Antiresorptive therapy in combination with radiation results in enhanced risk for necrosis and associated complications

Katharina Theresa Obermeier, DMD, MD,[a] Wenko Smolka, DMD, MD,[a] Benjamin Palla, MD,[b] Moritz Kraus, MD,[a] David Steybe, DMD, MD,[a] Jens Tobias Hartung, DMD, MD,[a] Florian Nepomuk Fegg, DMD, MD,[a] Tim Hildebrandt, DMD, MD,[a] Ina Dewenter, DMD,[a] Nicholas Callahan, MD,[b] Philipp Poxleitner, DMD, MD,[a] and Sven Otto, DMD, MD[a]

Objective. Patients exposed to a combination of antiresorptive medication and radiotherapy of the head and neck area developing necrosis of the jaw in the course of treatment are extremely rare. Therefore, the aim of this study was to identify the outcome and complications in this highly vulnerable patient cohort.

Study Design. Seventeen patients who received both antiresorptive treatment and radiotherapy (medication-related osteonecrosis of the jaw/osteoradionecrosis = the [MRONJ/ORN] group) in the head and neck area were enrolled in this study. Included patients were treated in our department between 2005 and 2022. Four hundred twenty-four patients with MRONJ (the MRONJ group) and 138 patients with ORN of the jaw were enrolled as two control groups (the ORN group). Demographic data, lesion localization, date of primary diagnosis, clinical symptoms, type of therapy (surgical or non-surgical), details on antiresorptive treatment, outcome, and complications were recorded.

Results. Pathological fractures, continuity resection, and recurrence appear more often in patients who receive a combination of antiresorptive treatment and radiotherapy in the head and neck area compared with patients undergoing only one of these treatments. There was a statistically significant difference ($P < .001$) between the MRONJ/ORN group and the MRONJ group and the MRONJ/ORN group and the ORN group considering recurrence, fracture, and continuity resection. Patients with ORN combined with MRONJ have a 4-times higher risk for developing recurrence compared with patients with MRONJ and a 1.5-times higher risk for recurrence compared with patients with ORN. Jaw fracture and continuity resection appear more often in patients with MRONJ/ORN.

Conclusions. Patients under antiresorptive therapy in combination with radiation therapy in the head and neck area have a higher risk for developing complications in case of osteonecrosis of the jaw. Therefore, a strict follow-up care schedule is highly recommended. (Oral Surg Oral Med Oral Pathol Oral Radiol 2025;139:11−19)

Medication-related osteonecrosis of the jaw (MRONJ) is defined as exposed bone with or without fistula in the jaw bone persisting for more than 8 weeks in patients with antiresorptive therapy.[1−3] In most cases, MRONJ is associated with antiresorptive therapy with bisphosphonates or RANKL-inhibitors; however, this pathology is also observed in patients treated with other agents like tyrosinkinase-inhibitors,[4,5] VEGF-inhibitors (bevacizumab), or EGFR-inhibitor (cetuximab).[6,7] The dosage of antiresorptive therapy as well as the route of administration (oral application vs intravenous application) play a fundamental role in developing MRONJ. Oncological patients receive high intravenous doses, resulting in a 10-fold higher risk for developing MRONJ, compared with patients receiving antiresorptive treatment for osteoporosis.[8] Local risk factors associated with necrosis of the jaw are a poor oral hygiene, tooth extraction under antiresorptive therapy, dental or periodontal disease, or implant placement during antiresorptive therapy.[9,10] Otto et al., in 2010, showed that a high concentration of bisphosphonates and a local acid milieu, which is often found in infections, play an important role in pathogenesis.[11]

Osteoradionecrosis (ORN) of the jaw is an adverse side event of radiation therapy of patients in the head and neck area primarily due to underlying oncological disease in the head and neck area.[12] ORN is defined as the presence of exposed bone that does not heal spontaneously for more than 3 months and the lack of evidence of tumor recurrence.[13] Preferential localization

Statement of Clinical Relevance

This study is of high clinical relevance because this rare group of patients is special. Patients with radiation therapy in the head and neck area and antiresorptive therapy are rare. This study shows complications in this special group compared with patients with other types of necrosis of the jaw.

[a]Department of Oral and Maxillofacial Surgery and Facial Plastic Surgery, University Hospital, LMU Munich, Germany.
[b]Department of Oral and Maxillofacial Surgery, University of Illinois at Chicago, Chicago, IL, USA.
Corresponding author: Katharina Obermeier, DMD, MD. E-mail address: katharina.obermeier@med.uni-muenchen.de
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is the mandible, clinical symptoms like pain, swelling fistula, halitosis, hyp- and paresthesia, and pathological bone fracture are described.[14] Risk factors are poor oral hygiene, teeth extraction, malnutrition, smoking, vascular diseases, and a dose of radiation therapy higher than 60-70 Gy or additional chemotherapy during radiation therapy.[15,16] The actual pathogenesis of ORN is not fully understood. Marx et al., in 1983, stated that radiation therapy leads to cellular death and hypoxia and can result in secondary infection.[17] Another study claims that radiation therapy induces reactive oxygen species (ROS), which can induce cytokine production and lead to reduced vascularity and fibrosis.[18]

Prevention of MRONJ and ORN is focused on good oral hygiene and extensive tooth rehabilitation before and during treatment.[19] In cases of exposed bone, surgery including osteotomy of any kind, sequestrotomy, saliva-proof wound closure, and pre- and postoperative antibiotic administration are recommended.[20,21]

In some rare cases, patients are exposed to both antiresorptive medication and additional radiation therapy to the head and neck area. As there are no studies on the extent and course of these necrosis, this retrospective study aimed to examine the outcome of complications of necrosis of the jaw in patients with combined antiresorptive therapy and radiation therapy in the head and neck area.

MATERIALS AND METHODS

This retrospective study was approved by the institutional review board of the University Hospital of Munich, Germany (Munich, Germany; UE Nr 22-0445). The study comprised 3 groups, consisting of patients treated at our department between 2005 and 2022 who met the following inclusion criteria:

The MRONJ/ORN group

This group included patients with antiresorptive therapy, as well as radiation therapy in the head and neck who developed osteonecrosis of the jaw.

The MRONJ group

This group included patients with antiresorptive therapy and a diagnosis of MRONJ, as defined by the AAOMS (American Association of Oral and Maxillofacial Surgeons).

The ORN group

This group included patients with radiation therapy in the head and neck area and a diagnosis of ORN as defined by Marx et al., in 1983, as an area $>$ 1 cm of exposed bone in a field of irradiation that showed no healing for at least 6 months.[22]

Inclusion criteria

Demographic data, localization of the lesion, date of primary diagnosis, (all oncologic data) clinical symptoms, type of therapy (surgical or conservative therapy), clinical characteristics (localization of bone necrosis, recurrence, radiation dose, occurrence of pathologic fractures, continuity resection), and average follow-up time were collected.

Exclusion criteria

Patients with radioiodine therapy, patients who received gamma-knife/cyber-knife treatment, patients with radiation therapy outside of the head and neck region, and patients who received antiresorptive therapy but did not show signs of necrosis were also excluded. Patients who received conservative treatment were excluded to obtain comparable groups.

Statistical analysis

Statistical analysis was conducted using the software SPSS Statistics 26 (IBM). Age was analyzed as a continuous variable and reported as mean and standard deviation (SD). Categorical variables were summarized using frequencies and percentages. Differences in demographics and clinical characteristics across treatment groups were evaluated using Pearson's Chi-squared test for categorical variables, Kruskal-Wallis rank sum test for ordinal variables, and Fisher's exact test for variables with small expected frequencies. A P value of less than .05 was considered statistically significant.

RESULTS

A total of 579 patients were included in this study.

The ORN/MRONJ group

Demographic data, clinical symptoms, and treatment. This group consisted of a total of 17 patients. Ten patients (58.8%) were women and 7 patients (41.2%) were men. The average age at first diagnosis was 68.6 $\pm$ 8.2 years. In 10 patients (58.8%), necrosis of the jaw was located in the mandible, in 5 patients it was located in the maxilla (29.4%), and in 2 cases (11.8%) it was located in the maxilla and the mandible. All patients had symptoms of pain, swelling, and pus, and 70% of all patients had a positive Vincent symptom, which means hypesthesia of the lower lip. Demographic data, oncologic data, and data of patient-specific irradiation and dose are shown in Table I. The average dose of Gray in group 1 amounted to 45.31 $\pm$ 12.01 Gy. Two patients received combined radiochemotherapy.

All patients received surgical therapy, including resection of the necrotic tissue and sequestrectomy. Six surgeries (24%) were fluorescence guided. Due to extensive necrosis, continuity resection of the mandible jaw

Table I. Demographic table

Patient #	*Age at necrosis*	*Sex, M/F*	*Primary disease*	*Comorbidities*	*Localization of radiation*	*Radiation dose in gray*	*Anti-resorptive agent*	*Stage of necrosis*	*Initiation bone exposure*	*Treatment*	*Complications during follow-up*
1	77 years	M	Plasmacytoma, adenocarcinoma OSCC	DM2, peripheral neuropathy, past hepatitis	Oropharynx, neck	57.6 Gy 52.2 Gy	Zoledronate	II	Right maxilla and left mandible	Fluorescence-guided necrosis ablation, continuity resection and fibula transplant	Pathological fracture of the mandible jaw 6 years after first surgery continuity resection
2	73 years	F	Plasmacytoma	Heart attack 2004, pathological mandible fracture 2009	Mandible jaw	45 Gy	Zoledronate	III	Left mandible	Debridement of left mandible and mucoperiosteal flap	Extraoral fistula, path. Fracture of the mandible jaw 1 year after the first surgery, recurrence after 2 years.
3	63 years	F	Breast cancer		Neck	55 Gy	Zoledronate	III	Left maxilla	Tooth extraction, osteotomy	-
4	73 years	F	Breast cancer	Hypothyroidism	Neck	39.7 Gy	Denosumab	III	Right mandible	Fluorescence-guided necrosis ablation, modeling osteotomy and mucoperiosteal flap	-
5	78 years	F	Plasmacytoma	Pneumococcal meningitis, hypothyroid, renal insufficiency, osteochondrosis	Neck	45 Gy	Zoledronate, Bondurant	III	Right mandible	Fluorescence-guided necrosis ablation, osteotomy and mucoperiosteal flap	Recurrence on other location
6	61 years	F	Bronchial carcinoma	Hyperthyroidism, WPW syndrome	Neck	50 Gy	Zoledronate	III	Left maxilla	Fluorescence-guided necrosis ablation, flap with bichat fat plug and mucoperiosteal flap	-
7	74 years	M	Prostate cancer	Adenocarcinoma, hypopharynx carcinoma	Hypopharynx of the neck	50 Gy (+boost 66 Gy	Zoledronate	III	Right mandible	Necrosis ablation, osteotomy and mucoperiosteal flap	-
8	54 years	F	Thyroid cancer, breast cancer	Pneumothorax, pulmonary emphysema	Neck	45 Gy	Zoledronate	II	Right maxilla	Necrosis ablation, osteotomy, and mucoperiosteal flap	-
9	71 years	F	Breast cancer	Thyroidectomy, adnexectomy, HTN	Supra-/ infraclavicular	50.4 Gy	Zoledronate	III	Left mandible	Sequestrotomy, osteotomy, tooth extraction, laser therapy (HELBO), insertion of sulmycin fleece and Ossix-membrane, mucoperiosteal flap	-
10	62 years	M	Angiosarcoma	Arm vein thrombosis, hepatitis B	Neck	50 Gy	Zoledronate	III	Left mandible	Tooth extraction, osteotomy, necrosis ablation, mucoperiosteal flap	Recurrence on other location
11	67 years	M	OSCC of the nose		Jaw and nose	50 Gy	Denosumab	III	Left mandible	Tooth extraction, modeling osteotomy, necrosis ablation, HELBO, collagen-membrane (Ossix) and flap	-
12	84 years	M	Plasmacytoma, prostate cancer, OSCC	Femur fracture, Child-Pugh B liver cirrhosis	Neck	30 Gy	Zoledronate	II	Left mandible	Necrosis ablation, neurolysis of N. alveolaris inferior, wound closure with M. mylohyoid transplant and PRF	Pathological fracture of the mandible jaw
13	70 years	M	Prostate cancer	Myocardial infarction, Struma multinodular, coronary heart disease, neuropathic pain syndrome, valve insufficiency	Mandible jaw	20 Gy	Denosumab, Zoledronate	II	Right mandible	Mandibular continuity resection, recon plate, pectoralis-major transplant, tracheotomy	-
14	69 years	M	Thyroid cancer	Leg vein thrombosis, kinetosis, hypothyroidism, renal insufficiency	Neck	50 Gy	Zoledronate	III	Right mandible	Necrosis ablation, sequestrotomy, neurolysis of N. alveolaris inferior, recon implant	Pathological fracture of the jaw
15	58 years	F	Breast cancer	Arm vein thrombosis	Supraclavicular	50 Gy +Boost 16 Gy	Denosumab	I	Right maxilla	Tooth extraction, sequestrotomy, gingivoplasty	Exposed bone chronic connection between oral cavity and sinus recurrence on other location
16	75 years	F	Plasmacytoma	Renal insufficiency	Orbital neck	24 Gy, 26 Gy	Zoledronate	II	Right maxilla	Fluorescence-guided necrosis ablation, sequestrotomy, modeling osteotomy, insertion of PRF membrane, mucoperiosteal flap	Recurrence on other location
17	57 years	F	Breast cancer		Neck	50 Gy	Denosumab	III	Right mandible	Abscess incision and drainage	-

OSCC, oral squamous cell carcinoma; *DM2*, diabetes mellitus type 2; *WPW*, Wolff-Parkinson-White; *HTN*, hypertension; *PRF*, platelet rich fibrin.

Table II. Percentage of complications in groups 1, 2, and 3

	Group 1 (both)	*Group 2 (MRONJ)*	*Group 3 (ORN)*
Recurrence	47%	18.1%	37.7%
Fracture	23.5%	8.2%	32.6%
Continuity resection	52.9%	1.4%	26.8%

MRONJ, medication-related osteonecrosis of the jaw; *ORN*, osteoradionecrosis.

was necessary in 4 patients (23.5%). Reconstruction with a microvascular flap was performed in all 4 patients (3 fibula transplants, and 1 deep circumflex iliac artery [DCIA] transplant). Two patients (8%) received a nerve graft. In 2 patients, the initial bone reconstruction was not successful and these patients received subsequent reconstruction with a pectoral flap. Table II shows complication rates in all groups.

Local recurrence and complications. Follow-up time in all patients amounted to 90.3 months SD ± 34.4 (range = 3 to 121 months). Overall, 8 patients (47%) suffered from recurrence and complications during long time follow-up. In 4 patients, necrosis occurred in a different location of the jaw, in 4 cases in the same location. In 4 cases (23.5%), necrosis led to a pathological fracture of the jaw in combination with fistula formation with extraoral pus leakage. Continuity resection was performed in 4 patients during follow-up due to pathological fracture of the jaw.

Figure 1 shows an example of a panoramic radiograph of one patient with oral squamous cell carcinoma, adenocarcinoma of the parotid gland and plasmacytoma (Zoledronate and 57.6 Gy and 52.2 Gy radiation dose). Due to extended findings and multiple previous interventions (including tumor resection with neck dissection) computer-aided design/computer-aided manufacturing (CAD/CAM) surgery was planned in this patient.

The MRONJ group

Overall, 424 patients with MRONJ were included in the control-group. Medium age at diagnosis of necrosis was 70.2 years ± 10.8 years. Two hundred sixty-two (262) patients (61.8%) were women and 162 patients (38.2%) were men. Patients presented with typical clinical symptoms of MRONJ; pain, swelling, pus, and exposed bone. Figures 2 and 3 shows the primary disease and necrosis. Two hundred sixty-eight (268) patients (63.2%) suffered from MRONJ located in the mandible, 119 patients (28%) from MRONJ located in the maxilla, and 37 patients (8.7%) from MRONJ located in the mandible and the maxilla simultaneously. One hundred thirty-seven (137) patients (32.3%) received denosumab as antiresorptive therapy, 23 patients (5.4%) received alendronate, 25 patients (5.9%) received ibandronate, 179 patients (42.2%) received zolendronate, 23 patients (5.4%) received pamidronate, and 37 patients (8.7%) received different antiresorptive drugs during treatment. In 77 patients (18.1%), local recurrence occurred during follow-up. A

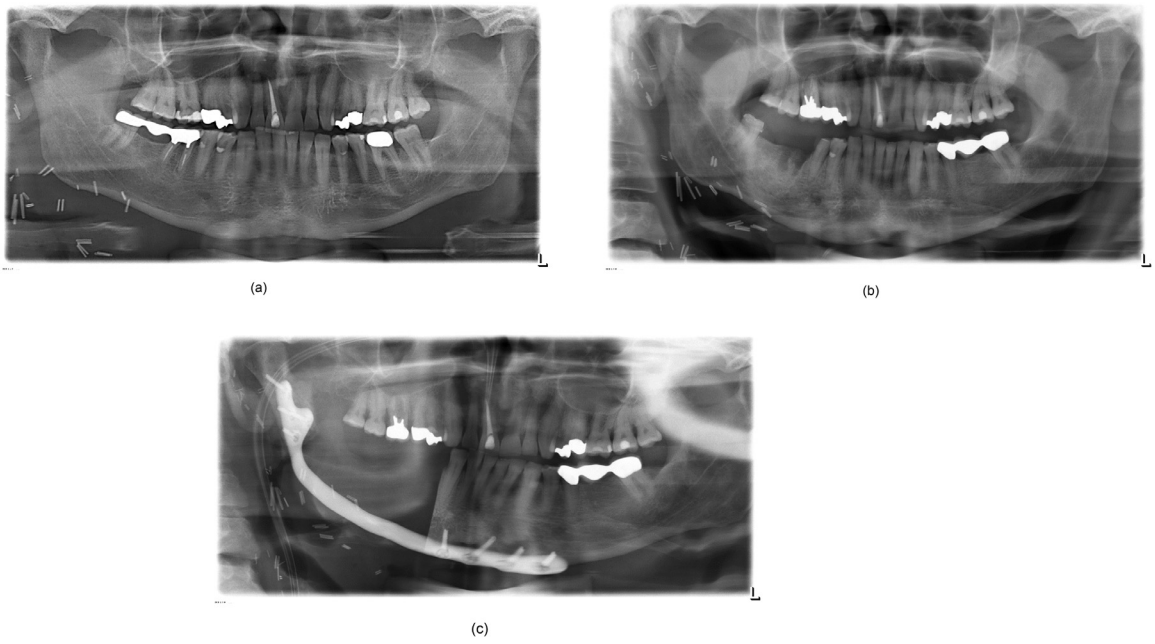

Fig. 1. (a) First diagnosis of necrosis 2016, status post tumor resection with neck dissection. (b) Recurrence of necrosis 2023. (c) Patient after surgery with continuity resection.

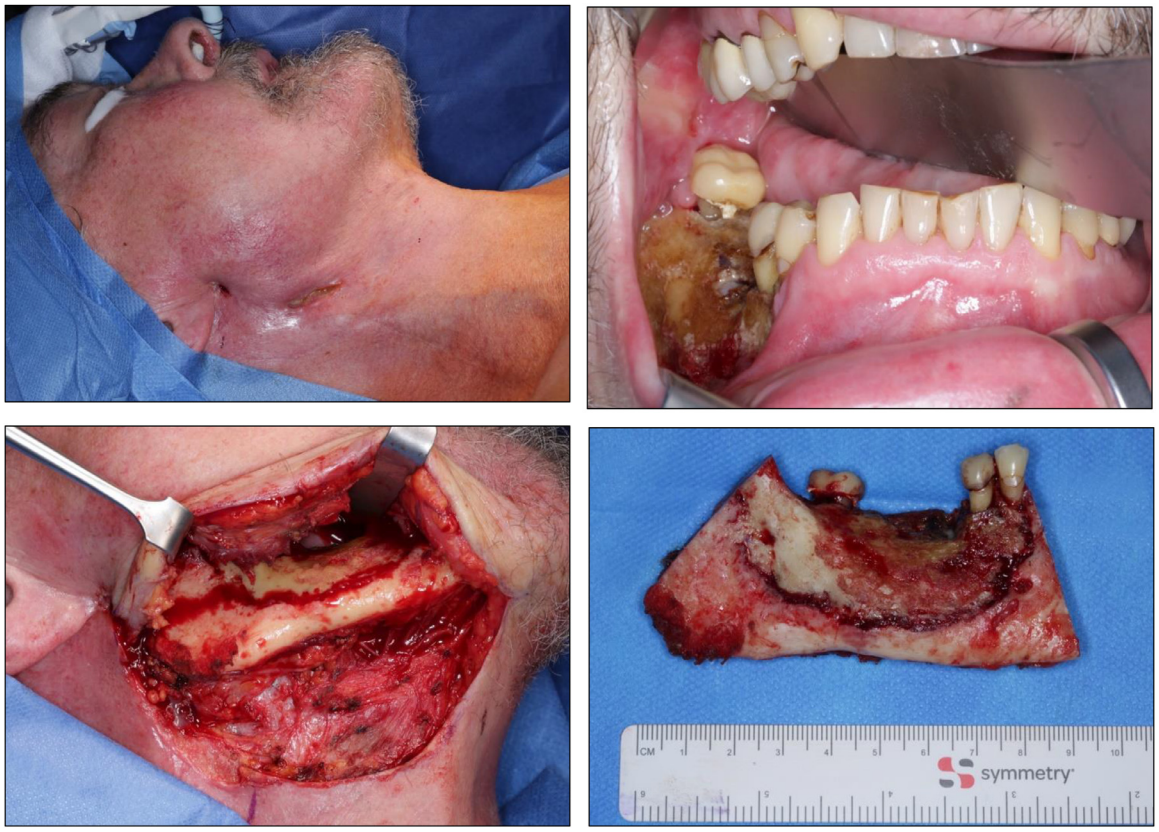

Fig. 2. Previous patient with ORN and MRONJ of the mandible jaw due to OSCC, adenocarcinoma of the parotid gland, and plasmacytoma (intra-operative situs during continuity resection and reconstruction with fibula transplant). (d) (a) Fistula. (b) Necrosis intra-operative. (c) Exploration of the mandible jaw. (d) Mandible resectate. *ORN*, osteoradionecrosis; *MRONJ*, medication-related osteonecrosis of the jaw; *OSCC*, oral squamous cell carcinoma.

pathological fracture due to necrosis was found in 35 patients (8.2%). The average follow-up time amounted to 60.8 ± 37.0 months. All patients included in group 2 received surgical treatment, meaning osteotomy and resection followed by a tight, tension-free wound closure, if possible, in multiple layers. Depending on the localization of the defect, fibers of the mylohyoid muscle or the corpus adiposum buccae were prepared as an additional layer as part of the wound closure, mobilized vestibular over the alveolar ridge and fixed there. In 6 patients (1.4%), continuity resection of the mandible with consecutive osseous reconstruction (fibula-transplant, iliac crest flap, or scapula-flap) was necessary. No failed microvascular transplant was found in those patients during follow-up time.

The ORN group

Overall, 138 patients with ORN were included as the control group. Medium age at diagnosis of necrosis was 60 years ± 9.5 years. Thirty-three (33) patients (23.9%) were women and 105 patients (76.1%) were men. All patients (100%) suffered from ORN located in the mandible. All patients suffered from pain, swelling, and exposed bone. The average radiation dose amounted to 64.36 ± 6.72 Gy. In 36 patients (26.1%), it was located on the edge of the tongue, in 49 patients (35.5%), it was located in the floor of the mouth, in 38 patients (27.5%), it was located on the alveolar ridge, in 12 patients (8.7%), it was located in the planum buccae, and in 3 cases (2.2%), it was located in the maxilla. Forty-five (45) patients (32.6%) presented with a pathological fracture of the mandible. In 37 patients (26.8%), a continuity resection with consecutive osseous reconstruction (fibula-transplant, iliac crest flap, or scapula-flap) was necessary. Four (4) patients (10.8%) had microvascular failure. These patients received surgical revision of the flaps. Complete graft failure was found in 1 patient who received a pectoral flap during follow-up. Fifty-two (52) patients (37.7%) suffered from recurrence of ORN during the follow-up time.

Statistical analysis

Results of statistical analysis are shown in Tables III, IV and V. There was a statistically significant difference ($P < .001$) between the MRONJ/ORN group and the

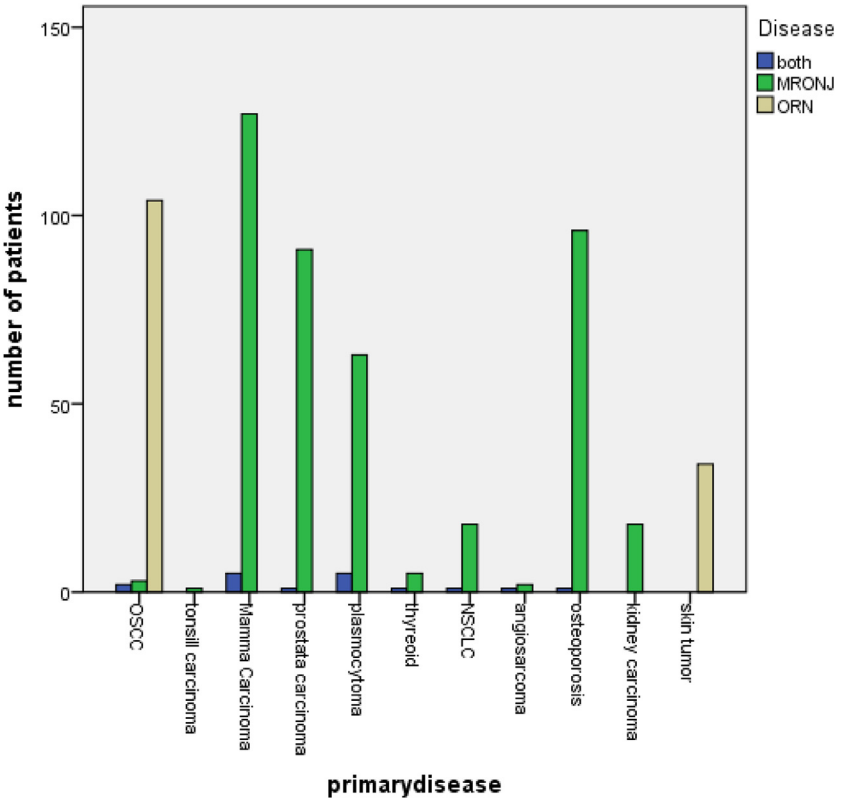

Fig. 3. Underlying oncological disease and kind of necrosis.

MRONJ group and the MRONJ/ORN group and the ORN group considering recurrence, fracture, and continuity resection. When patients with osteoporosis were excluded, the comparison of the MRONJ/ORN group and the MRONJ group also showed statistically significant differences between the MRONJ/ORN group and the MRON group in terms of pathological fractures, continuity resections and recurrences ($P < .01$).

Table III. Statistical analysis of groups 1, 2, and 3

Group 1 vs group 2	P *value*
Recurrence	< .01
Fracture	< .01
Continuity resection	< .01
Group 1 vs group 3	
Recurrence	< .01
Fracture	< .01
Continuity resection	< .01

Table IV. Comparison of demographics

Group 1 vs group 2	P *value*
Age	.402
Gender	.145
Group 1 vs group 3	
Age	.546
Gender	.669

DISCUSSION

MRONJ has been under intensive investigation for the past years. The American Association of Oral and Maxillofacial Surgeons (AAOMS) defines MRONJ as an exposed area of bone, or a bone that can be probed through an intra- or extra-oral fistula that has persisted for more than 8 weeks, in a non-irradiated jaw, free of metastatic disease, of a patient treated with antiresorptive therapy alone, or in combination with antiangiogenic or immune modulator agents.[22] MRONJ is a severe disease and can lead to reduced quality of life due to problems with nutrition and pain.[23] ORN is a detrimental complication of radiotherapy in the head and neck area. ORN of the jaw is defined as exposed

Table V. Calculated odds ratio considering group 1 vs group 2 and 3

	Group	*Odds ratio*
Recurrence	Group 1 vs group 2	4 times higher in group 1
Fracture	Group 1 vs group 2	2.67 times higher in group 1
Continuity resection	Group 1 vs group 2	2.67 times higher in group 1
Recurrence	Group 1 vs group 3	1.5 times higher in group 1
Fracture	Group 1 vs group 3	0.5 times lower in group 1
Continuity resection	Group 1 vs group 3	0.65 times lower in group 1

irradiated bone that fails to heal over a period of 3 months without any evidence of persisting or recurrent tumor.[24,25] Furthermore, ORN should only be considered as a diagnosis when lesion radiation exposure amounts > 40 Gy.[26] Although known as a side effect of radiation therapy to the head and neck for decades, the pathogenesis of ORN is not fully elucidated; however, radiation arteritis leading to the development of a hypocellular, hypovascular, and hypoxic environment is believed to play an important role.[27] In addition, radiation-induced fibrosis in patients with head and neck cancer is a severe treatment side effect,[28] resulting in an increased operation risk and risk for following microvascular reconstruction.[29] Neoadjuvant or adjuvant radiation to the head and neck area is indicated in different tumor entities. Radiation therapy is recommended in patients with oral squamous cell carcinoma in case of metastases, bone infiltration, perineural invasion, or advanced tumor stages adjuvant therapy.[30] Moreover, adjuvant radiation to the head and neck is applied for tonsillar carcinoma and multiple myeloma.[31–33] In all those mentioned cancer entities, there can be an indication for antiresorptive therapy in case of osseous metastases.[34] In very rare cases, there may be patients who have received both radiotherapy to the head and neck, but also antiresorptive therapy due to osseous metastases, multiple myeloma, or manifest osteoporosis. To our knowledge, there are no case series in the literature describing patients with both mentioned oncological therapies.[26] To avoid bias and for comparison, we included 2 control groups; the MRONJ group and the ORN group. When comparing all 3 groups, local recurrence of necrosis appeared in 18.1% in patients with MRONJ, 37.7% in patients with ORN, and in 47% in patients with antiresorptive and radiation therapy. The combination of radiotherapy and antiresorptive therapy appears to increase the risk of recurrence. These findings are not yet reported in the current literature. Pathological fracture due to necrosis of the jaw appeared more often in patients with ORN (32.6%) than in patients of the MRONJ/ORN group (23.5%). Only 8.2% of all patients with MRONJ suffered from pathological fracture, which goes along with the current literature reporting significantly more patients with pathological fractures ($P < .0001$), skin fistulae, and pain ($P = .0108$) in the ORN group compared with the MRONJ group.[29] This could be caused by the long-term use of high-dose antiresorptive therapy, which would result in highly mineralized bone and disturbed repair of microcracks by inhibition of bone remodeling.[35] More than half of the patients in group 1 needed continuity resection due to necrosis during long-term follow-up. Overall, patients with ORN and MRONJ had a 4 times higher risk for developing recurrence and 2.7 times higher risk for pathological fracture and continuity resection compared with patients with MRONJ.[36] Comparing the MRONJ/ORN group and the ORN group, the risk for recurrence was 1.5 times higher in patients with ORN and MRONJ. However, patients with ORN only had a slightly higher risk for developing pathological fracture and continuity resection.

When observing the vascular microarchitecture of the soft tissues around bone lesions in MRONJ and ORN, decreased vascular density, mean perimeter and diameter of the vessels are observed in both entities.[37] In a combination of both pathological entities, as in our cohort, the reduction of vascular density might lead to the observed higher risk of pathological fracture, recurrence, and, as a result, the increased need for continuity resection. In addition, in vivo studies revealed that radiation exposure might elicit a proresorptive state that is associated with high numbers of osteoclasts.[38] Even though, in MRONJ, patients commonly profit from antiresorptive treatment, the effect of bisphosphonates on their target cells remains enigmatic because many studies report no differences in osteoclast numbers in patients with antiresorptive treatment. However, there are even studies reporting long-term alendronate treatment associated with an increase in the number of osteoclasts, including distinctive giant, hypernucleated, detached osteoclasts that are undergoing protracted apoptosis.[39] Even though osteoclast activity in MRONJ is inhibited, the bisphosphonate-mediated prevention of apoptosis must also be considered indicating that non-apoptotic osteoclasts still affect bone metabolism with the remaining gene expression.[40]

In addition, studies observing changes in the organic and inorganic bone matrix components showed that organic bone matrix type I and V collagen are not destructed in MRONJ, whereas collagen fiber network is destructed in bone ORN.[41,42] Therefore, a combination of reduced bone mineral metabolism combined with the destructed fiber network might lead to an increase in pathological fractures and recurrence.

Limitations

This study illuminates a very rare and small group of patients with antiresorptive therapy and radiation therapy in the head and neck area. Due to this small number of patients, a statistical analysis is only of limited significance. A small number of cases in the ORN group as well as in the MRONJ/ORN group present with lower radiation doses than 40 Gy. Therefore, the risk of developing ORN might be reduced in this group. In addition, patients with osteoporosis were not excluded in the control MRONJ group As these patients receive lower total doses of antiresorptive medication, the lower risk of the development of

MRONJ should be considered. Anyway, an exclusion of these patient did not influence the outcome of this study.

CONCLUSION

Patients under antiresorptive therapy in combination with radiation therapy have a higher risk for developing complications in case of necrosis. Pathological fracture, continuity resection, and recurrence appear more often in this special group of patients.

DECLARATIONS OF INTEREST

None.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Katharina Theresa Obermeier: Writing – original draft, Visualization, Project administration, Methodology, Data curation, Conceptualization. **Wenko Smolka:** Project administration, Methodology, Formal analysis, Data curation. **Benjamin Palla:** Project administration, Methodology, Data curation, Conceptualization. **Moritz Kraus:** Methodology, Formal analysis. **David Steybe:** Writing – original draft, Visualization, Validation, Software. **Jens Tobias Hartung:** Methodology, Formal analysis, Data curation, Conceptualization. **Florian Nepomuk Fegg:** Writing – review & editing, Visualization, Validation, Supervision, Conceptualization. **Tim Hildebrandt:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Ina Dewenter:** Visualization, Data curation, Conceptualization. **Nicholas Callahan:** Writing – review & editing, Project administration, Methodology, Data curation. **Philipp Poxleitner:** Writing – review & editing, Resources, Conceptualization. **Sven Otto:** Writing – review & editing, Supervision, Project administration.

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