Stephan Brachmann, Knut Adam, Frank Tavassol, Ingmar Staufenbiel

Manifestation pattern of 343 antiresorptive-related osteonecroses of the jaw considering the etiologic factor – consequences for the dental practice

Introduction: Antiresorptives are used in patients with osteoporosis and malignant tumors to inhibit resorption processes in the bone. Antiresorptive-related osteonecrosis of the jaw (ARONJ) is an adverse drug reaction and is associated with a considerable impairment of quality of life. Therefore, prevention and early identification of ARONJ events are crucial.

Methods: The data of 249 patients (mean age: 68.8 ± 10.4 years) with 343 ARONJ events were retrospectively assessed according to etiology (extraction-related, denture-related, idiopathic), risk profile (high, moderate, low), and localization (maxilla/mandible; buccal/crestal/oral). For this purpose, Pearson's □²-test and t-test for independent samples were applied. The significance level was set at □ = 0.05.

Results: The majority (88.4 %) of patients received the antiresorptive drug as part of the oncologic treatment and thus exhibited a high risk profile. Extraction-related ARONJ (51.6 %) were most frequently observed, followed by denture-related (30.3 %) and idiopathic (18.1 %). Most ARONJ were located in the mandible (69.4 %). Regarding oro-buccal extension of the ARONJ, the buccal sites were significantly more often affected in the maxilla compared to the mandible ($p < 0.001$), whereas the oral sites were significantly more often affected in the mandible compared to the maxilla ($p < 0.001$). In this context, it should be noted that 75.6 % of idiopathic ARONJ of the mandible extended to the oral sites. Molars were significantly more frequently affected (51.8 %; $p < 0.001$) than premolars and anterior teeth.

Discussion and conclusion: Patients with a high risk profile are known to be susceptible for the development of ARONJ following tooth extractions. The high proportion of denture-related ARONJ underlines that high risk patients wearing removable partial and complete dentures should be closely monitored in the dental practice. Particular caution is required in patients with a thin soft tissue layer and missing keratinization. These anatomical peculiarities seem to predispose for idiopathic ARONJ and may explain the high occurrence in the area of the mylohyoid ridge.

Keywords: antiresorptive-related osteonecrosis of the jaw (ARONJ); etiology; tooth extraction; denture; idiopathic; risk profile; localization

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Introduction

Human bone tissue undergoes continuous remodeling throughout life, with apposition and resorption processes balancing each other under physiological conditions [4, 9, 22]. Osteoporosis and bone metastases of malignant tumors represent common diseases that sensitively interfere with this bone homeostasis. In Germany, the annual incidence for osteoporosis is reported to be approximately 620,000 [8], for breast cancer approximately 69,000, and for prostate cancer approximately 60,000 [28]. Different antiresorptive drugs are used to inhibit the progression of osteoporosis and bone metastases by favoring bone apposition. Bisphosphonates (BP; e.g. Aredia® or Zometa®) are synthetically produced analogues of pyrophosphate and inhibit osteoclast activity [7]. The half-life of these drugs is very long, ranging from 10–12 years [32]. The monoclonal antibody (MAB) denosumab (e.g. Prolia® or XGEVA®) interferes with the signaling pathway of RANK (Receptor Activator of NF-□B) and its ligand (RANKL). In this way, the differentiation of osteoclastic progenitor cells and the activity of mature osteoclasts are inhibited [3]. The half-life of these drugs is 24–26 days [32]. Angiogenesis inhibitors (AI) such as bevacizumab (e.g. Avastin®) exert their antiresorptive effects through specific inhibition of vascular endothelial growth factor (VEGF) in vascular endothelia [35]. The half-life of bevacizumab is comparable to that of denosumab and is approximately 20 days [32].

Previous studies have shown that drug therapy with antiresorptives has reduced the incidence of pain and pathologic bone fractures in both oncologic [26, 32] and non-oncologic patients [13], thereby improving the overall quality of life. However, there is evidence that antiresorptive drugs can cause an adverse drug reaction in the form of osteonecrosis of the jaw (ONJ). This was first described in the 2003 publication by Marx as bisphosphonate-related osteonecrosis of the jaw (BRONJ) and has since presented a new challenge to patients, dentists and oncologists [20]. Since osteonecrosis of the jaw is associated not only with bisphosphonates but also with other antiresorptive drugs, the term BRONJ was replaced by ARONJ (antiresorptive-related osteonecrosis of the jaw). The risk of developing ARONJ depends on the duration of medication, dosage, mode of application, and combination of different preparations [32]. Local microbial ports of entry play a central role in the etiology and pathogenesis of ARONJ. Invasive dental procedures (tooth extractions) as a dentogenic cause are considered scientifically confirmed [36], denture-related and non-reconstructible (idiopathic) injuries are discussed as other etiological factors. Since ARONJ cannot be treated predictably, their early detection and prevention are of crucial importance. Therefore, the present retrospective study aimed to address the following questions:

1. What is the most common local risk factor (tooth extraction, denture pressure area, or idiopathic) for the development of ARONJ?
2. Are there predilection sites (maxilla versus mandible, anterior teeth versus premolars versus molars, buccal versus crestal versus oral) for ARONJ?

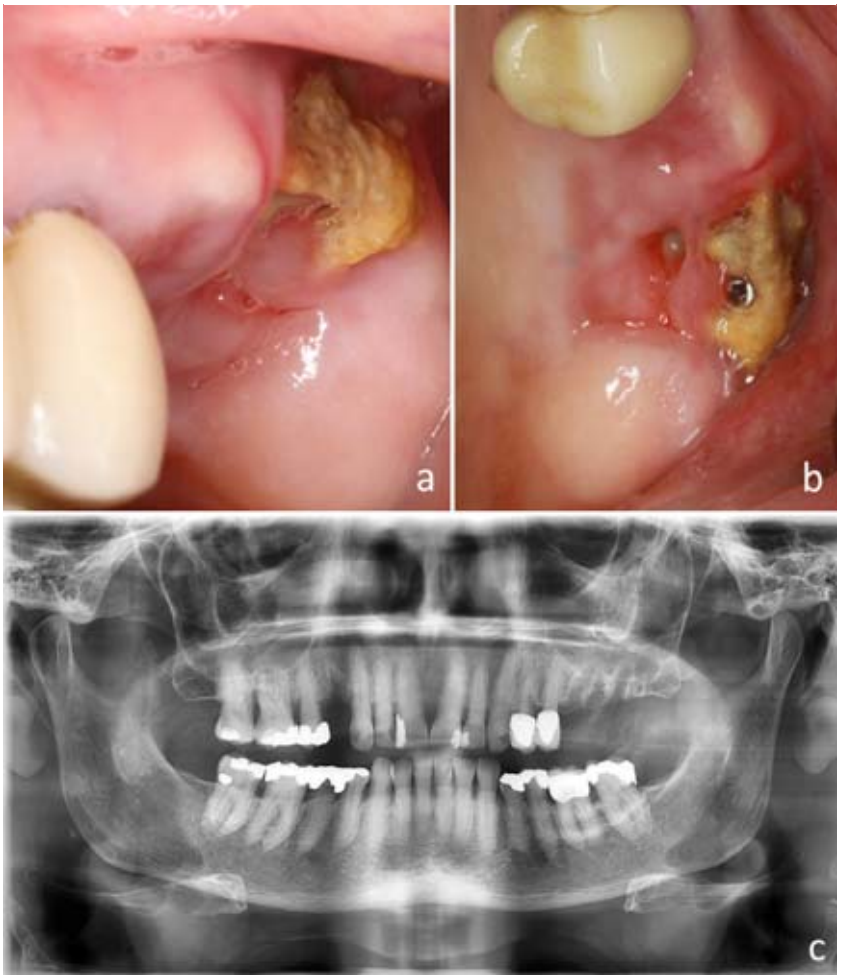

Fig. 1–3: MKG-Chirurgie, Fig. 4 and 5: Knut Adam

Figure 1a–c Antiresorptive-related osteonecrosis of the jaw regio 27 occurring after extraction of the teeth 14, 26 and 27 in a female patient (date of birth: 26.09.1933, primary disease: breast cancer with bone metastases)
1a: extension of the necrosis, buccal view
1b: extension of the necrosis, occlusal view
1c: orthopantomogram recorded at first visit

Materials and methods

In the present retrospective study, all patients presenting with ONJ at the Department of Oral and Maxillofacial Surgery of the Hannover Medical School (MHH) between 2006 and 2017 were included. For this purpose,

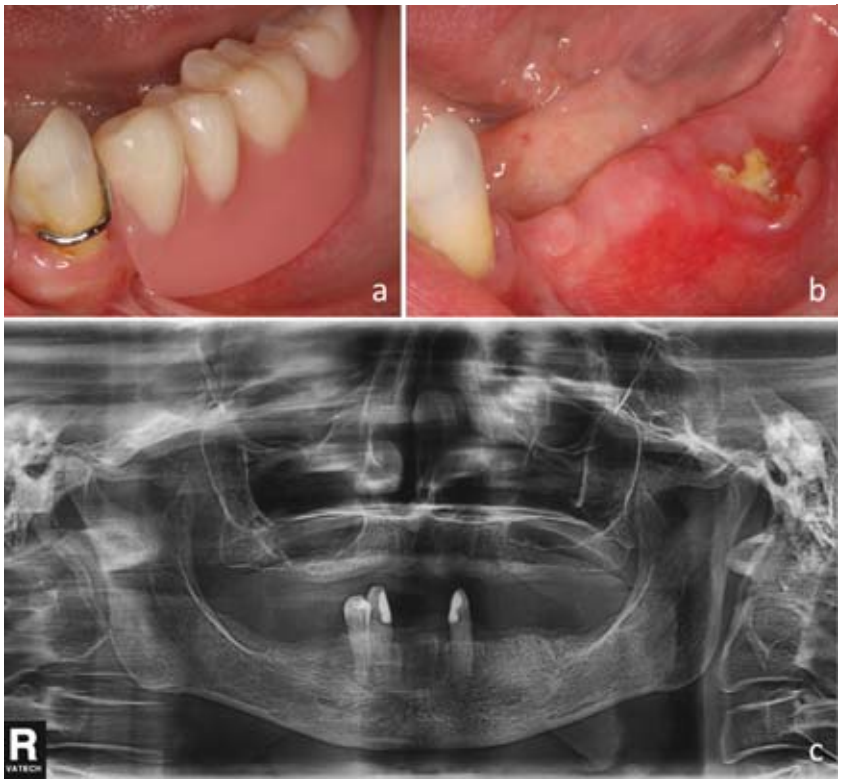

Figure 2a–c Antiresorptive-related osteonecrosis of the jaw regio 36/37 in a female patient (date of birth: 23.11.1941, primary disease: breast cancer with bone metastases) wearing a removable partial denture
2a: extension of the necrosis, buccal view with denture
2b: extension of the necrosis, buccal view without denture
2c: orthopantomogram recorded at first visit

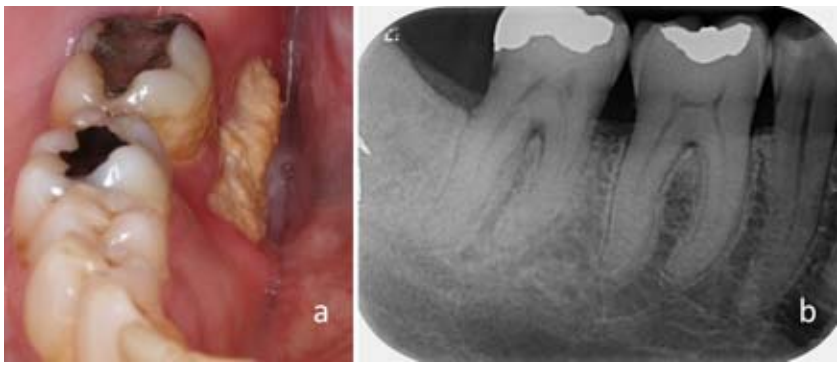

Figure 3a–b Antiresorptive-related osteonecrosis of the jaw region 47 without recognizable cause (idiopathic) in a male patient (date of birth: 23.11.1946, primary disease: prostate cancer with bone metastases)
3a: extension of the necrosis, lingual view
3b: X-ray of the teeth 45 to 47

the Center for Information Management of the MHH provided a patient list that recorded the following codes using the International Classification of Diseases (ICD): ICD-10 code M87.18 (bone necrosis due to drugs: other in neck, head, ribs, trunk, skull, spine) and ICD-10 code K10.28 (other more specifically described inflammatory conditions of the jaws). This list initially included 1256 patients with 2018 treated ARONJ events. In addition, patients were identified from the digital photo archive of the Department of Oral and Maxillofacial Surgery using the search terms ARONJ and BRONJ. This photo archive contains all patients who had been treated for ARONJ at the MHH since 2007. In addition to the initial findings, the course of the disease, second interventions and the final findings were photo-documented. The data from the different sources were combined into a working list and resulted in 1598 patients. A review of patient records, physician's letters, and radiographs took place for all potential cases. The following inclusion criteria were formulated:

1. Stage 2 or 3 ONJ according to the position paper of the American Association of Oral and Maxillofacial Surgeons [30],
2. Proven use of antiresorptive drugs.

The following exclusion criteria were applied:

1. Concurrent presence of malignant tumor disease in the oral cavity,
2. Radiation in the head and neck region,
3. Tooth extraction under antiresorptive therapy without complications in terms of ARONJ.

There were 249 patients with 343 treated ARONJ events included in the present retrospective study. Initially, 3 etiologic factors were distinguished on the basis of available documents and, in particular, clinical photographs:

1. **Tooth extraction:** In this group, a tooth extraction in the area of the ARONJ could be reliably elicited by the medical history, a referral, file entries and/or radiographs (Fig. 1a–c).
2. **Removable denture:** The second group included patients with denture-related pressure areas as the etiologic factor for the ARONJ. In most cases, pressure areas could be identified from the clinical photographs. Further clues could be documentation of necessary adjustments, such as relining or extension, and instructions not to wear the denture. In addition, tooth extraction and/or other invasive procedures in the area of ARONJ had to be excluded. To determine the type of removable denture, patient records, dental laboratory orders, radiographs, and the comprehensive photo

Etiologic factor	Osteonecroses of the jaw [n (%)]					
	Total	Localization		Risk profile		
		Maxilla	Mandible	Low	Moderate	High
Extraction	177	54 (30.5 %)	123 (69.5 %)	9 (5.1 %)	8 (4.5 %)	160 (90.4 %)
Denture	104	30 (28.8 %)	74 (71.2 %)	5 (4.8 %)	8 (7.7 %)	91 (87.5 %)
Idiopathic	62	21 (33.9 %)	41 (66.1 %)	3 (4.8 %)	2 (3.2 %)	57 (91.9 %)
Total	343	105 (30.6 %)	238 (69.4 %)	17 (5.0 %)	18 (5.2 %)	308 (89.8 %)

Table 1 Number of antiresorptive-related osteonecroses of the jaw differentiated according to localization, risk profile and etiologic factor

archive were consulted in addition to the thorough dental examination. Thus, the existing dentures could be identified and assigned both in situ and via the retention elements (clasp rests, telescopes, attachments, bars and implants). In addition, the data collection took into account whether the removable denture was a partial denture (with or without free end) or a complete denture (Fig. 2a–c).

3. **Idiopathic cause:** The third group included all patients in whom ARONJ had occurred spontaneously without any detectable cause (Fig. 3a–b).

In addition to age, sex and date of first presentation, the underlying disease, the drug group(s), the mode of application, the duration of administration, and the intake interval of the antiresorptives were recorded for each patient. According to the currently valid S3 guideline, each patient was assigned to a low, moderate or high risk profile [32]. This risk stratification was instrumental in the subsequent statistical analysis. In order to systematically record the localization of the ARONJ and to identify possible predilection sites, the affected regions were documented according to the FDI dental scheme. Additionally, it was differentiated which areas (buccal, crestal, oral) were affected by ARONJ. Multiple answers were possible.

Statistical analysis was performed using IBM SPSS Statistics 26 software (IBM Corp., Armonk, NY, USA). Patients were assigned to groups based on etiology (extraction-related, denture-related, idiopathic) and risk profile (low, moderate, high). Pearson's chi-square test and t-test for independent samples were used for group comparisons. The significance level for all statistical tests was □ = 0.05. For the presentation of descriptive data, the patient was defined as the statistical unit. The statistical analysis was performed event-specific and tooth type-specific (anterior teeth, premolars, molars).

Results

A total of 99 men and 150 women were included in the study. The mean age at initial presentation was 68.8 ± 10.4 years, with the youngest patient being 27.9 and the oldest patient being 91.9 years old. The underlying disease was primary or secondary osteoporosis in 29 patients and malignant tumor disease in 220 patients. Here, osseous metastatic breast cancer was most common in women (n = 93) and osseous metastatic prostate cancer in men (n = 66). The different underlying diseases are shown in Figure 4. Most patients (82.3 %) were receiving antiresorptive monotherapy (BP: 70.3 %, MAB: 11.2 %, AI: 0.8 %) at the time of onset of ARONJ. Dual drug therapy was used in 16.1 % of patients (BP and MAB: 10.0 %, BP and AI: 5.6 %, MAB and AI: 0.4 %) and drug therapy with 3 antiresorptives was used in 1.6 % of patients. Patients who were prescribed bisphosphonates received them predominantly intravenously (86.7 %). Finally, 16 patients could be assigned to a low risk profile, 13 to a moderate risk profile, and 220 to a high risk profile. On average, ARONJ occurred 3.8 ± 3.0 years (minimum: 0.1 years, maximum: 24.0 years) after the start of antiresorptive therapy in the patients studied. In 46 patients (18.5 %), this complication occurred within the first year. The duration of antiresorptive medication until the occurrence of ARONJ showed no significant difference between the different risk profiles. Numerous patients had other general diseases in addition to the underlying disease. Thus, 83 patients (33.3%) suffered from coronary heart disease, 46 (18.5 %) from renal insufficiency, and 44 (17.7 %) from diabetes mellitus. Among the 249 patients, 61 were smokers (24.5 %) and 109 (43.8 %) had radiographically confirmed periodontitis.

Because some patients had multiple ARONJ events, some with different etiologies, the statistical unit was changed for the following analysis. The patient-based evaluation was replaced by an event-based analysis. Among the 249 patients, a total of 343 ARONJ events were identified (Table 1). These were first distinguished with respect to their etiology. Tooth extraction was identified as the etiologic factor in 177 ARONJ events (51.6 %), denture pressure areas were identified in 104 ARONJ events (30.3 %), and no etiologic factor was identified in 62 ARONJ events (18.1 %). The majority of ARONJ events were located in the mandible (69.4 %). This over-

Etiologic factor		Osteonecroses of the jaw						
		Total	Buccal		Crestal		Oral	
			n (%)	p-value*	n (%)	p-value*	n (%)	p-value*
All	Maxilla	105	89 (84.8 %)	<0.001	60 (57.1 %)	0.958	15 (14.3 %)	< 0.001
	Mandible	238	105 (44.1 %)		133 (55.9 %)		114 (47.9 %)	
Extraction	Maxilla	54	46 (85.2 %)	<0.001	34 (63.0 %)	0.634	8 (14.8 %)	0.002
	Mandible	123	68 (55.3 %)		80 (65.0 %)		46 (37.4 %)	
Denture	Maxilla	30	28 (93.3 %)	<0.001	15 (50.0 %)	0.752	3 (10.0 %)	< 0.001
	Mandible	74	24 (32.4 %)		39 (52.7 %)		37 (50.0 %)	
Idiopathic	Maxilla	21	15 (71.4 %)	0.003	11 (52.4 %)	0.166	4 (19.0 %)	< 0.001
	Mandible	41	13 (31.7 %)		14 (34.1 %)		31 (75.6 %)	

Table 1 and 2: Knut Adam

Table 2 Jaw-specific manifestation pattern of antiresorptive-related osteonecroses of the jaw differentiated according to etiologic factor and oro-buccal extension (*: Pearson's chi-square test)

representation of the mandible was present regardless of the etiologic factor. The next step was to assess whether there was a clustered occurrence of ARONJ in the buccal, crestal, or oral region depending on the localization (maxilla, mandible) and the etiologic factor (tooth extraction, denture, idiopathic). This analysis revealed that ARONJ of the maxilla extended significantly more frequently to the buccal jaw sections than those of the mandible. Conversely, the oral regions of the mandible were significantly more frequently affected by ARONJ than those of the maxilla. These phenomena were evident both when all ARONJ events were considered and when differentiated by etiologic factors (Table 2). Known risk factors for the development of ARONJ such as smoking habits, diabetes mellitus, and a history of periodontal disease were subsequently evaluated. Among the 343 ARONJ events, 91 smokers, 62 diabetics, and 162 periodontitis cases were identified. It was investigated whether these risk factors were homogeneously distributed in all 3 etiology groups. The chi-square test showed an overrepresentation of diabetics with $p = 0.007$ and an overrepresentation of smokers with $p = 0.016$ in denture-related ARONJ. When all ARONJ events were considered, the proportion of removable dentures was high at 59.8 % (n = 205). Of these, 75.1 % (n = 154) were partial dentures and 24.9 % (n = 51) were complete dentures. The proportion of complete denture wearers was even higher (32.7 %) in cases of proven denture-related ARONJ. In addition, only three partial dentures (4.3 %) in this group were designed to treat a situation with a tooth bounded gap, whereas the vast majority (95.7 %) were designed to treat a free-end situation.

Since many ARONJ were not limited to one tooth position, the following statistical analysis was performed on a tooth type-specific basis. In total, the 343 ARONJ events covered 602 tooth positions. Molars (51.8 %) were significantly more frequently affected compared with anterior teeth (21.3 %) and premolars (26.9 %) (χ^2: $p < 0.001$). This overrepresentation of the molar region was present in both jaws, in all three etiologic factors, and in the presence of the high risk profile (Fig. 5).

Discussion

Osseous metastases of solid tumors lead to a negative bone balance due to osteolytic processes and, in advanced disease stages, to skeletal-associated events (pathological fractures, spinal compression syndrome, hypercalcemia, anemia), which are associated with a significant impairment of quality of life. Given this background, antiresorptives are a blessing for affected patients because they have been shown to reduce the risk of skeletal-associated events and contribute to improved life expectancy [15, 19, 24]. In addition to these beneficial effects, patients with a high risk profile are at particular risk of developing ARONJ. The literature describes highly variable event rates for patients with a high risk profile depending on the study design. In a recently published prospective study with a study period of 4 years, the prevalence of ARONJ was 1.0 % with

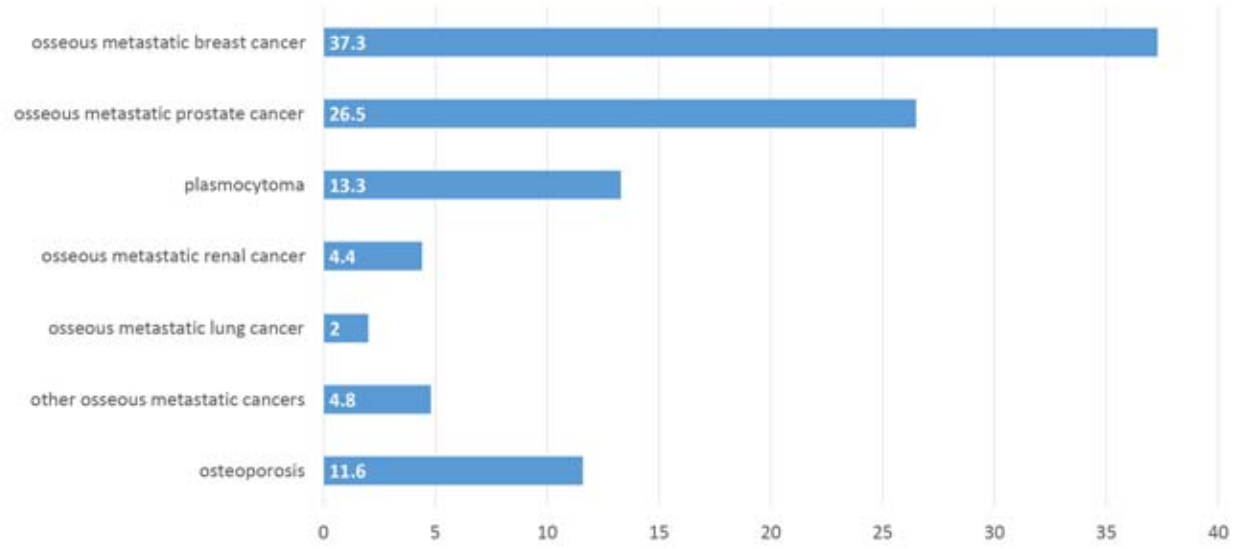

Figure 4 Percentage distribution of primary diseases
The following tumor entities are summarized under "other carcinoma": urothelial carcinoma, hepatocellular carcinoma, endometrial cancer, malignant neoplasm of vulva, cancer of unknown primary and Non-Hodgkin lymphoma

intravenous bisphosphonate therapy and 3.6% with high-dose denosumab therapy [10]. Another study demonstrated a prevalence of 2.1% in patients with breast cancer, 3.8% in patients with prostate cancer, and 5.2% in patients with multiple myeloma [29]. A significantly lower prevalence has been described for patients with a low or moderate risk profile [29]. Accordingly, in a Brazilian cross-sectional study, 153 osteoporosis patients were treated with bisphosphonates and none of them developed ARONJ within the study period [33]. Consistent with these data, the proportion of patients with a high risk profile in the present study was 88.4%, whereas patients with a low (6.4%) and moderate risk profile (5.2%) were represented in much lower proportions. When differentiated by underlying disease, osseous metastatic breast cancer (37.3%), osseous metastatic prostate cancer (26.5%), and multiple myeloma (13.3%) were most frequently represented. In a paper published by Hoefert in 2012, 195 patients with BRONJ were studied [12]. Again, breast cancer was the most common underlying disease at 39.1%, followed by multiple myeloma at 21.7% and prostate cancer at 14.0%.

In the present study, 51.6% of ARONJ events were due to a previous tooth extraction, 30.3% to a denture pressure area, and 18.1% to an idiopathic cause. In the 2014 American Academy of Oral and Maxillofacial Surgeons position paper, surgical procedures in the dento-alveolar region and specifically tooth extractions are cited as a major local risk factor for the development of ARONJ [31]. In a retrospective study examining 149 patients with ARONJ, 53.7% of cases were associated with tooth extraction, 8.1% with a removable denture, and 36.2% with an idiopathic cause [36]. While the percentage of extraction-related ARONJ was essentially the same as that of our study, the percentages of denture-related and idiopathic ARONJ were significantly different from our results. In this context, it is likely that the comprehensive photographic documentation made it easier for us to reconstruct the cause of the ARONJ and, in particular, to identify denture-related ARONJ compared with other retrospective evaluations.

The stage of ARONJ at diagnosis is a significant prognostic factor for the success of both conservative and surgical therapy. The earlier ARONJ is diagnosed, the greater the chances of successfully treating it conservatively [25]. The extent and success rate of surgical interventions also depend largely on the stage of ARONJ [16]. Therefore, early identification of ARONJ during dental screening examinations is of crucial importance. In this regard, it is of interest to the practicing dentist which areas of the maxilla and mandible are at increased risk for developing ARONJ. In our study, 69.4% of ARONJ events were localized in the mandible and 30.6% in the maxilla. The preferential manifestation in the mandible has been scientifically confirmed [1, 2, 14]. Also, that the ARONJ in both jaws were significantly more frequently localized in the posterior than in the anterior region has already been demonstrated by other research groups [2].

However, no data exist to date as to whether ARONJ in oro-vestibular extension exhibit a jaw-specific pattern. In this regard, it was observed for the maxilla that necrosis showed buccal involvement in 84.8% of cases, whereas the crestal and palatal areas of the alveolar ridge were affected in only 57.1% and 14.3% of cases, respectively. This pattern was observed in extraction-related, denture-related, and idiopathic ARONJ, with denture-related ARONJ showing the highest percentage of buccal involvement (93.3%). Compared with the maxilla, mandibular ARONJ were significantly more frequently localized lingually. This phenom-

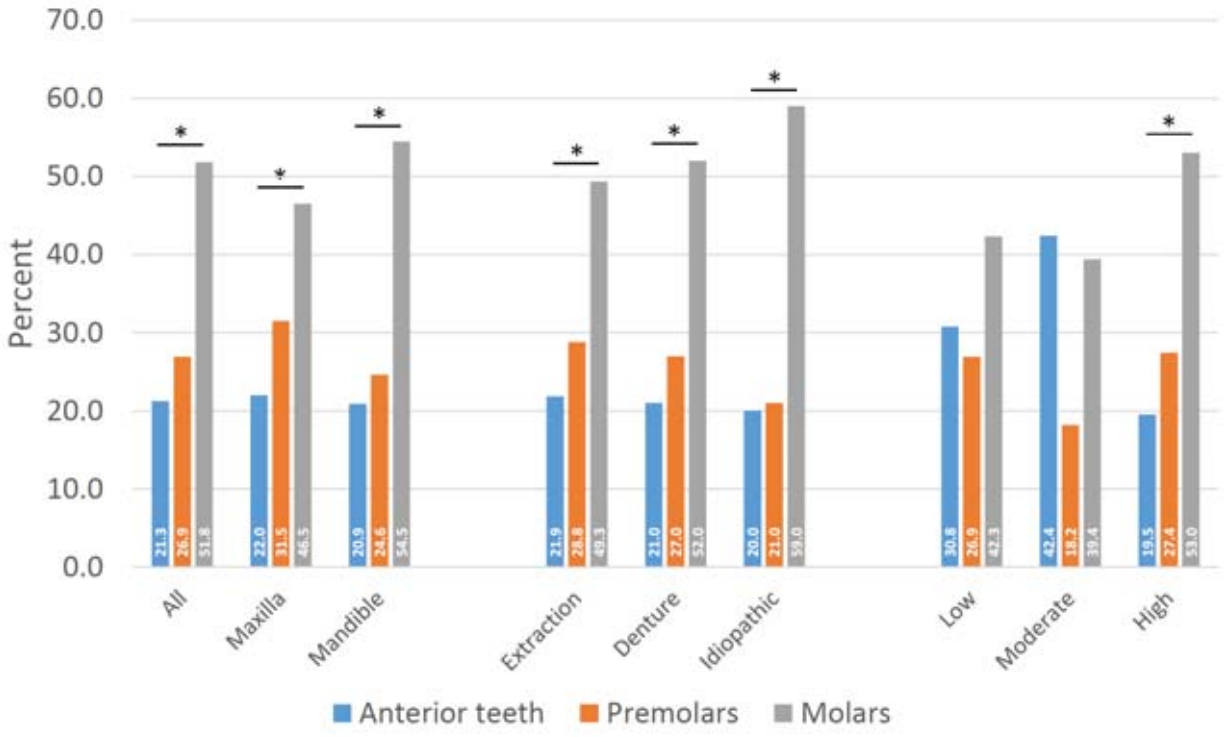

Figure 5 Percentage distribution of jaw necrosis events in the different tooth regions (anterior teeth, premolars, molars) differentiated by localization (maxilla, mandible), etiology (extraction, denture-related, idiopathic) and risk profile (low, medium, high)
* $p < 0.001$; chi-squared test

enon was detectable for all etiologic factors, but was particularly striking in ARONJ of idiopathic origin, which appeared on the lingual aspect of the alveolar ridge in 75.6 % of cases. Since the oro-vestibular extension of ARONJ has not been investigated so far, no information exists in the literature on possible causes of the described phenomena. In our opinion, an interplay of traumatic, functional, anatomical, and prosthetic factors is responsible. It is known that continuous medication with antiresorptive drugs leads to an increased accumulation of microcracks in the bony skeleton [17]. Areas of intense stress such as the molar regions of the maxilla and mandible seem to be particularly affected by this [11]. Colonization of microcracks by oral microorganisms may be an explanation, particularly for ARONJ of idiopathic origin. Mucosal ulceration mostly resulting from a local trauma represents another cause for the development of ARONJ [6, 34]. In this regard, areas with a thin mucosa appear to be significantly more susceptible to ulceration than those with a thick, keratinized mucosa. In the literature, the lingual region of the mandible, and specifically the linea mylohyoidea, has repeatedly been associated with idiopathic ulcers [18, 27]. This area has a very thin mucosal covering and is subject to particular stress due to its exposed position. In contrast, the maxilla is lined with a very thick masticatory mucosa in the palatal region, which appears to effectively protect the underlying bone from traumatic injury. Accordingly, we observed palatal involvement in only 14.3 % of all ARONJ events, and specifically denture-related ARONJ extended to the palate in only 10.0 % of cases.

In patients with removable, tegument-supported dentures, the maxilla and mandible are exposed to pressure loads that lead primarily to centripetal-directed atrophy of the maxilla and centrifugal-directed atrophy of the mandible. This results in altered prosthesis statics and altered loading of the prosthesis bearing. With increasing atrophy, it is known, especially during laterotrusion, that the maxilla is subjected to increasing pressure loads from the buccal side and the mandible from the lingual side. This is a possible explanation for the fact that denture-related ARONJ are localized predominantly buccally in the maxilla and lingually in the mandible. In addition, studies demonstrate that a large proportion of removable, tegument-supported dentures have a poor fit and thus require relining [21, 23]. Insufficient congruence between the denture base and bearing means that pressure peaks and consequent mucosal injury are likely to occur, leading to the development of ARONJ.

The results of this study underline the importance of eliminating local risk factors in the oral cavity ideally before starting antiresorptive therapy. Consistent with this demand, Bonacina et al. 2011 demonstrated that the identification and treatment of dental risk factors (residual roots, caries, periapical lesions, periodontitis, dentures with insufficient tegumental support) make a decisive contribution to preventing the development of ARONJ [5].

Conclusion

Every dentist will encounter patients in clinical practice who have been prescribed antiresorptive drugs. It is well known that surgical interventions such as tooth extractions can cause ARONJ in such patients. However, the results of the present study underscore the importance of denture-related ARONJ. Every dental practice can contribute to a reduction of ARONJ events by disciplined follow-up of patients with tegument-supported dentures. This also applies to patients with complete dentures and should include monitoring of static and dynamic occlusion as well as denture fit. Early relining, if necessary with soft-retaining materials, can help to reduce the risk of ARONJ.

Conflict of interest

The authors declare that there is no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors.

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