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ORIGINAL ARTICLE

Volumetric analysis of MRONJ lesions by semiautomatic segmentation of CBCT images

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Abstract

Purpose The purpose of this study was to evaluate potential differences in volumes of areas of osteolysis caused by medication-related osteonecrosis of the jaw (MRONJ) between the upper and lower jaw. We aim to analyze the clinical relevance of volumetric measurement of osteolytic lesions for surgical planning of MRONJ patients.

Methods Sixty-seven patients who were clinically and histopathologically diagnosed with MRONJ were retrospectively included in this study. Cone beam computed tomography (CBCT) images were evaluated according to localization, affected anatomical structures, and volumetric measurement of osteolytic lesions caused by MRONJ in appliance of CBCT datasets by using ITK-SNAP.

Results The most frequently affected localization is the mandible, whereas female patients show significantly more often lesions of the maxilla. The cortical bone was predominantly affected. Furthermore, the affection of teeth, sinus floor, inferior alveolar nerve canal, or even a pathological fracture of the mandible are infrequently existing. The volumetric measurements revealed a statistically significant greater absolute osteolysis volume in males.

Conclusions Image analysis and volumetric measurements of osteolytic lesions of MRONJ patients is a helpful tool to further understand the clinical appearance and identify compromised anatomic landmarks. Volumetric analysis aids in pre-surgical planning and visualizes the individual extent of the disease for each patient.

Keywords: MRONJ · Osteonecrosis of the jaws · Volumetric parameters · Pre-surgical planning · Jaw's anatomy

Introduction

In recent history, cone beam computed tomography (CBCT) has become an important tool for clinical diagnostics and process control of MRONJ patients. CBCT technology provides metrically accurate three-dimensional (3D) data with lower radiation dosages compared to medical computed tomography (CT) [1, 2]. The open-source software ITK-SNAP provides a useful tool for analysis of these 3D medical images. The software enables segmentation of anatomical structures in 3D datasets and was initially used for MRI image analysis of the caudate nucleus and lateral ventricle [3]. The method of active contour segmentation allows elucidating the morphometry and volumes of physiological and pathological structures in 3D imaging. The application of CBCT datasets by using ITK-SNAP was published previously [4]. Hereby, the authors validated the method by analyzing dento-maxillary osteolytic lesions and compared the accuracy of three different semiautomatic segmentation methods with the accuracy of manual segmentation [4]. It was shown that the method of region-based active contour segmentation was a semiautomatic segmentation procedure comparable with manual segmentation [4]. Based on these results, other studies investigated that the combination of semiautomatic and manual segmentation can be used for an improved and precise volumetric measurement

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of pathological structures in craniomaxillofacial regions by using CBCT datasets and ITK-SNAP [5, 6].

Earlier investigations have analyzed the characteristics and the progress of osteonecrosis by application of CT scans. Common radiological findings in MRONJ patients include mainly areas of osteolysis, sclerotic and lytic lesions, cortical erosion, increased periosteal bone formation, and sequestration [7]. The main focus of the investigators was the relation of the MRONJ lesion to maxillary sinus, size of the sequestrum, periosteal reactions, and cortical bone perforations [8, 9]. Moreover, CBCT images were applied to evaluate the cortical bone thickness, intracortical and cancellous bone density, diameters of mental foramen, and incisive canal as well as widths of the mental foramen in a small cohort of 25 patients [10]. Especially MRONJ lesions with an osteolytic impact are found in the majority of MRONJ patients [8]. Regarding prior studies, to our knowledge, no research has been published yet, investigating the volumetric parameters of the osteolytic MRONJ lesion and the digital volumetric anatomy of the affected jaws. Thus, we conducted the present study.

In the present study, we intended to evaluate potential differences in occurrence and volumes of osteolytic MRONJ lesions between the upper and lower jaw. Also, gender and age of the MRONJ patients were investigated as potentially relevant parameters for the volumetric extension and morphology. In addition, we investigated the type of surgical procedure and the number of surgical approaches needed to achieve a stable state of the disease.

Furthermore, we investigated if absolute and relative osteolysis volumes can predict the surgical technique needed to remove the MRONJ lesions.

Materials and method

Sixty-seven patients (32 female and 35 male) who were clinically and histopathologically diagnosed with MRONJ between 2016 and 2017 at a University hospital clinic were retrospectively included in this study. All included patients had previous or current treatment with bisphosphonates or denosumab; patients with radiotherapy in the area of the head and neck in their history were excluded. As part of clinical diagnostics, cone beam computed tomographic (CBCT) scans were applied before treatment using a GALILEOS® cone beam CT device (Sirona, Bensheim, Germany) with a matrix of 512 × 512 pixels and a resolution of 300 mm or 2.5 line pairs/mm. Only patients with a full data set and sufficient CBCT images were included.

At the time of diagnosis, the mean age of the patients was 71 years (ranging from 50 to 93 years). All included patients suffered from an exposed or necrotic bone of the upper or lower jaw. The upper and lower jaw was subdivided into four quadrants (upper right and left and lower right and left) to describe exact localization of the necrosis.

Various anatomic landmarks were investigated if they were affected by the MRONJ lesion: cortical bone or tooth affection, centerline exceedance, the affection of zygomatic alveolar crest or the sinus floor for maxillary lesions, and affection of the inferior alveolar nerve canal or pathological fracture in the mandible.

The patients' clinical data, e.g., gender, age, underlying malignancy or osteoporosis, medical history, clinical course, preoperative image acquisition, and type and number of surgical interventions were reviewed as well. All patients underwent surgical treatment, which can be subdivided in local decortication, extended decortication (> 3 tooth width), decortication plus sequestrectomy, marginal resection, and segmental resection as well as hemi-maxillectomy respectively. All patients at least underwent one of the four surgical approaches to reach a stable state of the disease. The follow-up was 12 months. In patients who received more than one surgical intervention, the most invasive procedure was registered.

In detail, for pre-surgical CBCT images, evaluation was conducted as further described:

The localization of the MRONJ lesions was categorized: one or multiple lesions, affected anatomical structures, and the size of the osteolytic lesions. The volumetric measurement was subdivided into the absolute and relative volume. The absolute volume was analyzed in cubic millimeters, the relative volume in percentage according to the volume of the affected jaw.

The absolute and relative lytic necrosis volume of the 67 patients is presented as median, range, minimum, and maximum. For volume measurement of the MRONJ lesions, the open-source software ITK-SNAP (Penn Image Computing and Science Laboratory) was used [3]. The pre-surgical CBCT images were imported as DICOM datasets. The program showed the CBCT images in slices of the axial, sagittal, and transversal plane and as 3D reconstruction. The volumetric measurement was realized by ITK-SNAP (Penn Image Computing and Science Laboratory) via semiautomatic segmentation followed by manual segmentation for detailed measurement and corrections (Fig. 1). Mainly, areas of lower bone density have been measured by active contour segmentation. In case of unclear demarcation from the physiological surrounding in the cancellous bone, the procedure was supplemented by manual segmentation. In addition, MRONJ lesions with sequestrums and teeth or dental implants in the region of interest made an additional manual segmentation indispensable. Therefore, in our study, two independent examiners performed the semiautomatic segmentation and inaccuracies were corrected by manual segmentation. The performance of semiautomatic segmentation enables

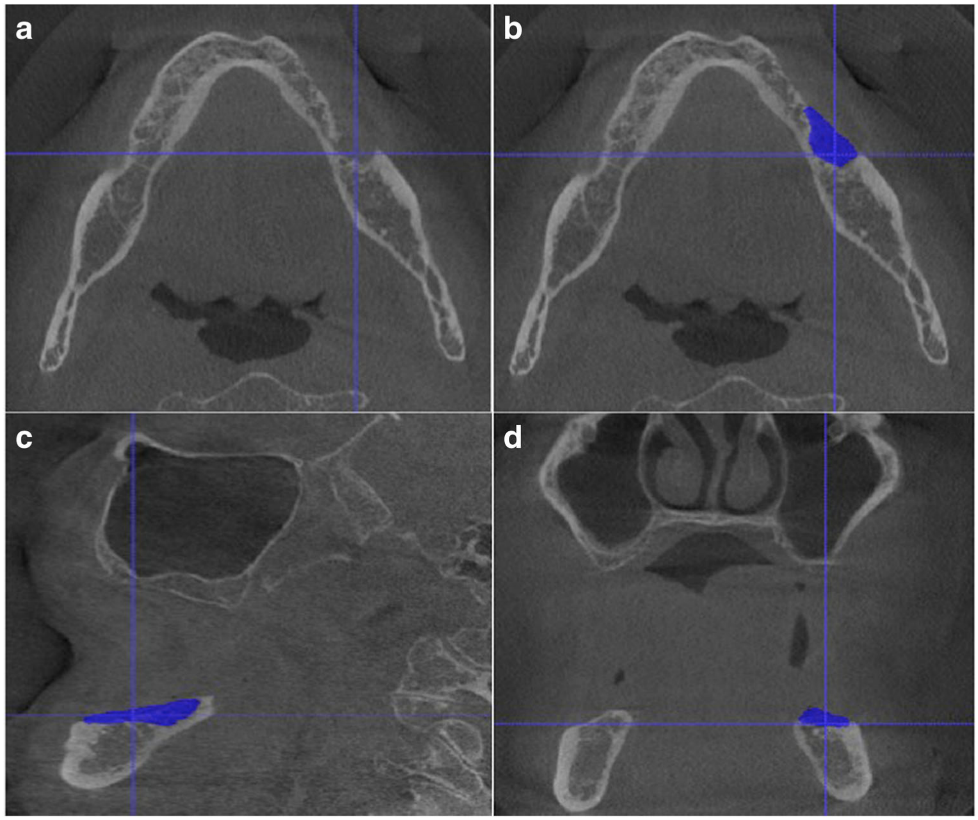

Fig. 1 Native CBCT image in axial plane (**a**) and segmentation of MRONJ lesion in the left part of the mandible in axial (**b**), sagittal (**c**), and coronal plane (**d**)

the combination of efficiency and repeatability of automatic segmentation and the precise delineation of manual segmentation [11]. ITK-SNAP (Penn Image Computing and Science Laboratory) provides geodesic active contour and region competition methods and thus enables manual and semiautomatic segmentation to analyze the volumes of anatomical regions of interest [3]. The software was initially validated for MRI image analysis of the caudate nucleus and lateral ventricle of the brain [3]. The results for craniomaxillofacial imaging have been confirmed by multiple consecutive studies [5, 6].

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki (2002). Due to the pure retrospective nature of this study, local ethics committee exempts this study from a specific ethic vote. All patients' data were anonymized when extracted from the clinic's database for this research.

The chi-square test was applied for statistical analysis of proportions across levels of categorical variables. We used Mann-Whitney U test for the determination of the correlation between osteolysis volume of the upper and lower jaw and of the correlation between osteolysis volume and patient characteristics like gender or age. The Kruskal-Wallis test was applied for determination of the correlation between absolute and relative osteolysis volume and type and number of surgical interventions. Level of significance (p value) was set to $p < 0.05$.

Results

Patients' characteristics according to sex and age are described below. The analyzed 67 patients present a gender balance of 35 male (52%) and 32 (48%) female patients. The age median was calculated as 71 years. Thirty-four patients (51%) were below and 33 patients (49%) were above the median age at the time of examination. The age range was 50 to 93 years.

The MRONJ lesions were categorized by their localization and affected jaw quadrants, Table 1. In 17 patients, the

Table 1 Location characteristics of MRONJ lesions of 67 patients (*chi-square test, $p < 0.05$)

	Patients (n)	Percentage
Maxilla	17*	25*
Mandible	58*	87*
Maxilla + Mandible	8	12
Upper right quadrant	10	15
Upper left quadrant	11	16
Lower left quadrant	38	57
Lower right quadrant	36	54
One affected quadrant	44	66
Two affected quadrants	19	28
Three affected quadrants	2	3
Four affected quadrants	2	3

MRONJ lesions were located in the maxilla, whereas in 58 patients showed lesions in the mandible. Eight patients had MRONJ lesions in both jaws at the time of examination. For our cohort, MRONJ lesions occurred significantly more often in the lower jaw ($p = 0.000$). In 10 cases, the lesion was located in the upper right and in 11 cases in the upper left quadrant. In 38 cases, the lesion was in the lower left and in 36 cases in the lower right quadrant. Forty-four of 67 patients had MRONJ lesions in only one region. Nineteen patients presented two affected quadrants. Lesions in 3 quadrants were detected in 2 patients and further 2 patients showed MRONJ lesions in all quadrants at the time of examination. The maxilla was involved significantly more often in female patients than in males ($p = 0.029$); on the contrary, the mandible was not significantly more involved in males ($p = 0.292$).

No significant correlation was detected between patients' age and the occurrence of MRONJ lesions in the maxilla ($p = 0.293$) or the mandible ($p = 0.215$). Additionally, gender ($p = 0.190$) and age ($p = 0.629$) did not correlate with detection of lesions in a certain quadrant.

The MRONJ lesion's morphologic characteristics and affected anatomic landmarks are displayed in Table 2. In 59 out of 67 cases, the lesions' extents reached the cortical bone. Teeth were located within the lesions in 32 cases. Moreover, in 4 cases, the centerline was exceeded. For maxillary lesions, in 6 out of 17 cases, the zygomatic alveolar crest and in 4 cases the sinus floor was necrotic. For mandible lesions, the osteonecrosis reached the inferior alveolar nerve canal (IANC) in 22 cases. Five patients presented a pathologic fracture of the mandible at the time of examination.

The osteolytic MRONJ volume of the analyzed 67 patients can be found in Table 3. It is shown as absolute volume in mm^3 and grouped in lytic necrosis volume of all locations, of the maxilla and of the mandible. The median lytic necrosis volume in total was 803 mm^3 with a range of 4338 mm^3. The minimum total lytic necrosis volume was 73 mm^3 and the maximum in total 4411 mm^3. Accordingly, the maxilla's median volume was 797 mm^3 (1116 mm^3 range). The minimum volume for maxillary lytic osteonecrosis was 165 mm^3 and the maximum volume of lytic osteonecrosis in the maxilla was 1281 mm^3. The median lytic osteonecrosis volume located in the mandible was measured with 827 mm^3 (4338 mm^3 range). The minimum volume for mandible osteolysis was 73 mm^3 and the maximum volume of osteolysis in the mandible was 4411 mm^3. The results did not show any significant differences between the absolute volumes of the osteolysis and the locations in either lower or upper jaw ($p = 0.474$). Male patients showed significantly greater absolute volumes of the osteolysis than female patients ($p = 0.01$). No significant difference was detected between absolute lysis volumes and age ($p = 0.715$).

Table 2 Morphologic characteristics and affected anatomic landmarks of MRONJ lesions of 67 patients

	Patients (*n*)	Percentage
Cortical bone invasion	59	88
Contact to tooth/teeth	32	48
Centerline exceedance	4	6
Zygomatic alveolar crest	6	35
Sinus floor affection	4	24
IANC affection	22	38
Pathologic mandible fracture	5	9

Table 3 Absolute and relative osteolytic necrosis volume in total, of the maxilla and mandible in 67 patients with MRONJ lesions (*Mann-Whitney *U* test, $p < 0.05$)

	Abs. volume (mm^3)	Rel. volume (%)
Volume median	803	3.3
Volume range	4338	15.1
Volume min	73	0.3
Volume max	4411	15.4
Volume maxilla median	797	6.4*
Volume maxilla range	1116	8.7
Volume maxilla min	165	1.6
Volume maxilla max	1281	10.3
Volume mandible median	827	3*
Volume mandible range	4338	15.1
Volume mandible min	73	0.3
Volume mandible max	4411	15.4

Furthermore, the MRONJ lesions were assessed with regard to the volume of the affected jaw (Table 3). The median relative lytic necrosis was in total 3.3% (15.1% range). The minimum of relative osteolysis was in total 0.3% and the maximum 15.4% of the volume of the respective jaw. For maxillary osteolysis, the median relative volume was 6.4% (8.7% range). In the maxilla, osteolysis showed a minimum relative volume of 1.6% and a maximum relative volume of 10.3%. The median relative lytic necrosis volume of the mandible was 3% (15.1% range). In the mandible, osteolysis showed a minimum relative volume of 0.3% and a maximum relative volume of 15.4%. The results showed a significant difference between the relative osteolytic necrosis volume and the affected jaw. The median relative volumes of the maxillary lesion were significantly larger than the volumes of the mandible ($p = 0.018$). Moreover, relative volumes of the osteolysis and gender, considered as independent parameters, did not show any correlation ($p = 0.366$). Additionally, a similar observation was found for the relative volumes of the osteolysis and patients' age ($p = 0.792$).

Table 4 displays the type of surgical intervention and the number of surgical interventions needed to reach a stable state of the disease. The majority of patients, 34 (51%) underwent

Table 4 Type and number of surgical interventions of 67 patients with MRONJ lesions. According to patients who underwent more than one surgical intervention, the most invasive procedure was registered

	Patients (*n*)	Percentage
Local decortication	34	51
Extended decortication	13	19
Decortication + sequesterectomy	17	25
Marginal resection	1	2
Segmental resection/hemimax.	2	3
One surgical intervention	41	61
Two surgical interventions	16	24
Three surgical interventions	8	12
Four surgical interventions	2	3

local decortication, followed by 17 (25%) patients with decortication plus sequestrectomy, and 13 (19%) patients with extended decortication. One patient (2%) needed a marginal resection and two patients (3%) a segmental resection. Forty-one (61%) patients underwent one surgical intervention to reach a stable state of the disease without any recurrence in a 12-month follow-up. Furthermore, 16 (24%) patients received two surgical interventions. Eight (12%) patients underwent three and two (3%) patients four surgical interventions. Eventually, our results did not present any statistically significant correlation between the type of surgical intervention for neither the absolute osteolytic necrosis volume ($p = 0.477$), nor the relative osteolytic necrosis volume ($p = 0.113$). Likewise, no statistically significant correlation was observed for the number of surgical interventions in regard to the absolute ($p = 0.108$) or the relative ($p = 0.119$) osteolytic necrosis volume.

Discussion

In this retrospective analysis, we investigated the MRONJ lesions of 67 patients according to their occurrence, localization, and volumetric measurements by analyzing and segmentation of CBCT datasets. For our cohort, demographic results are in line with earlier studies; thus, in regard to demographic results, there is nothing new to add to the known data [12–15].

In this study, eight patients presented simultaneous onset of MRONJ in upper and lower jaw. On the contrary, most patients presented MRONJ lesions only in the mandible (Table 1). Earlier studies reported a similar tendency for higher frequency of osteonecrosis in the lower jaw [8, 16, 17].

On the contrary, we found a significant rate of MRONJ lesions in the upper jaw for females compared to males ($p = 0.029$) in our cohort. With regard to further studies, a gender-specific higher frequency of a specific localization has not yet been reported [13, 14, 18, 19].

In addition, we did not detect a gender-specific accumulation of MRONJ lesions in any quadrant.

In this study, MRONJ patients younger than median age (< 71 years) presented more frequently lesions in the upper jaw, whereas patients above median age (> 71 years) had more lesions in the lower jaw. Notably, this observation remains without any significance for our cohort ($p > 0.05$). With regard to the underlying disease, an earlier study observed significant differences in gender and mean age between osteoporosis versus oncologic patients; in addition, they reported the oncologic patients to be 10.6 years older on average on disease onset [20]. In comparison, our cohort is more heterogeneous, because we focused on the volumetric changes of the jaw's anatomy in general for all MRONJ patients. However, the destruction of the cortical bone causes an imprecise margin during volumetric measurement. Hence, manual segmentation had to be performed, in order to prevent the volumetric analysis from crossing the original anatomical border of the jaw, which might generate imprecise values. In addition, MRONJ lesions with sequestrums and teeth or dental implants in the region of interest made an additional manual segmentation indispensable. Thus, a clear weakness of our segmentation technique is revealed.

Therefore, we investigated the anatomical characteristics of MRONJ lesions and affected anatomical structures. The majority of patients (88%) showed an affection of the cortical bone with only five patients (9%) presenting a pathological fracture of the mandible. Merely, pathological fractures are observed for a minority of patients; on the contrary, the perforation of the buccolingual seems to be quite frequent if the cortical bone is affected in the mandible [8]. Generally, the cone beam CT scans of our cohort proved to be as effective as regular CT scans, conducted by different researchers, in the detection of sequestrum, periosteal reaction, bone expansion, cortical perforation, and pathological fracture images [8].

Increased buccal and apical cortical bone thickness, decreased intracortical radiodensity, and a narrowing of the incisive canal are characteristics which can help the clinician to estimate the extension of the MRONJ lesion [10]. Similarly, in the investigation of our cohort, we observed an affection of the cortical bone and inferior alveolar nerve canal's integrity. In addition, we analyzed if destruction of the zygomatic alveolar crest or the sinus floor is present for maxillary MRONJ lesions. In cases of sinus floor destruction, commonly MRONJ patients suffer from unilateral maxillary sinusitis [8, 21]. This symptom should alarm clinicians, and radiographic diagnostics, for instance cone beam CT scans, can aid in revealing the symptom's origin.

Moreover, we examined the volumetric measurements of osteolytic MRONJ lesions. The median absolute osteolysis volume of 803 mm^3 of all lesions was greater than the median volume of the maxillary lesion (797 mm^3) and smaller than the mean of lesions in the mandible (827 mm^3). Thus, mandibular lytic MRONJ lesions show bigger volumes. Furthermore, the volumetric measurements showed a wide range with a minimum of 73 mm^3 and a maximum of 4411 mm^3. However, this might be explained by the heterogeneity of the cohort. All patients showed MRONJ stages II and III, yet the underlying disease and prescribed antiresorptive drugs varied [7]. Nevertheless, the bacterial flora of the MRONJ lesions itself or co-factors like vitamin D deficiency might further contribute to the lesion sizes [22–24]. Therefore, in future studies, a bigger sample size along with meticulous investigation of all subgroups might generate more individualized data.

The methods used in our study present some weaknesses, namely, the active contour segmentation image analysis. If a lesion does not clearly demarcate from the physiological surrounding in the cancellous bone, obtaining precise volumetric measurements is difficult to perform and demands experienced examiners. Previous studies investigated, that even the most accurate semiautomatic segmentation technique was negatively influenced by destruction of the cortical bone [4]. The destruction of the cortical bone causes an imprecise margin during volumetric measurement. Hence, manual segmentation had to be performed, in order to prevent the volumetric analysis from crossing the original anatomical border of the jaw, which generates imprecise values. Furthermore, MRONJ lesions with sequestrums and teeth or dental implants in the region of interest make an additional manual segmentation indispensable. Therefore, in our study, two independent examiners performed the semiautomatic segmentation and inaccuracies were corrected by manual segmentation. Furthermore, the volumetric analysis could be only carried out for areas of decreased bone density or osteolysis. Although the majority of MRONJ lesions present this radiological finding besides sclerosis, it can only give a rough estimation of the dimension of MRONJ lesions.

Nevertheless, in contrast to earlier studies analyzing the osteolytic area of MRONJ lesions with CBCT scans [10, 25, 26], to our knowledge, this is the first study to incorporate volumetric measurements of the osteolytic MRONJ lesions by semiautomatic segmentation into the detailed morphologic investigations. Moreover, the three-dimensional analysis is a versatile tool that allows a more precise investigation than unidimensional images and enables volumetric measurement.

For our cohort, male patients showed a significantly higher absolute osteolysis volume than female patients ($p = 0.01$). On the contrary, no significance in results was detected with regard to age or absolute volumes. Male patients presented bigger absolute osteolysis volumes; thus, it might be reasoned by the simple fact that male human skulls are larger than female ones [27]. Consequently, we measured the volumes of the affected jaw and calculated the relative volumes of MRONJ osteolysis. As a result, we found that the relative osteolysis volumes of male patients were also larger than those of female patients, yet no significant difference was observed. In contrast, the comparison between the affected jaw and the relative volume revealed significant differences: relative osteolysis volumes of maxillary lesions were significantly larger than lesions of the mandible. It was shown, that about 6.2% of the maxilla was affected by areas with decreased bone density caused by MRONJ. This might be explained by the smaller volume of the maxilla in general compared to the mandible. Alternatively, the anatomical bone thickness of the maxilla could allow for an easier spread of the MRONJ lesion [8].

The American Association of Oral Maxillofacial Surgeons recommends a clinical staging system not including any radiological findings [28, 29]. Nevertheless, radiological diagnostic is compulsory and an important part at baseline examination of MRONJ patients [30]. Especially for evaluation of the MRONJ extent, the clinical examination seems to provide only insufficient data [31, 32]. In comparison to panoramic radiography (PR), CBCT and CT scans offer a more precise detectability for MRONJ lesions [8]. Whereas typical pathological findings like woven bone formations and periosteal thickening are detectable, disadvantages are the limited two-dimensional projections and a difficult differentiation between necrotic and healthy bone [33]. Tools of second-line diagnostic of MRONJ patients are provided by CT and CBCT. CT scans detect accurately alterations of the bone, periost, and soft tissue surrounding [33]. But findings like thicker cortical bone or more sclerotic bone marrow are actually described by analyzing CBCT images as well, while afflicting patients with lower radiation dosages than regular CT scans [25, 26]. Thus, the analysis of CBCT offers additional information compared to PR and CT and afflicts the patients with lower radiation dosages than regular CT scans [1]. In comparison with CT, CBCT provides a higher spatial resolution which improves the image quality in particular for cancellous bone [34]. On the other hand, CBCT shows a limited soft tissue discrimination caused by a low-contrast resolution. Nevertheless, both imaging modalities provide sufficient information for further diagnostic of MRONJ patients [33].

Treatment planning can aid in limiting harm to sensible anatomic structures in the surrounding tissue; this procedure can be supported by volumetric information. For our cohort, local decortication, extended decortication, or decortication plus sequestrectomy showed no evidence of pre-surgical imaging in regard to the lesions' volume. Perhaps, larger cohorts are needed to detect the benefits of volumetric analysis for MRONJ patients. In this context, the MRONJ stage as well as the underlying disease and prescribed antiresorptive drugs and doses should be investigated as well.

Conclusion

For surgeons, imaging tools are vastly integrated into their routine. Thus, volumetric measurement of MRONJ lesions in CBCT images might aid in the planning of a surgical procedure. Therefore, we analyzed the type and number of surgical interventions in regard to the volume of the osteolytic MRONJ lesions. For our cohort, no statistically significant correlation was detected; hence, the clinical relevance for planning of a surgical procedure is disputable. Further improvement of the segmentation technique and greater cohort may reveal different results. Hitherto, patients' benefits remain uncertain.

Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study (retrospective study), formal consent is not required.

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