extent of sequestrs or osteolysis of jaw bone was determined in CT in individually adapted planes parallel to the hard palate as parameters for assessment of necrotic bone.

CT measurements were taken in mesiodistal direction assessing the widest diameter of osteolysis/sequestrum. The widest diameter of osteolysis/sequestrum was measured with an electronic calliper on a remote work station (Multimodality work place, 3D tool, Siemens, Forchheim, Germany) in mesiodistal direction (Fig. 3).

A contiguous signal loss of maxillar or mandibular bone marrow in T1-weighted images as a characteristic feature of necrotic bone transformation was measured similarly in axial planes in the MRI images [3]. The extent of T1-signal loss was also taken in mesiodistal direction using the same software tool as for the CT measurements (Fig. 4). When BONJ could not be identified in one of the imaging techniques, “0” was chosen as the value of the widest diameter of BONJ. Measurements were taken twice by two examiners after a minimal period of at least 4 weeks.

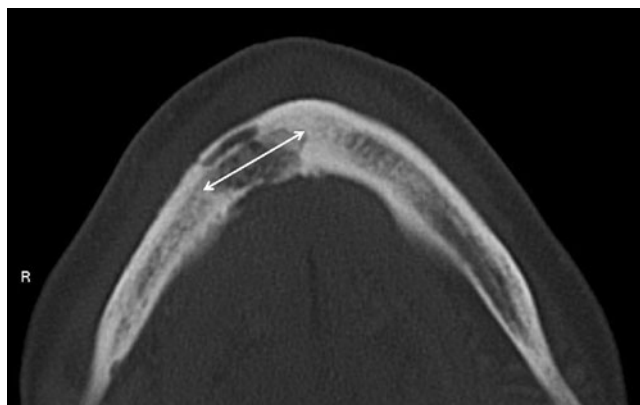


Fig. 3 Computed tomography of the aforementioned patient. The widest mesio-distal diameter of osteolysis was measured to be 2.4 cm

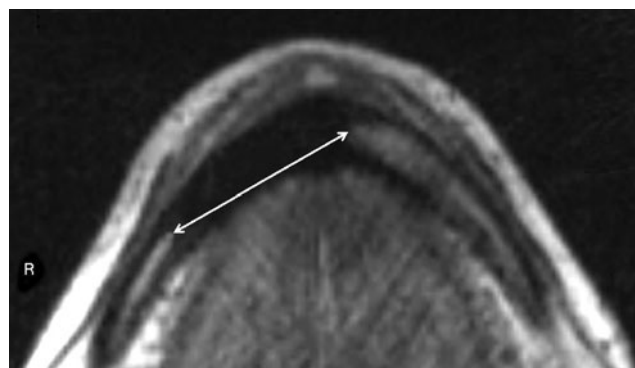


Fig. 4 Magnet resonance imaging of the aforementioned patient. The bar indicates the region of the mandible affected by BONJ (widest mesio-distal diameter of T1 signal loss 3.3 cm)

Measurements during surgery

All patients were treated under general anaesthesia. At the beginning of surgery the extent of exposed bone in the oral cavity was measured in mesiodistal direction by using a hand ruler.

Thereafter, mucoperiosteal flaps were reflected in the region of BONJ. Again, the extent of visible affected bone was measured in mesiodistal direction. Signs for osteonecrosis were an altered colour and the lack of bleeding from the bony surface (Fig. 5). No radiological markers were used to facilitate the identification of the bone region affected by BONJ. Sequestrotomy of visible necrotic bone was carried out until there was only sound bone remaining that showed bleeding from the bony surface macroscopically. Subsequently, primary wound closure was performed.

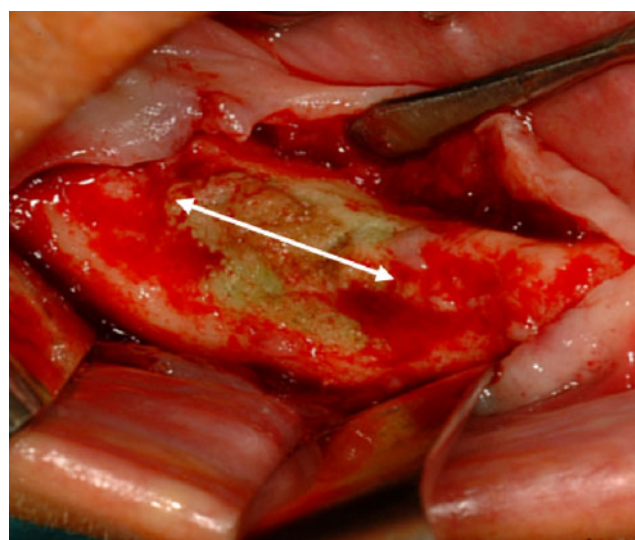


Fig. 5 Lesion of osteonecrosis after elevation of mucoperiosteal flaps (arrow widest mesio-distal diameter, 2.3 cm)

Table 1 Cross table of the distribution of BONJ lesions detected by the different imaging techniques

		BONJ lesion not detectable in CT	BONJ lesion detectable in CT	Total
BONJ lesion not detectable in panoramic radiograph	BONJ lesion not detectable in MRI	0	1	1
	BONJ lesion detectable in MRI	0	10	10
BONJ lesion detectable in panoramic radiograph	BONJ lesion not detectable in MRI	0	1	1
	BONJ lesion detectable in MRI	1	11	12
Total		1	23	24

Follow-up examinations

Follow-up examinations were carried out 3 and 6 months after surgery. The surgical field was checked for intactness of the mucosa and signs of recurrence of BONJ.

Statistics

Statistical analysis was carried out using SPSS for Windows (version 16; SPSS Inc., Chicago, USA). Medians and ranges were given. Mean values were calculated with standard deviation. The detectability of osteonecrosis in the different imaging techniques was calculated according to the formula:

$$\text{Detectability(\%)} = \frac{\text{number of positive diagnosed necrosis}}{\text{number of all included patients}} \times 100$$

Pearson product-moment correlation coefficient (r) was calculated to determine the correlation between intra-operative extent of osteonecrosis and the extent osteonecrosis in the imaging modality. Different groups were compared using the Wilcoxon rank-sum test. A p value ≤ 0.05 was considered statistically significant.

Inter- and intra-rater reliability were assessed for CT and MRI measurements by calculating intra-class correlation coefficients (ICC). An ICC coefficient can range from 0 to 1.0. An ICC coefficient of 0 indicates the reliability is no better than chance, whereas an ICC coefficient of 1.0 indicates excellent rater reliability.

The study was intended as an explorative data analysis. Therefore, adjustments for multiple testing were not carried out.

Results

Seven patients received pamidronate and 19 patients zoledronic acid. Two patients were administered a combination of both. In 18 patients, the lesions occurred in the mandible, in eight patients in the maxilla and in two patients in maxilla and mandible simultaneously.

During the follow-up period four patients had to be excluded from the study. One of these patients died 4 months after surgery because of progression of her malignant disease. In three patients, a recurrence of BONJ occurred during the follow-up period. Therefore, the analysis of data was carried out for 24 patients.

Table 2 Detectability in dependence of the stage of BONJ

Imaging technique	Stage of BONJ	Number of BONJ lesions detected	Detectability (%)
Panoramic radiograph	1	3 out of 8	37.5
	2	6 out of 8	75.0
	3	4 out of 8	50.0
Total		13 out of 24	54.1
MRI	1	7 out of 8	87.5
	2	7 out of 8	87.5
	3	8 out of 8	100
Total		22 out of 24	92
CT	1	8 out of 8	100
	2	8 out of 8	100
	3	7 out of 8	87.5
Total		23 out of 24	96

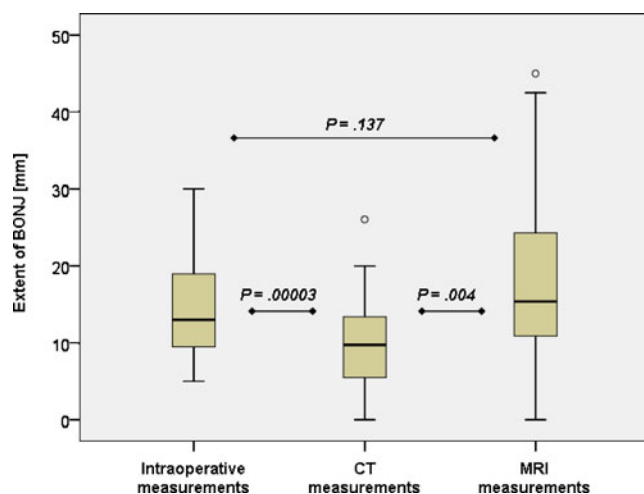


Fig. 6 Box plot distribution of measured extent of BONJ

The mean extent of exposed bone in a mesiodistal direction was 6.9 ± 5.9 mm. After elevation of the mucoperiosteal flap, the extent of bone affected by BONJ was significantly larger than the exposed bone and showed a mean length of 14.6 ± 6.4 mm in mesiodistal direction ($p=0.00023$).

Panoramic radiographs showed signs of osteonecrosis in 13 out of 24 patients (detectability, 54.1%). In 23 out of 24 patients, signs of osteonecrosis could be identified in the CT scans (detectability, 96%). In 22 out of 24 patients, signs of osteonecrosis could be identified in the MRI images by low signal in T1-weighted images of 22 patients (detectability, 92%, Tables 1 and 2). There was no clear-cut influence of the stage of BONJ on the detectability.

When comparing the applied imaging techniques, the measured extent of BONJ in MRI (17.1 ± 13.5 mm) was significantly larger than that in the CT scans (10.4 ± 5.8 mm, $p=0.004$, Fig. 6). The intra-operative extent of BONJ differed significantly from the measurements in CT scans ($p=0.00003$) but not from measurements on MRI scans ($p=0.137$). The intra-operative extent of bone affected by BONJ was correlated significantly with the measurements performed on the CT scans ($p=0.00004$) but not with the

Table 3 Pearson product-moment correlation coefficient (r) between intra-operative extent of visible affected bone and the measured values of the mesiodistal extent of osteonecrosis by computed tomography (CT) and magnetic resonance imaging (MRI)

	CT	MRI
Intra-operative extent of affected bone	$r=0.624$ $p=0.0004$	$r=0.220$ $p=0.241$

A range between $r=0.5$ and $r=1.0$ indicates a positive correlation between the two variables. p values ≤ 0.05 were considered statistically significant

Table 4 Inter- and intra-rater reliability of CT and MRI measurements by two examiners (ICC=intraclass correlation coefficient)

	Intra-rater reliability		Inter-rater reliability	
	Examiner I ICC	Examiner II ICC	Analysis I ICC	Analysis II ICC
MRI	0.94	0.94	0.84	0.81
CT	0.98	0.97	0.85	0.87

measurements performed on the MRI scans ($p=0.241$, Table 3). Intra- and inter-rater reliability for CT and MRI measurements are given in Table 4.

Discussion

Radiological and nuclear medicine imaging techniques are effective tools for detection of BONJ. To date, only few studies have been dedicated to the relevance of radiological imaging in cases of BONJ [3–6, 10]. Most of the studies are aimed to describe the different radiological findings which are related to the pathology of BONJ.

In a previous study, histological characteristics have been compared with radiological features in 11 patients suffering from BONJ [3]. It could be shown that CT and MRI had a close correlation to the histopathologic characteristics of BONJ. In the MRI, low water content characterised by low signal intensity in T1- and T2-weighted images was associated with the areas of bone exposed in the oral cavity. On the other hand, a high signal in T2-weighted images, suggestive of oedema and inflammation, was associated with bone covered by mucosa but still affected by BONJ.

Different imaging modalities have been proposed for the detection of BONJ [6]. It has been stated that CT and MRI are adequate in evaluating bone involvement and offer the advantage that destructive processes can be seen at a high resolution. Moreover, three-dimensional images can be generated if necessary. Besides CT and MRI, bone scintigraphy has been identified as a tool for the detection of early stages of BONJ. However, limitations exist due to a low spatial resolution and the difficulty in differentiating between inflammatory and malignant processes. An additional drawback is that a relevant metric analysis cannot be performed. Therefore, scintigraphy is not suitable for the metric analysis of BONJ.

The panoramic radiograph is the most often used radiological imaging technique in cases of BONJ. It has been shown previously that panoramic radiographs often showed persisting tooth sockets after extractions in cases of BONJ [10]. In advanced stages, an osteonecrosis appeared as an irregular area of osteosclerosis with a cotton-wool-like appearance. Moreover, osteolysis with a central portion

Table 5 Stage and extent of BONJ lesions

Patient no.	Stage	Extent of intraorally exposed bone before surgery (mm)	Intraoperative extent of BONJ (mm)	Extent of BONJ lesion in CT (mm)	Extent of BONJ lesion in MRI (mm)	BONJ lesion detectable on panoramic radiograph
1	1	4	16	12.8	25.8	Yes
2	2	7	13	7.8	14.0	Yes
3	1	6	18	16.5	0	No
4	1	1	9	6.5	7.5	No
5	2	3	14	11.8	17.8	Yes
6	1	3	15	6.4	7.5	No
7	1	5	23	24	33.0	No
8	2	14	13	12.0	16.5	No
9	3	2	8	5.5	25.8	Yes
10	3	11	13	9.5	42.5	No
11	2	25	30	26.0	42.0	Yes
12	3	20	30	8.0	14.0	No
13	2	7	20	18.0	0	Yes
14	2	10	20	15.3	14.3	Yes
15	1	5	13	11.5	16.5	Yes
16	1	1	11	12.3	10.3	Yes
17	2	6	8	5.5	11.5	No
18	2	5	10	5.0	21.5	Yes
19	3	0*	15	0	25.0	Yes
20	3	14	25	20.0	23.5	No
21	3	5	20	14.0	14.0	No
22	3	3	6	5.5	14.0	Yes
23	3	6	13	10.0	22.0	Yes
24	1	2	5	4.0	8.5	No
Median	/	5	13	9.8	15.4	/
Range (min–max)	/	0–25.0	5–30.0	0–26.0	0–45.0	/
Mean	/	6.9	14.6	10.4	17.1	/
SD	/	5.9	6.4	5.8	13.5	/

Min minimum, *Max* maximum, *stage* stage of the BONJ lesion according to the AAOMS classification [1]

*Extraoral fistula

of separated bone (sequestrum) is often present. The most common finding in bisphosphonate-associated osteonecrosis was osseous sclerosis, which varied from subtle thickening of the lamina dura and alveolar crest to attenuated osteopetrosis-like sclerosis [10].

However, although some studies have been performed on the topic, there is still controversy which imaging technique should be preferred in order to determine the extent of BONJ metrically. Therefore, it was the aim of the study to assess which imaging technique (panoramic radiograph, CT and MRI) predicts the extent of necrotic bone in cases of BONJ in most precisely.

In the present study, the detectability of osteonecrosis was calculated for the different imaging techniques. This detectability does not equal sensitivity. It just gives the

percentage of the existing osteonecrosis lesions that were found in the different imaging modalities. The results of the present study reveal that panoramic radiographs have a poor detectability for the determination of the extent of BONJ. In only 13 out of 24 patients signs of osteonecrosis could be identified. Moreover, it has to be kept in mind, that in panoramic radiographs, no metrical analysis of the extent of BONJ can be performed because the horizontal magnification on these images is not constant. Therefore, even if BONJ lesions can be detected on panoramic radiographs, an adequate assessment of the extent of BONJ is not possible.

The data of the present study show that MRI has a high detectability for BONJ lesions. The extent of the BONJ lesions assessed from MRI scans did not differ significantly

from the intra-operative situation. However, there was no significant correlation between MRI measurements and intra-operative measurements. In eight patients, the BONJ lesion was underestimated, and in 16 patients, the BONJ lesion was overestimated (Table 5). In some patients, an overestimation of up to 31 mm was found. Therefore, it seems that MRI sometimes has limitations in assessing the extent of BONJ in the individual patient preoperatively [5, 8].

It has been shown previously that CT scans are useful in providing detailed information about cortical and trabecular bone and allow estimating real extent of osteonecrosis and distinguishing BONJ from malignant diseases like plasmocytoma or bony metastases [4, 14].

In the present study, CT scans had the highest detectability for BONJ lesions. Moreover, there was a significant correlation of the intra-operative extent of the BONJ lesions with the extent in the CT scans. However, the extent of the BONJ lesions measured intra-operatively and the extent assessed on the CT scans showed a statistically significant difference. In all but one CT scan measurements, BONJ lesions were underestimated. The extent of the lesions on the CT scans was only in the range of approximately 50% of the intra-operative extent of the BONJ lesions. Therefore, when CT scans are used to estimate the extent of BONJ lesions, it has to be kept in mind that there is a high probability that the intra-operative situation will present a significantly larger BONJ lesion.

Conclusion

Although MRI as well as CT have a high detectability for BONJ lesions that exceeds that of panoramic radiographs, by far, both techniques show problems with the exact assessment of the extent of BONJ lesions in the individual patients. Therefore, the relevance of MRI and CT for the preoperative assessment of the extent of BONJ lesions is limited. Future research should focus on the identification of imaging techniques that allow assessing the extent of BONJ lesions with a higher accuracy.

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Conflict of interest The authors declare that they have no conflict of interest.

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