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Original article

Management of incidental discovery of microscopic squamous cell carcinoma in zones of osteoradionecrosis of the mandible

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ABSTRACT

Objectives: Osteoradionecrosis (ORN) of the mandible is a common complication of head and neck radiotherapy and often requires surgical treatment. Squamous cell carcinoma (SCC) can be exceptionally discovered within zones of ORN on histological examination of the operative specimen. The authors discuss the management of these lesions based on a short patient series.
Materials and methods: This single-centre retrospective study was based on patients managed between 2012 and 2014 for ORN with incidental discovery of microscopic SCC.
Results: Five patients with incidental discovery of microscopic SCC in a zone of ORN of the mandible were included in this study. The mean time to onset of ORN after the end of radiotherapy for locally advanced SCC of the oral cavity or oropharynx was 42 months. Surgical treatment consisted of marginal or segmental mandibulectomy with free flap reconstruction. No recurrence was observed with a mean follow-up of 35 months [24–46].
Conclusion: The incidental discovery of microscopic SCC in a zone of ORN of the mandible is a rare event and has not been reported in the literature. Optimal management cannot be reliably defined due to the lack of data in the literature, but the present study supports careful histological examination of ORN specimens. Treatment must be as conservative as possible to avoid excessively invasive surgery.

1. Introduction

Radiotherapy plays a major role in the treatment of head and neck tumours, as part of various management strategies, possibly comprising surgery and chemotherapy. Osteoradionecrosis (ORN) of the mandible is one of the well-known complications of radiotherapy, occurring within 6 months or sometimes more than 5 years after treatment [1–3]. ORN was described for the first time by Regaud in 1920, and treatment of this complication remains challenging.

The incidence of ORN ranges from 0.9% to 35% according to various authors [4,5]. This marked variation of the incidence may be related to heterogeneous study populations, variable follow-up periods and patient selection.

ORN typically starts with mucosal dehiscence and persistent exposure of bone for more than 3 months [1,6,7]. In some patients, ORN presents as a pathological fracture of the mandible, not necessarily associated with bone exposure. The natural history of ORN is often complicated by trismus, frequently neuropathic pain that is sometimes difficult to treat, fistulas, and acute episodes of infection and inflammation. Pathological fractures, bone sequestra and pharyngostomes make oral feeding difficult or even impossible. These patients also frequently experience all of the long-term adverse effects of radiotherapy (i.e. xerostomia, chronic trismus, dysphagia, decreased tongue mobility). All of these lesions have a negative somatic, psychological and emotional impact, with a high risk of under nutrition, which further impairs wound healing.

ORN arises in irradiated and therefore hypovascular zones [1,7,8] (radiation-induced endarteritis) with hypocellular bone marrow, periosteum and endothelium and decreased extracellular matrix production [9,10].

High radiation doses (70 Gy) and/or surgical trauma predispose to the early development of ORN, i.e. during the first two years after completion of radiotherapy [11–13]. More delayed onset of ORN

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Table 1
Patient characteristics.

Patient	Site	Stage	Treatment
1	Oropharynx	III	Surgery Adjuvant chemoradiotherapy
2	Oral cavity	IV	Neoadjuvant chemotherapy Surgery Adjuvant chemoradiotherapy
3	Oropharynx	IV	Neoadjuvant chemotherapy Surgery Adjuvant radiotherapy
4	Oral cavity	IV	Neoadjuvant chemotherapy Surgery Adjuvant radiotherapy
5	Oropharynx	III	Neoadjuvant chemotherapy Surgery Adjuvant radiotherapy

is often secondary to dental trauma in a context of hypovascular, hypocellular and hypoxic mandibular bone. Trauma to this very fragile bone results in the formation of a chronic wound [3,14].

Multiple criteria must be taken into account in the optimal management of ORN [15]. When surgery is indicated, it can be either simple, consisting of debridement, decortication and sequestrectomy, or more complex, possibly requiring segmental mandibulectomy with free flap reconstruction [16,17]. The incidental discovery of microscopic sites of SCC within a zone of ORN has not been reported in the literature, even in the largest published series [4], and the management in this specific setting has not been defined.

We report a series of patients in whom microscopic SCC was discovered incidentally within a larger zone of ORN of the mandible.

2. Material and method

In this single-centre retrospective study, we reviewed the charts of patients managed between 2012 and 2014 for ORN of the mandible, in whom a microscopic site of SCC was discovered incidentally on histological examination of the surgical specimen.

All patients had been managed for their primary tumour and secondary ORN by surgery and radiotherapy in our centre. The primary tumour site, patient characteristics, treatments and management of ORN were recorded.

3. Results

Five patients (1 woman, 4 men) with ORN of the mandible, in whom a microscopic site of SCC was discovered incidentally between 2005 and 2012 following treatment for squamous cell carcinoma of the oral cavity ($n = 2$) or oropharynx ($n = 3$), were included in this study. Mean age at the time of treatment of ORN was 64 years [53–73] and mean follow-up after the primary tumour was 76 months [33–105]. Treatment of these locally advanced, stage III ($n = 2$) and IV ($n = 3$) primary tumours comprised neoadjuvant chemotherapy ($n = 4$), followed by surgery and radiotherapy ($n = 5$), with concomitant chemotherapy in 2 patients.

Radiotherapy doses to the tumour ranged from 50 to 70 Gy. The mean time to onset of ORN after completion of radiotherapy was 42 months [12–60] (Table 1).

Therapeutic curettage of the mandible was performed in 3 patients. Systematic histological examination revealed microscopic sites of SCC. After multidisciplinary team discussion, it was decided to perform more extensive surgical excision: marginal mandibulectomy ($n = 2$) or segmental mandibulectomy with fibula free flap reconstruction ($n = 1$). Meticulous histological examination of the mandibulectomy operative specimens did not detect any signs of residual squamous cell carcinoma, but exclusively osteoradionecrosis.

In the other 2 patients, curettage confirmed the diagnosis of extensive ORN lesions, which were then treated by segmental mandibulectomy of osteoradionecrotic bone. Only one of these two patients was suitable for fibula free flap reconstruction, as the other patient presented a poor general state and a third tumour (laryngeal). Histological examination of mandibulectomy specimens revealed microscopic squamous cell carcinoma within the known ORN.

Regular follow-up was proposed by the multidisciplinary team in all patients. No recurrence was observed with a mean follow-up of 35 months [24–46] (Table 2).

4. Discussion

ORN is one of the many adverse effects of radiotherapy for head and neck cancer, which is particularly complex and difficult to manage. Optimal timing and extent of surgery are central issues in the management of ORN. Various authors have proposed several different treatment algorithms. Surgery is indicated in the presence of bone sequestra, extensive ORN, or inefficacy of medical treatment [9,18]. Extensive ORN usually requires segmental mandibulectomy with reconstruction, whenever possible. Free flap success rates in this indication can be as high as 98% [19,20] despite the irradiated tissues. The preservation, and ideally improvement, of the quality of life of these patients who have already undergone invasive treatments is also essential, and an overly aggressive approach to the treatment of ORN can have a negative impact on quality of life [21]. Jacobson et al. [22] reported a series of 42 patients, who, despite surgical treatment of ORN, sometimes combined with free flap reconstruction, experienced persistent trismus and oedema, but surgery nevertheless provided partial pain relief. Despite many publications on the evaluation and management of ORN, very few randomized, prospective, controlled trials have been conducted [9]. Most published studies were based on small cohorts, reflecting a single centre's practice, and not always specifying the duration of follow-up or the long-term outcome. To our knowledge, no case of incidental discovery, on histological examination, of microscopic sites of squamous cell carcinoma in ORN of the mandible has been reported in the literature.

In this series, we report 5 cases of patients treated for ORN of the mandible, in whom microscopic squamous cell carcinoma was discovered incidentally on histological examination of the operative specimens. Due to the very low incidence of this type of event, large patient series cannot be established, even in centres like our own, specialized in the management of head and neck cancers. None of the 5 patients had presented tumour at the site of the ORN: primary tumours were located in the oropharynx in 3 patients and in the

Table 2
Treatments of ORN.

Patient	Time to onset of ORN after RT (months)	Biopsy	Type of surgery	Histology	Follow-up (months)
1	42	SCC	Marginal mandibulectomy	ORN	24
2	12	SCC	Marginal mandibulectomy	ORN	30
3	60	SCC	Segmental mandibulectomy + free flap	ORN	33
4	38	ORN	Segmental mandibulectomy + free flap	SCC	42
5	60	ORN	Segmental mandibulectomy	SCC	46

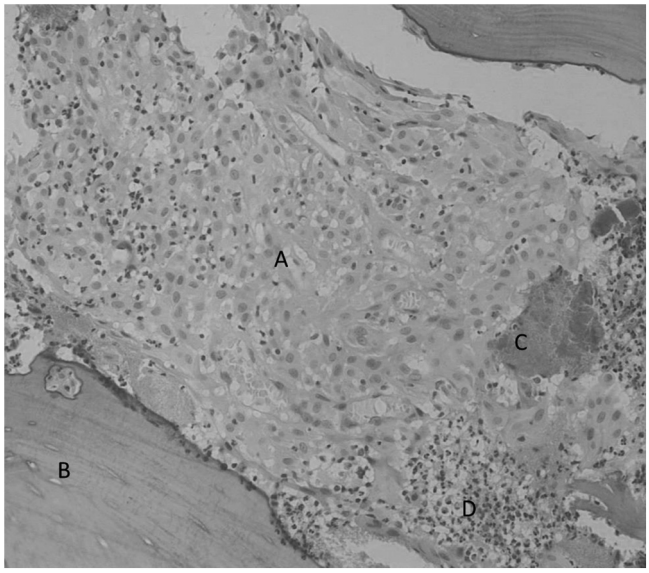

Fig. 1. Squamous cell carcinoma in a zone of osteonecrosis (ORN) of the mandible. Haematoxylin-eosin stain, 10 ×. A. Microscopic site of squamous cell carcinoma. B. ORN: hypocellular, fibrosis. C. Bacteria. D: inflammatory cells.

tongue in the other 2 patients with no extension to the floor of the mouth or the mandible.

All patients presented typical but non-specific chronic features of ORN: pain, non-resolving bone exposure, trismus, chronic infection, but no signs suggestive of a new malignant tumour. Cancer follow-up physical examination was also reassuring. However, ORN and a new tumour can present with the same non-specific signs: pain, chronic wound, trismus, oedema, chronic inflammation.

Two patients in this series required segmental mandibulectomy due to the severity and extent of ORN, but ORN was more limited in the other 3 patients, allowing simple curettage, and the more extensive, mutilating surgery was only decided on the basis of the histological results. However, no residual tumour was detected on the mandibulectomy specimens of these patients, suggesting that less invasive management could have been proposed.

Histological examination of the operative specimens of this series of patients revealed typical features of ORN, but microscopic sites of squamous cell carcinoma were also observed (Fig. 1). The presence of nuclear atypia eliminated possible inclusion of epithelial cells in the specimens. As in well-differentiated carcinoma, immature/basal cells were situated in the periphery and more mature cells were found the centre of the lesion. Sites of carcinoma, presenting signs of neovascularization, were located in vast zones of ORN, with no invasion of the gingival mucosa or skin. The adjacent stroma was thinned and contained an inflammatory infiltrate (lymphocytes). Only careful histological examination of the operative specimen was able to identify these microscopic tumours.

Despite the obviously malignant nature of these lesions, their potential for growth and metastasis in this setting of ORN remains uncertain. The presence of numerous inflammatory cells, the poorly vascular tissue, and the necrotic bone surrounding the cancer, would constitute unfavourable conditions for tumour growth. The absence of residual tumour and/or recurrence in these patients would appear to support the hypothesis that tumour growth would be slowed by the unfavourable, poorly vascular local environment.

All published series, including the present series, are based on small cohorts, preventing any reliable conclusions. However, we have demonstrated a situation that has not been previously described: the presence of microscopic sites of squamous cell carcinoma in ORN of the mandible, demonstrated by meticulous histological examination, raising the problem of the management of these incidental tumours. Extensive, mutilating surgery may be proposed due to the fear of progression of a new malignant lesion, but the preliminary data from this series appear to suggest that overly aggressive surgery is unnecessary in this setting. The absence of recurrence with a mean follow-up of 35 months corroborates this hypothesis.

5. Conclusion

The discovery of microscopic sites of squamous cell carcinoma in a context of ORN of the mandible is rare and has not been previously described in the literature. This possibility justifies meticulous histological examination of all resected osteoradionecrosis lesions. The optimal medical and surgical management in these already frail patients is difficult to define due to the absence of data in the literature. This small series suggests that such lesions require minimal treatment associated with more frequent follow-up. Surgical treatment must be adapted to the course of ORN and the patient's general state.

Disclosure of interest

The author declares that he has no competing interest.

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