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Investigation into the cancer and radiation history of a cohort of patients with osteoradionecrosis following dental extractions in irradiated areas

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Abstract

Aim and Objectives: To investigate the cancer and radiation history of patients referred for hyperbaric oxygen therapy (HBOT) to treat osteoradionecrosis (ORN) associated with dental extractions in irradiated fields, in order to determine risk factors and thus potential methods of prevention.

Method: Data were collected from 51 patients referred for HBOT to treat ORN related to dental extractions in irradiated areas. Data collected included gender, age, cancer and radiotherapy details, details of extractions and of ORN.

Results: Previous advanced-stage tumours, time elapsed since radiotherapy, and mandibular extractions were all associated with the development of ORN. 50% (of the 36 patients from whom radiation dosage data were available) had received a total radiation dose of or lower than the 55 Gy threshold which is generally considered to be required for ORN to occur.

Conclusions: The authors recommend that dentists routinely enquire about patients' head and neck radiation history (no matter how long ago the radiotherapy was received). If a patient has received head and neck radiotherapy, particular caution should be taken if the teeth requiring extraction are mandibular. Prior to extraction, information should ideally be sought from the treating oncologist regarding the risk of ORN. A total radiation dose of < 55 Gy should not be regarded as low risk, because the risk of developing ORN cannot be determined by total radiotherapy dose alone.

Key words: *Osteoradionecrosis, dental extractions, radiotherapy, special care dentistry*

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Introduction

Osteoradionecrosis (ORN) is a potentially devastating consequence of head and neck radiotherapy (Huber and Terezhalmy, 2003). It is painful, debilitating and often difficult to treat and some patients feel that it is more detrimental to their quality of life than their original cancer (Vudiniabola *et al*., 1999). Signs and symptoms include: exposed necrotic bone, constant pain, sequestration, ulceration and soft tissue swelling (Vudiniabola *et al*., 1999; Kanatas *et al*., 2002). The mandible is more frequently affected than the maxilla; this is thought to be due to the decreased vascularity and greater bone density compared to the maxilla (David *et al*., 2001). It can occur spontaneously or after surgical insults such as dental extractions. Many different definitions exist for ORN, but Marx and Johnson (1987) defined it as 'an exposure of non-viable irradiated bone, which fails to heal without intervention'.

Theories of pathogenesis of osteoradionecrosis

Radiotherapy is a potent therapeutic tool for treating head and neck cancer, both as a primary therapy, with or without chemotherapy, and as an adjuvant to surgery (Koga *et al*., 2008). Despite efforts to minimise normal cell damage, such as fractionation, some non-cancer cells are inevitably killed or incapacitated during therapy (Marx, 1999). There are several theories regarding the pathogenesis of ORN. In 1970, Meyer hypothesised that three factors were responsible for the development of ORN: radiation, trauma and secondary infection. However, in 1983, Marx discovered that the deep necrotic bone was not septic, and proposed the 'Three H Principle' – that irradiated tissue is hypovascular, hypocellular and hypoxic, due to progressive endarteritis obliterans and fibrosis. The vascular injury means that although there may be sufficient residual blood flow to maintain the bone intact, if there is a surgical injury such as a dental extraction, then the energy, oxygen and structural precursor demands exceed the supply and healing is adversely affected (Marx, 1983).

More recently, Delanian and Lefaix (2004) proposed that ORN is predominantly a fibroatrophic process, involving damage to endothelial cells from free radicals or reactive oxygen species created during radiotherapy. Vascular thrombosis and local ischaemia ensue, creating poorly vascularised, fibrosed bone that tends to develop ORN if subjected to trauma. They argue that ORN may be partly reversible, based on early stage clinical trials using antioxidant therapy (Delanian *et al.*, 2005).

The incidence and risk factors of osteoradionecrosis

Most studies quote an ORN incidence of the mandible generally of between 5-15% (Reuther *et al.*, 2003; Annane *et al.*, 2004; Delanian *et al.*, 2005; Chang *et al.*, 2007). In relation to ORN caused specifically by dental extractions, Clayman (1997) states an incidence ranging from 0-65%, averaging 5.8%, although this is open to debate.

Many risk factors have been proposed for the overall development of ORN; these include: a previous advanced stage tumour, tumours located adjacent to bone, large tumours, high total doses of radiation (> 55 Gy), brachytherapy, malnutrition, tobacco, heavy alcohol consumption, surgical procedures (including dental extractions), denture irritation, poor oral hygiene, and low BMI (Kluth *et al.*, 1988; Maxymiw *et al.*, 1991; Vudiniabola *et al.*, 1999; Jereczek-Fossa and Orecchia, 2002; Reuther *et al.*, 2003; Goldwaser *et al.*, 2007).

Risk factors proposed for developing ORN related specifically to dental extractions include: extractions performed fewer than 21 days before radiotherapy, lack of ORN prophylaxis such as antimicrobials or hyperbaric oxygen therapy (HBOT), lack of alveolectomy, dental extractions in the mandible, surgical and traumatic extractions and the use of vasoconstrictor in local anaesthetics (Marx and Johnson, 1987; Clayman, 1997; Maxymiw *et al.*, 1991; Sulaiman *et al.*, 2003; Goldwaser *et al.*, 2007).

The purpose of this investigation was to try and determine the cancer and radiation history of patients already with ORN to see whether any risk factors could be identified. A retrospective analysis of cases presenting to a hyperbaric medical centre was undertaken to evaluate this information because it was an easily accessible and readily available data set.

Materials and methods

A retrospective analysis was performed on 51 patients who were referred to a hyperbaric medical centre for adjunctive HBOT to treat ORN related to dental extractions in irradiated areas. Data were collected on all patients fitting this criterion since 1994. Ethical approval was not required as this was a clinical audit-type study.

Patient files and an audit questionnaire were used to collect the data, including questions on gender, age, cancer and cancer treatment details, details about the extractions and of the ORN. Patients referred for treatment of osteonecrosis related to bisphosphonates were not included due to the differing pathogenesis. The authors also originally planned to capture data on medical history, smoking, alcohol usage, BMI and ORN prophylaxis; however, too few patients had this data available.

Certain pieces of information, for example tumour staging and past radiation dose, could not be found in some patient files. Letters had already been sent requesting this information at the initial referral stage, but further specific reminder letters were written to the referring practitioners, to which some useful replies were received.

Results

Patient characteristics

The 51 patients included in the study were referred for HBOT at the hyperbaric medical centre between 1994 and 2010: 42 (82%) were male and 9 (18%) were female. The mean age was 59 years (range 26-84 years).

Size, type and stage of tumours

Data on tumour type were available for 46 (90%) of 51 patients. Of these, 40 (87%) patients had previously had a squamous cell carcinoma, 3 (7%) an adenocarcinoma, 1 (2%) a basal cell carcinoma, 1 (2%) a non-Hodgkin lymphoma and 1 (2%) an adenoid cystic carcinoma.

Data on tumour location were available for 51 (100%) of 51 patients. The most common location for previous tumours was the tongue (16 (31%) patients), followed by 11 (22%) patients having a tonsillar tumour.

Tumour staging (Huber and Terezhalmy, 2003) could only be found for 27 of 51 patients (53%). Of those from whom staging was available, 5 (19%) patients were Stage I, 5 (19%) were Stage II, 7 (26%) were Stage III and 10 (37%) were Stage IV.

Radiation and cancer therapy details

Details of radiation dose were only available for 36 (71%) of the 51 patients in the series, and details of the actual fields of radiation were only available for 28 (55%) patients, a serious issue which is discussed below. Two patients could not be included in the dose assessment because their radiation therapy was delivered via brachytherapy rather than external beam radiotherapy.

The average total radiation dose was 56.5 Gy (range 36-68 Gy) (excluding the brachytherapy cases): 18 of 36 patients (50%) had received a total dose of 55 Gy or less (*Table 1* and *Figure 1*). The majority of patients who received 60 Gy or more were treated with 2 Gy per fraction over approximately 6 weeks but lower doses were given over 3 to 4 weeks using larger sized fractions.

The average approximate time between radiation and ORN diagnosis was 5 years and 4 months (range 2 months–20 years, from data available for 45 (88%) patients). The 'diagnosis' date of ORN was assumed to be the date of referral for the purposes of this investigation. The authors are aware that some definitions of ORN insist on 3-6 months of non-healing (Marx, 1983; Kanatas *et al.*, 2002a). However, although some of these patients were referred before 3 months had elapsed, they all fitted this criterion by the time they actually arrived at the hyperbaric medical centre.

Details of dental extractions

Data on location of extractions were only available for 33 (65%) of 51 patients. Of these, 29 (88%) patients had had mandibular extractions, 1 (3%) had had maxillary extractions, and 3 (9%) had had both maxillary and mandibular extractions.

Details of ORN

Data on location of ORN were available for all 51 (100%) patients: 45 (88%) were reported as having ORN in the mandible. Three (6%) had ORN of the maxilla and mandible and three (6%) had ORN of the maxilla only.
review.

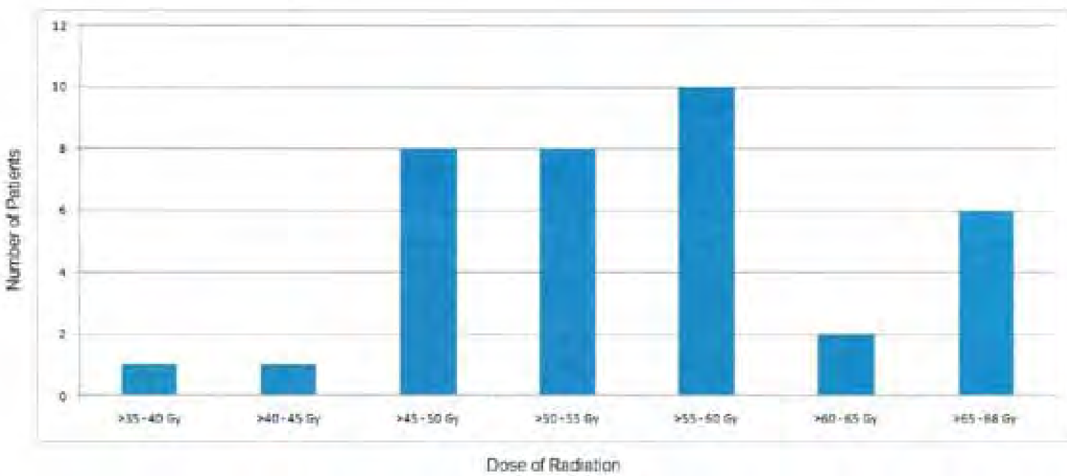

Figure 1. Bar chart demonstrating number of patients with certain doses of previous radiation.

Case No.	Site 1	Total Dose (Gy)	Fractions	Site 2	Total Dose (Gy)	Fractions	Notes	Site of ORN
1	Palate and upper neck	60	30	Lower neck	45	20		Left and right body of mandible
2	Nasopharynx and upper neck	52.5	20	Lower neck	52.5	20		Region of LL6, LL7, LL8
3	Tonsil and upper neck	60.8	Unknown	Lower neck	54.4	Unknown	Further treatment to left neck 50Gy/25 fractions/52days	Region of LR6
4	Oropharynx and neck	64	30					Right body of mandible
5	Unknown	55	22	"Booster"	35	Unknown	Booster dose may not be correct (unusual dose)	Left mandible - premolar region
6	Unknown	57	25					Right mandible
7	Tonsil	60	Unknown					Region of LL8
8	Included whole mandible	55	25					Region of LL5, LL6
9	Parotid and right neck	60	30					Region of lower 5, 6 (side unknown)
10	Unknown	60	Unknown					Left mandible
11	Oropharynx and bilateral neck	55	20					Region of UR8 and LL7, LL8
12	Nasopharynx and neck	66	33	Right neck node boost	4	2		Right mandible

13	Right tonsil	50	Unknown					Right mandible
14	Left oral cavity and neck	60	25					Region of LL5 and LL3
15	Unknown	68	34					Right mandible
16	Mouth	50	15					Right mandible
17	Left chin	45	10				Superficial X-rays (120KV)	Left posterior mandible
18	Right tonsil	55	20					Right posterior mandible
19	Anterior neck	50	25	Left neck	34	17		Left posterior mandible
20	Unknown	50	20					Region of LL8
21	Unknown	50	20					Right mandible
22	Whole pharynx and bilateral neck	60	30					Right mandible
23	Left oral cavity and upper neck	66	33	Left lower neck	50	25	Also boost to left posterior neck 10Gy/3 fractions/5days	Left posterior mandible
24	Right tonsil	48	15					Right posterior mandible
25	Hard palate	60	30					Right maxilla
26	Oropharynx and bilateral neck	60	30					Left mandible - premolar region
27	Unknown	55	22					Right posterior mandible

28	Unknown	52	20					Left posterior mandible
29	Palate and upper neck nodes	50	19					Right posterior mandible
30	Unknown	50	22					Left mandible
31	Left parotid and upper neck	60	30					Left mandible and maxilla
32	Upper mantle extending to left parotid area	36	18	Mediastinal boost	4	2		Left maxilla - molar region Region of LL8
33	Unknown	55	20					Anterior maxilla
34	Neck and supraclavicular area	66	33					Right mandible
35	Tonsil region and supraclavicular fossa	66	33					Right maxilla
36	Left mandible	66						Left mandible
Average		56.5						

Table 1. Radiation fields, doses and locations of ORN for all patients from whom this data was available (excluding the two brachytherapy cases)

Discussion

Most (82%) of the patients were male, which is similar to a study by Reuther et al. (2003), who found that ORN was 3-fold higher in men. This may be because tobacco and alcohol abuse is higher in male ORN patients, as this is thought to be a risk factor for ORN. However, it is more likely to be due to the higher incidence of head and neck cancer in men (Cancer Research UK, 2007).

The average age of the patients was 59 years, suggesting that older patients may be more susceptible to ORN, but again, this may be because older patients are statistically more likely to have had head and neck radiotherapy in the past. The age profile also generally reflects the head and neck cancer patient profile (Cancer Research UK, 2007). Nevertheless, one of the patients was only 26 years old and had undergone radiotherapy for multiple myeloma that extended to the left parotid area.

The majority of patients (87.0%) had previously had squamous cell carcinomas, which is almost certainly a reflection of oral cancer trends, because 90% of oral cancers are squamous cell carcinomas (Cancer Research UK, 2007). Oral cancer trends also account for the most common tumour location being the tongue.

ORN is thought to be more common in patients with more advanced tumours (Kluth *et al*., 1988; Jereczek-Fossa and Orecchia, 2002; Reuther *et al*., 2003). The tumour staging was unknown for almost half of the patients, however, of those who were staged, more than half (63%) were indeed stages III and IV.

A radiation dose above 55 Gy is a well recognised risk factor for the development of ORN (Vudiniabola *et al*., 1999); however, 50% of the patients in this study (from whom data was available) had received 55 Gy or less (*Table 1* and *Figure 1*). This is a considerable number of patients developing ORN with total doses of radiation previously thought to be below the threshold or risk limit. It is possible that for some of these patients, the larger radiation fraction size and shorter duration of treatment may have caused greater normal tissue damage than expected, which emphasises the need for caution when interpreting radiotherapy doses. Biological effect is more important than a single number.

Many studies have noted that the risk of ORN does not decrease with time elapsed since radiation (Marx and Johnson, 1987; Vudiniabola *et al*., 1999; Chavez and Adkinson, 2001; Oh *et al*., 2009). This is thought to be because the greater the time lapse since radiotherapy when dental extractions occur, the less vascularity (due to endarteritis obliterans) and the more fibrosis there is, therefore, the tolerance to wounding decreases (Marx and Johnson, 1987). Our study demonstrates this, because the average approximate time between radiotherapy and ORN diagnosis (of the 45 patients from whom these data were available) was 5 years and 4 months, with several patients being diagnosed up to 20 years after radiotherapy.

The current study found that the majority of patients (88%) had undergone mandibular extractions which subsequently led to ORN. Again, this is in line with the published literature (Clayman, 1997).

Reuther *et al*. (2003) found that the mandible was the most common site for ORN. This was also true in the current study, with 88.2% of patients having ORN of the mandible. This may be due to the fact that this is a commonly irradiated site, but the compact bone structure of the mandible and its poorer vascular supply may contribute to the development of ORN. Dental extractions in the mandible do appear to carry a higher risk of ORN.

Limitations

Clearly, this was a non-random sample and it was not possible to comment on those patients who developed ORN from dental extractions in irradiated areas who were either not treated with HBOT at all, or were not treated at this centre. It is possible that there was some selection bias involved, as patients referred for HBOT may be those with ORN most resistant to conservative treatment.

The retrospective nature of the study meant that there were certain items of data which proved impossible to obtain for some patients, including details on teeth extracted, tumour staging and past radiation dose. The information was mainly collected from referral letters, which often lacked important details. After requesting specific pieces of information, it became apparent that many consultants were unable to obtain these details themselves, which was a concern in itself. Lastly, assumptions had to be made, such as assuming all consultants used the same criteria for diagnosing ORN.

It would be interesting to repeat the study at similar institutions across the United Kingdom. The most all-encompassing method of data collection would be to conduct such a study within maxillofacial units, where the majority of cases of ORN are usually treated.

Conclusions

Most of the findings were in line with the current published literature. A new finding was the cases of ORN occurring in patients who had received radiation doses of 55 Gy or less, which is generally considered to be the threshold dose for ORN to occur. Despite its drawbacks, the authors feel that enough data were available for some practical recommendations to be made:

- Oncologists should continue to emphasise to irradiated head and neck patients that there is an ongoing risk of ORN with time and instruct them to advise any dentist that they visit in the future of their radiation history
- Dentists should enquire specifically about previous head and neck radiotherapy in their medical history

questionnaires, no matter how long ago the radiotherapy was received
- A total radiotherapy dose < 55 Gy should not be regarded as low risk
- If there is a history of radiotherapy, those performing extractions should be particularly cautious if the teeth involved are mandibular
- If extractions are essential, the operator should consider seeking information from the treating oncologist regarding the risk of ORN and should not assume that this is low on the basis of quoted total dose alone.

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