Fluorescence-guided Surgery of Osteoradionecrosis of the Jaw: A Retrospective Study

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Abstract

Background

Osteoradionecrosis of the jaw (ORNJ) is one of the most severe head and neck complications in patients treated with radiotherapy (RT), and it is one of the diseases difficult to manage. The goal of the treatment is to achieve mucosal healing or suppress ORNJ progression. Currently, surgical removal of the necrotic bone is an effective management approach for advanced stages of ORNJ. This study aimed to identify the outcomes of fluorescence-guided surgery for ORNJ.

Methods

Nineteen ORNJ lesions in 15 hospitalized patients received fluorescence-guided surgery. Demographics, comorbidities, local preceding event, location, ORNJ stage, and treatment outcomes were retrospectively reviewed with a median follow-up period of 12 months.

Results

The first 12 lesions (63%) were operated under tetracycline fluorescence, and 7 lesions (37%) were operated under auto-fluorescence. Overall, 4 lesions (21%) achieved complete mucosal healing, 8 lesions (42%) showed partial mucosal healing with bone exposure and no signs or symptoms of inflammation, and 7 lesions (37%) were progressive. The results showed that either healing or ORNJ stabilization was achieved in 63% of the lesions (n = 12). No significant association was observed between healing and the fluorescence technique.

Conclusion

Fluorescence-guided surgery can be beneficial in curing or stabilizing ORNJ. Within the study limitations, autofluorescence-guided surgery seems to be as effective as tetracycline fluorescence-guided surgery for management of ORNJ.

Trial registration: not applicable

Introduction

Head and neck cancer is the seventh most known cancer, and the current advancements in head and neck cancer management offer a remarkable prognosis and achieve high survival rates. Radiotherapy (RT) combined with surgery and chemotherapy has become effective case management. While the prognosis offers a remarkable improvement, it comes with some limitations. For example, osteoradionecrosis of the jaws (ORNJ) is one of the severe adverse effects of craniofacial RT. The RT revolution, better clinical implementation, and prevention strategies have significantly decreased the ORNJ incidence from 37.5% decades ago to less than 5% presently [1–3]. Most cases appear within three years after RT with a median of 13 months between RT and ORNJ (ranges 2-122 months) [2, 4]. ORNJ affects the mandible more than the maxilla thanks to the higher vascularity and less density of the maxillary medullary bone.

Despite the large body of literature focusing on ORNJ, no consensus among scholars regarding ORNJ definition. The most widely accepted definition of ORNJ is based on clinical presentation: irradiated jaw bone is exposed through the overlying mucosa or skin without healing for at least three months in patients with RT history for the head and/or neck without malignancy recurrence at the affected site [5–8]. ORNJ occurs spontaneously or is triggered by local infection, denture-related trauma, and extraction [9–10]. Thus, careful dental evaluation and treatment of oral infection or trauma before RT prevents ORNJ.

Surgical removal of necrotic bone is challenging, as it is crucial to keep it as preservative as possible to avoid jaw fracture or persistent mandibular bone loss. At the same time, complete removal of necrotic bone must be established to decrease the relapse risk. Many surgeons use bone bleeding to indicate vital bone despite its unreliable evidence [11]. Numerous imaging techniques are effective in estimating the necrotic bone. However, they cannot be used as a guide for bone excision as they lack sensitivity and specificity [12, 13]. In 2009, Pautke et al. introduced fluorescence-guided bone excision for the treatment of medication-related osteonecrosis of the jaw (MRONJ) [14–15]. The technique was prospectively investigated in 15 patients with 20 MRONJ lesions, which revealed an 85% reported healing rate after a 4-week follow-up [16]. Several studies also found fluorescence-guided bone excision as an effective tool in discriminating between viable and necrotic bone, thereby aiding more preservative yet complete bone removal [17–20]. Another study validated histopathology the ability of the fluorescence-guided surgical technique to differentiate between vital and necrotic bone based on the results of the specimen analysis of fluorescent and non-fluorescent bone [11]. An interesting finding was that histological evidence of bone necrosis was detected for clinically vital bone, with normal color, texture, and bleeding which failed to display fluorescence under a fluorescence illumination lamp. Thus, fluorescence guidance during necrotic bone removal is more accurate than relying on bone color, texture, and bleeding.

Ristow and Pautke reported that vital bone can demonstrate fluorescence (auto-fluorescence) under VELscope® System (LED Dental, White Rock, British Columbia, Canada) without prior administration of tetracycline [21]. The authors suggested the use of auto-fluorescence instead of tetracycline fluorescence for necrotic bone detection. Several studies reported the same observation regarding auto-fluorescence viable bone without tetracycline labeling [22–24]. Recent investigations used a mini-pig model to compare the two techniques and confirmed the lack of any macroscopic or histological difference [25].

Given that fluorescence-guided surgery offers good results in MRONJ patients in terms of healing rate and ease of use, this study aims to report our experience in auto-fluorescence and tetracycline fluorescence for ORNJ. In addition, we aim to investigate the correlation between healing and the patient-related variables, tumor-related variables, comorbidities, and ORNJ-related variables.

Material And Methods

Study design

A retrospective, single-center study was conducted on patients with biopsy-proven ORNJ and treated with fluorescence-guided surgery between February of 2012 and March of 2018 at the Department of Oral and Maxillofacial Surgery, Ludwig Maximilians University, Munich. ORNJ was clinically defined as the presence of exposed necrotic bone in the jawbones, irradiated with no history of antiresorptive medications or metastasis to the affected site. Ethical approval was obtained from Ludwig Maximilians University Research Ethics Committee (19–610).

The inclusion criteria were ORNJ diagnosis in patients treated with RT alone or in combination with surgery and/or chemotherapy, persistent bone exposure for 3 months or more, treatment of ORNJ using fluorescence-guided surgery, histologically proven ORNJ, and a follow-up period of 6 months or more. Exclusion criteria were history of antiresorptive treatment before, during, or after RT, evidence of recurrent malignancy of the jaws, and a follow-up period of less than 6 months.

Diagnostics

ORNJ diagnosis was established based on clinical and radiological findings. ORNJ lesions were classified into 3 stages based on the Notani et al. classification [26] (Table 1).

Table 1
Staging system used to classify ORNJ lesions

Staging system	Stages
Notani et al. [26]	Stage I: ORNJ limited to the alveolar bone
	Stage II: ORNJ limited to the alveolar bone and/or the mandible above the level of the mandibular alveolar canal
	Stage III: ORNJ that extended to the mandible below the level of the mandibular alveolar canal and lesions and/or skin fistula and/or pathologic fracture.

The outcomes

At the last follow-up visit, the treatment outcomes were recorded and divided into 3 categories: completely healed, not healed but stable (with no signs and symptoms of infection), and progressive lesions.

Data Analysis

The following data were collected: patients’ demographic data, malignancies site and clinical stage, radiation dose, systemic comorbidities, preceding oral events, ORNJ stage and site, surgical treatment, and their outcomes. A descriptive data assessment was conducted. In the present study, the primary outcome was mucosal ORNJ healing in absence of ORNJ- signs and symptoms, including pain, exposed bone, intra- or extra-oral fistula, and pathologic fracture. We established a correlation between independent and dependent variables and provided the analysis of the two variables. The independent variables were age, gender, tumor site and stage, dose of radiation, systemic comorbidities, and ORNJ-related variables as mentioned above, and the technique of fluorescence. The dependent variable was mucosal healing of ORNJ after a fluorescence-guided surgical procedure. The variables were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics v.22, New York, NY, USA). Chi-square test, Student's t-test, and Kruskal Wallis test were used for the analysis. The significance level was set at $p = 0.05$.

Results

Patients

Fifteen consecutive patients with 19 lesions were detected. Twelve (80%) were males, and 3 (20%) were females with a mean age of 64 ± 10 years (ranges from 51 to 78). Table 2 presented the sites and stages of primary tumors and their associated comorbidities. The mean period between the first radiation dose and ORNJ diagnosis was 33 ± 28.5 months (a range of 3 to 89 months). The mean radiation dose was 62.7 ± 7.4 Gy (from 50 to 70 Gy).

Table 2
Initial tumor characteristics and comorbidities

Variable	Category	Number of patients (percentage)
Malignancy	Tongue	3 (20%)
	Pharynx	3 (20%)
	Tongue and floor of the mouth	2 (13.3%)
	Palate	1 (6.7%)
	Floor of the mouth	2 (13.3%)
	Skin	1 (6.7%)
	Tonsils	1 (6.7%)
	Alveolar process	21 (6.7%)
	Thyroid	1 (6.7%)
Tumor stage	1	3 (15.8%)
	2	4 (21.1%)
	3	6 (40%)
	4	2 (13.3%)
Comorbidities	Diabetes mellitus	3 (20%)
	Cardiovascular disease	9 (60%)
	Smoking	9 (60%)
	Alcohol	8 (53.3%)
	Chemotherapy	9 (47.4%)
	Corticosteroids	0 (0%)

Approximately half of the lesions occurred with no associated dental event or pathology (n = 8, 42%). However, 4 lesions were preceded with tooth extraction (21%), in which one of the associated denture pressure spots was reported. Marginal and periapical periodontitis were observed at the ORNJ site in 3 lesions (n = 4, 21%). However, marginal periodontitis was identified in two lesions (n = 2, 10.5%). A remaining root was found in one case (n = 1, 5%).

All lesions were located in the mandible (89.5%) except two lesions in the maxilla (10.5%). The lesions sites are summarized in Table 3. Regarding the ORNJ stage, 6 stage I lesions (31.6%), 10 stage II lesions (52.6%), and 3 stage III lesions (15.8%) were observed.

Table 3
Sites of ORNJ

Region	Number of lesions (percentage)
Molar area	6 (31.6%)
Premolar area	4 (21%)
Premolar and molar area	3 (15.8%)
Anterior area	1 (5.3%)
Anterior area extending to premolar area	2 (10.5%)
Anterior area extending to posterior teeth area	2 (10.5%)
Whole alveolar process	1 (5.3%)

Panoramic radiographs and computed tomography scans were conducted for all patients to determine the extent of ORNJ cases. Biopsies were taken from all lesions to rule out malignancy.

Surgical treatment

Fluorescence-guided surgery with tetracycline bone labeling was performed for the first 10 patients (first 12 lesions), and the patients received 100 mg of doxycycline twice a day for 7 to 10 days preoperatively. After surgery, the patients were given intravenous ampicillin/sulbactam (2 gm/1 gm) 3 times daily or clindamycin of 1,800 mg dose daily, in case of allergy to penicillin; the dose continued for 3 to 4 days (till hospital discharge).

Auto-fluorescence was performed for the remaining 5 patients (7 lesions). However, they did not receive doxycycline but were given the second intravenous course of antibiotics mentioned above at least a day preoperatively.

Afterward, all patients switched to oral antibiotics for 10 days after hospital discharge (amoxicillin/clavulanic acid (875 mg/125 mg) 3 times daily or clindamycin 600 mg 3 times daily for patients allergic to penicillin).

All patients were operated on under general anesthesia. All ORNJ lesions underwent fluorescence-guided surgery. First, mucoperiosteal flap was elevated. As detailed by Otto et al., fluorescence, using the VELscope® System (LED Dental, White Rock, British Columbia, Canada), was used to distinguish necrotic bone [17–18]. Bone with dull or no fluorescence was removed gradually, till bright fluorescent bone was evident. Any teeth within the necrotic bone were extracted. After removal of necrotic bone, smoothening of sharp bone edges was performed, followed by tension-free watertight primary closure of mucoperiosteal flaps (Serafit 3 – 0, SERAG-Wiesner GmbH Germany).

Treatment outcomes

The median of the follow-up period was 14.8 ± 9.7 months (a range of 6 to 37 months). Four lesions (21%) were resolved; 8 lesions (42%) showed partial mucosal healing in the absence of clinical or radiological progression with ORNJ signs and symptoms. Four lesions (21%) recurred with progressive lesions, and 3 lesions (16%) recurred and were complicated by loss of mandibular continuity.

Of the lesions treated using fluorescence-guided surgery with tetracycline bone labeling, 16.7% were healed (n = 2). On the other hand, 28.6% of the lesions operated with auto-fluorescence guidance demonstrated complete mucosal healing (n = 2). Table 4 provides the outcomes of the fluorescence technique and the ORNJ initial stage.

Table 4
Outcomes in relation to the stage and fluorescence technique

Stage	Fluorescence technique	Outcome			
		Resolved	Stable	Progressive With no loss of mandible continuity	Progressive with loss of mandible continuity
I	Tetracycline fluorescence Auto-fluorescence	2 2	1 1	0 0	0 0
II	Tetracycline fluorescence Auto-fluorescence	0 0	4 0	1 3	2 0
III	Tetracycline fluorescence Auto-fluorescence	0 0	1 1	0 0	1 0

Healing was significantly correlated with stage of ORNJ ($p = 0.004$). However, no statistical significance was found between healing and gender ($p = 0.519$), type of malignancy ($p = 0.462$), tumor stage ($p = 0.541$), diabetes mellitus ($p = 0.330$), cardiovascular disease (p = 0.581), smoking ($p = 0.581$), alcohol ($p = 0.906$), chemotherapy ($p = 0.435$), tetracycline labeling ($p = 0.539$), site of lesion within the dental arch ($p = 0.874$), suppuration ($p = 0.581$), pain ($p = 0.440$), the period between RT and ORNJ onset ($p = 0.993$), and the dose of radiation ($p = 0.362$).

Discussion

ORNJ management remains controversial with no evidence-based guidelines. ORNJ management ranges from non-surgical treatment, surgical excision to large resections. Regardless of the modality, ORNJ treatment is challenging with limited success rates, which may lead to non-healing wounds, progressive lesions, and rarely to loss of continuity defects or large resections. Many studies have advocated non-surgical measures yet to be validated by high-level clinical evidence [27–28]. Annane et al. conducted a multicenter randomized, placebo-controlled, double-blind trial from the ORN96 Study Group and found worse outcomes in the hyperbaric oxygen arm [29]. Thus, the trial was stopped. A recent systematic review evaluated pentoxifylline–tocopherol or pentoxifylline–tocopherol–clodronate for ORNJ management and concluded that randomized controlled clinical trials were crucial to draw evidence-based conclusions about their efficacy [30]. Since the necrotic bone can never be revitalized, surgical resection is a reasonable management approach particularly for advanced ORNJ stages. A diverse 116 ORN patients confirmed that radical resection of necrotic bone was a valuable treatment owing to the positive clinical outcomes [31].

Early lesions management could prevent ORNJ progression and offer a better treatment response. Thus, surgical treatment combined with antibiotic therapy is crucial even for early ORNJ stages. As reported by other studies, advanced ORNJ stages have poorer curing rate after surgical treatment [3, 26]. In the present study, a significant correlation has been observed between the ORNJ stage and healing (p = 0.004). Accordingly, the healing rate for stage I lesions was higher than that of stage II and III lesions (66.7% for stage I ORNJ versus 0% for stage II and III ORNJ). Among the six-stage I lesions, 4 lesions (66.7%) resolved. However, two (33.3%) were persisting in the absence of any signs and symptoms (stable). Thus, ORNJ treatment remains challenging with a limited success rate as it requires several surgical interventions owing to the impaired repair capacity of irradiated bone [32]. Based on this consideration, the treatment objective is to stabilize ORNJ to prevent its progression and improve patients' quality of life. It is noteworthy that ORNJ management strategy should be selected with the individual patient status in mind.

Fluorescence imaging has been used to detect resection margins of the necrotic bone secondary to MRONJ [14–17]. A prospective cohort study of 20 MRONJ patients who underwent fluorescence-guided surgery reported complete mucosal healing in all but one patient over a follow-up of 18 months [19]. This technique was based on tetracycline derivatives that showed fluorescence properties under certain excitation light. Tetracycline has a high affinity for calcium and can accumulate during active bone remodeling. Thus, vital bone shows a bright green fluorescence under VELscope® System (LED Dental, White Rock, British Columbia, Canada), whereas necrotic bone omits no or dull fluorescence. Afterward, successful auto-fluorescence-guided necrotic bone removal (without the prior intake of tetracycline), verified by histopathological investigations, was found to have a good healing rate [21]. A randomized clinical trial has demonstrated the healing rate after fluorescence-guided bone surgery with and without tetracycline [33]. As reported in that trial, healing was observed in 89% of the tetracycline fluorescence group and 94% of the auto-fluorescence group. A recent study reported the absence of macroscopic and microscopic differences between tetracycline-induced fluorescence and auto-fluorescence in both viable and necrotic bone [25]. Similarities between the two techniques are attributed to auto-fluorescence of collagen and cell-filled bone lacunae.

In the present study, 12 lesions (63%) were operated on using tetracycline fluorescence-guided surgery while auto-fluorescence-guided surgery was used for 7 lesions (37%). In each group, 2 lesions demonstrated complete mucosal healing in the absence of relapse-related signs and symptoms (16.7% and 28.6%, respectively). Moreover, ORNJ stabilization was established in 50% and 28.6% of the tetracycline-fluorescence group and auto-fluorescence group, respectively. The aforementioned healing rates are for the first surgical intervention, which is not usually successful due to the progressive nature of ORNJ. Thus, it is common to apply several revision surgeries for ORNJ treatment. As reported by Notani et al., the cure rate after the first surgery was significantly lower than that of the second surgery, 50% and 86.7% respectively [26]. In the present study, the first surgical intervention using fluorescence guidance has healed ORNJ or stabilized ORNJ in 63% of the lesions.

It is well recognized that ORNJ is more progressive than MRONJ with a higher rate of complications such as pathologic fractures and extra-oral fistulae [34, 35]. Periosteal blood supply is more affected in ORNJ than MRONJ, probably explaining the worse ORNJ treatment outcomes [36]. A recent study reported a complete mucosal healing rate of 81.7% (67 of 82) after fluorescence-guided bone removal in MRONJ patients [20]. However, it was only 21% in the present study. From our experience and the results of several studies conducted in our institute, the outcomes of fluorescence-guided surgery for ORNJ are worse than that for MRONJ [16, 18, 20]. This is because ORNJ is a more severe type of bone necrosis that could be associated with hypoxia, hypocellularity, and hypovascularity as direct effects of RT [7].

Numerous factors contribute to ORNJ risks. Total radiation dose, smoking, alcohol, local oral factors including poor oral hygiene, periodontitis, mucosal trauma, and extraction were all linked to increased risk of ORNJ [9]. A radiation dose of over 65 Gy has been reported to predispose the patient to ORNJ [37]. In line with that, the mean radiation dose in the present study was 62.7 ± 7.4 Gy. ORNJ has been frequently linked to dental extraction after RT [1]. In a multicenter retrospective study of 392 patients, periapical periodontitis and tooth extraction after RT are significant independent risk factors for ORNJ development [38]. Contrarily, in a case-control study of 1023 patients who underwent RT for oral cavity cancer and oropharyngeal cancer, 44 patients developed ORNJ with no associated dental event in 83% of them [9]. In the present study, ORNJ occurred without prior local event or surgical intervention in about half of the lesions (n = 8, 42%). However, extraction and periodontitis were identified for 21% (n = 4) and 11% (n = 2) of the lesions, respectively.

Conclusion

ORNJ remains a challenging and severe complication of RT. This study is the first to investigate the use of autofluorescence-guided surgery in ORNJ. The goal of management is mucosal healing or at least prevention of ORNJ progression, aiming to control pain and improve patients' quality of life. Despite the inherent limitations of the current study due to its retrospective nature and its small sample size, it demonstrates that fluorescence-guided surgery is a valuable intraoperative tool that can ease the identification of necrotic bone and offer reliable and accurate guidance during bone excision. Randomized clinical trials are needed to evaluate this tool for ORNJ management.

Declarations

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Authors’ contributions

SA contributed to data collection, analysis and development and editing of the manuscript. TB and AC contributed to supervision of data gathering and interpretation of results. RF and NB contributed to study design and writing of the manuscript. SO contributed to study design, supervising the study conduction and editing the manuscript. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets analyzed in this study are available from the corresponding author upon request.

Ethical approval

Ethical approval was obtained from Ludwig Maximilians University Research Ethics Committee (19-610).

Consent for publication

Informed consent was obtained from all individual participants. All authors have viewed and agreed to the submission.

Competing interests

All authors declare no competing interests.

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