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The efficacy of hyperbaric oxygen therapy related to the clinical stage of osteoradionecrosis of the mandible

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Abstract. This study aimed to evaluate the success of hyperbaric oxygen therapy (HBOT) and surgery in the treatment of mandibular osteoradionecrosis (ORN) in relation to the extent of the ORN. Twenty-seven patients with ORN were identified from a total of 509 patients with a history of primary oral or base of the tongue cancer; these patients had been treated with radiation therapy with curative intent between 1992 and 2006, with a radiation dose to the mandible of ≥50 Gy. The ORN was staged according to the classification of Notani et al. The time from completion of radiation therapy to the development of ORN varied (median 3 years). Forty HBOT sessions were offered. After HBOT alone, 3 of 11 stage I lesions, 0 of 8 stage II lesions, and 0 of 8 stage III lesions had healed ($P = 0.0018$). An absolute incidence of 5.3% ORN was found in this population. Of all sites irradiated in this study, the floor of the mouth was most associated with ORN (8.6%), whereas the cheek was least associated (0%). Based on the results of this study, HBOT can be recommended for stage I and II ORN and for selected cases of stage III ORN.

Key words: hyperbaric oxygen therapy; mandible; osteoradionecrosis; radiation therapy.

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Osteoradionecrosis (ORN) of the mandible is a serious complication after radiation therapy for head and neck cancer. It can be defined as a non-healing condition in which the irradiated necrotic bone becomes exposed through dehiscence of the overlying mucosa or skin. The first description of ORN of the mandibular bone after radiation therapy was given by Regaud in 1922.[1] The incidence of ORN varies widely, with an estimated incidence of between 1.2% and 15% in head and neck oncology patients treated with radiation therapy.[2–7] In a review of studies, Clayman reported an overall incidence of ORN of 11.8% before 1968 and

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5.4% after 1968,[8] due to changes in the way radiotherapy was applied. However, it should be noted that in most studies, the absolute incidences were given without correction for the reduction in number of patients at risk over time. Therefore these studies underestimated the real, actuarial incidence of ORN.

The severity of mandibular ORN in head and neck cancer patients varies widely from exposed bone with a loss of soft tissue to pathological fractures due to necrotic bone.[4] The interval between radiation therapy and the onset of ORN varies between 4 months and as much as 20 years,[9] with a peak incidence at 2–4 years and a remaining lifelong risk, albeit to a lesser degree.[8] The main cause of ORN is a high radiation dose to the mandible, sometimes (but not necessarily) followed by a trauma.[3,10–16] Although chemotherapy, because of its potential to induce vascular damage, could theoretically contribute to ORN, no significant association has been shown in clinical studies.[17,18] Late stage ORN is observed several years after radiation therapy and is often directly related to trauma to the irradiated tissue.[3,10,19]

The optimal treatment for ORN of the mandible remains a matter of debate. Patient- and therapy-related factors such as poor oral hygiene, trauma, alcohol and tobacco use, and a low body mass index (BMI), may influence the onset and progression of the disease.[18,20–22]

The outcome of the treatment of ORN is usually assessed clinically. Several staging systems have been suggested for the assessment of the severity of mandibular ORN.[2,23,24] These range from simple datasets of limited radiological features, with or without some clinical parameters, to extensive datasets with many clinical parameters as well as radiological features. The staging system used in this study was described by Notani et al. and is based on a radiological description of the extent of the ORN lesion in the mandibular bone.[25] Patients are divided into three categories: those with lesions of stage I, II, or III. Some staging systems come with guidelines for the purpose of guiding the clinician to make more standardized decisions on the treatment of ORN.[24,25]

In 1983 Marx suggested combined hyperbaric oxygen (HBO) and surgical treatment for ORN.[19,23] His four criteria for success were the absence of pain, mandibular salvage or reconstruction, restoration of mandibular function, and survival of the overlying oral mucosa.[26] This approach has since been adopted by others, but there is a lack of high-level evidence for the efficacy of HBO therapy (HBOT) in the treatment of ORN due to an absence of well-designed randomized trials. Many studies advocate the use of HBOT, whereas several recent studies have questioned the added value of its use.[3,7,20,26–33] Concern about the possibility that HBOT could promote tumour growth lacks evidence.[34,35]

The objective of the present study was to evaluate the effect of an HBOT–surgery protocol related to the stage of ORN of the mandible according to the staging system of Notani et al. The emphasis of this study was on the clinical outcome.

Patients and methods

Patient and tumour characteristics

ORN was defined as a wound-healing problem due to bone necrosis after radiation therapy, which failed to heal over a period of 6 months.[3,23]

A total of 509 patients treated during the period 1992–2006 with primary or adjuvant radiation therapy for an oral or base of the tongue tumour, with the mandible in the high volume area, were evaluated. Within this patient group, 134 patients had a carcinoma of the border of the tongue, 133 had a tumour of the base of the tongue, 128 had a tumour of the floor of the mouth, 53 had a tumour of the retromolar trigone, 31 had a tumour of the cheek, and 30 had a tumour of the inferior alveolar process (Table 1). Patients with tumours of the oral cavity mostly underwent surgery with postoperative radiotherapy, whereas oropharyngeal tumours were generally treated with primary radiotherapy. Of these 509 patients, 27 had one episode of histologically proven ORN of the mandible and received HBOT in combination with surgery as necessary. Their data were retrieved from the databases of the radiation oncology department of the university medical centre and the hyperbaric treatment facilities.

Patients with ORN at locations other than the mandible were excluded. Of the 27 patients included, 11 had a floor of the mouth carcinoma, nine had a base of the tongue carcinoma, five had a border of the tongue carcinoma, one had a retromolar trigone carcinoma, and one had an inferior alveolar process carcinoma (Table 1).

The ORN classification was determined both clinically and radiologically. A panoramic radiograph was used for the radiological assessment. A biopsy was taken for histopathological confirmation and to exclude malignancy.

Treatment

All patients underwent radiation therapy as a primary or adjuvant therapy after surgery for a primary oral or base of the tongue carcinoma with curative intention, with the mandible in the target area. All patients underwent clinical and radiological dental screening prior to radiation; if necessary, focal infections were eliminated. Radiotherapy was started after confirmed healing of the treated dentoalveolar focus site. During radiotherapy, patients received instructions from an oral hygienist who also followed them up and treated them.

The radiation dose to the ORN site varied between 50 Gy and 70 Gy. Three patients were re-irradiated for a recurrence or secondary primary tumour in the same

Table 1. Absolute incidence of osteoradionecrosis per tumour site.

Site	Number	ORN	Incidence (%)
Border of the tongue	134	5	3.7
Base of the tongue	133	9	6.8
Floor of the mouth	128	11	8.6
Retromolar trigone	53	1	1.9
Cheek	31	0	0
Inferior alveolar process	30	1	3.3
Total	509	27	5.3

ORN, osteoradionecrosis.

Table 2. Radiation therapy dose related to osteoradionecrosis stage at the time of diagnosis.

Radiation therapy dose, Gy	Number	ORN stage		
		I	II	III
50–60	2	1	1	0
60–70	21	9	4	8
>70	4	1	3	0

ORN, osteoradionecrosis.