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Original Article

Tooth extraction prior to radiotherapy for oropharyngeal cancer increases the risk of osteoradionecrosis

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Abstract

Purpose: Osteoradionecrosis of the jaw is a therapy-resistant condition that may occur after treatment for head and neck cancer. The aim of this study was to investigate the incidence of osteoradionecrosis in patients with oropharyngeal cancer in relation to tooth extraction prior to radiation therapy.
Methods: Patients who had undergone radiation therapy for oropharyngeal cancer 5-10 years earlier were included and evaluated for the development of osteoradionecrosis ($n = 75$).
Results: Among the 75 patients, 62 had molar teeth present in the >50 Gy radiation field and 36 of those patients had teeth extracted prior to radiation therapy. Extraction of molars before radiotherapy significantly increased the risk of developing osteoradionecrosis ($P < 0.05$). There were no identifiable statistically significant correlations between the time from tooth extraction and the start of radiation therapy, the number of teeth in the radiation field, smoking habits, human papillomavirus-status, gender, age or tumor location and the development of osteoradionecrosis.
Conclusion: Tooth extraction prior to radiation therapy increases the risk of developing osteoradionecrosis. For patients with good oral hygiene and absence of dental disease, avoidance of tooth extraction in the radiation field could therefore reduce the risk of complications.

Keywords: head and neck cancer, oropharyngeal cancer, osteonecrosis of the jaw osteoradionecrosis, radiation therapy

Introduction

Squamous cell carcinoma (SCC) is the most common malignancy in the head and neck area, and head-neck SCC is the sixth most common malignancy worldwide [1]. Prolonged exposure to tobacco-derived carcinogens is considered to be the primary risk factor for development of head-neck SCC, alone or in combination with excessive alcohol consumption [2].

Stronger associations between oropharyngeal SCC and strains of human papillomavirus (HPV) have been found in recent years, in particular HPV-16, but also to a lesser extent HPV-18, HPV-33, and HPV-35 [3]. Increased rates of HPV in western Europe and the USA have contributed to the relatively high prevalence of oropharyngeal SCC in these regions [4].

Treatment of oral cavity SCC depends on the disease stage. Surgical resection followed by adjuvant radiation therapy (RT) is the preferred treatment modality for most patients, but in selected cases chemotherapy and radiation therapy may be administered, particularly for pharynx or larynx cancers. The overall survival rate following treatment for head-neck SCC has improved only slightly over the last 30 years, and the evident improvement is most likely attributable to the increase in HPV-positive SCCs rather than advances in treatment modalities, as HPV-positive head-neck SCC has a more favourable prognosis overall than HPV-negative SCC [3]. However, more targeted therapy with reduction of radiation fields may have reduced the risk of radiation-related complications [5].

Osteoradionecrosis of the jaw (ORN) is a potential complication following radiation therapy, and may cause significant pain and suffering for patients, even after they have been cured of their primary disease. ORN is caused by radiation-induced damage to blood vessels causing hypoxia, cell death and subsequent tissue necrosis. Clinically it presents as devitalized bone that fails to heal over a period of 3 months in an area without a recurrent or persisting tumor [6]. The mandible is most frequently affected, and the clinical presentation of ORN is comparable to medication-related osteonecrosis of the jaw (MRONJ). The severity varies from non-exposed necrotic areas to larger lesions with exposed necrotic bone, recurrent infections, pain, and potential pathological fractures [7].

The question of when, and when not to remove teeth in the radiation field is an issue that clinicians must address when planning treatment for patients with oropharyngeal cancer. Extraction of teeth following head-neck RT has been associated with an increased risk of developing ORN, due to local trauma and exposure of the irradiated bone to the microflora of the oral cavity [8]. However, radiation therapy may also cause xerostomia, fibrosis and trismus, which in turn can increase the risk of dental disease, necessitating extraction of teeth in the years following cancer treatment [9]. While there is an obvious need to remove teeth in patients with an unfavorable prognosis and ongoing infection, extraction of intact teeth in patients with good oral hygiene is more controversial. Several additional factors including the age and life-expectancy of the patient need to be considered. Postoperative tooth extraction can lead to delayed RT, being different from situations where tooth extraction is performed as part of the procedure for tumor resection [10]. Therefore, in patients scheduled for both tumor resection and postoperative RT, it can be advocated that tooth extraction during tumor resection is preferable. A review paper has reported that in patients after RT, the overall incidence of ORN after tooth extraction was 7%, whereas this was reduced to 4% by prophylactic hyperbaric oxygen treatment [11]. A radiation dose >60 Gy represented the highest risk of developing ORN (12%), and antibiotics slightly reduced this risk [11]. Tooth extraction after RT requires additional measures to reduce the risk of developing ORN, for which the involvement of a multidisciplinary team may be necessary [12]. The timing of treatment may also influence outcome, and a lower incidence of ORN has been reported when tooth extraction is performed within 6 months [13]. So far, however, no randomized controlled trials have provided evidence for or against extraction of sound or unsound teeth prior to RT to minimize the risk of ORN [14].

Therefore, the aim of the present study was to compare the incidence of ORN in patients from whom teeth in the >50 Gy radiation field were extracted prior to RT with that in patients who did not undergo pre-RT tooth extraction.

Materials and Methods

Inclusion criteria

All patients treated at Haukeland University Hospital for oropharyngeal cancer in the period from 2010 to 2015 were considered for inclusion in the study. Data collection was performed for a minimum of 5 years after the end of treatment for all patients (range 5-10 years). Patients who died within 5 years of the initial diagnosis were excluded ($n = 26$). Patients who did not receive RT or had incomplete records were also excluded, leaving a total of 75 patients to be included in the study (Fig. 1).

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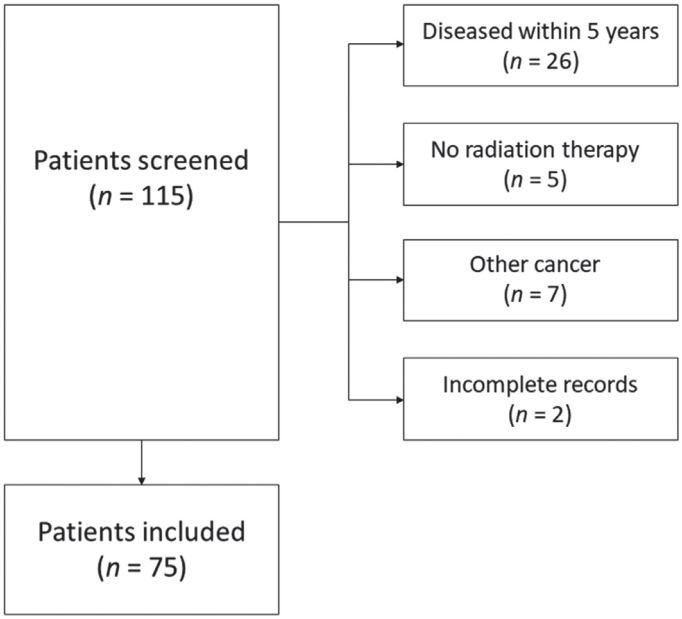

Fig.1 Inclusion of patients

Radiation therapy

The protocol for primary radiotherapy following The Danish Head and Neck Cancer Group guidelines has been described previously [15]. External beam radiotherapy with a linear accelerator was applied with doses of 2 Gy, 5 times per week. The accumulated dose for all treated tumors was 70 Gy with borders.

Surgical treatment

For patients undergoing primary surgery, tumor resections and neck dissections were performed using standard protocols [15,16]. Reconstruction with a radial artery-based forearm flap was performed if necessary. As described previously [15], if diagnostic tonsillectomy or lymph node resection was found to have removed the cancer tissue with sufficient margins, no additional surgical treatment was performed.

Follow-up and evaluation

Data were extracted from patients' electronic records (DIPS, Bodø, Norway). A minimum time point of 5 years after radiation therapy was selected due to the potential slow progression of dental disease. Registered parameters included radiation dose, dental treatment required and performed before and after RT, teeth present in the >50 Gy radiation field, teeth extracted before or after radiotherapy, age, gender, smoking habits, HPV status of the tumor, localization of the tumor, use or non-use of hyperbaric oxygen treatment, and presence of osteoradionecrosis as described by the treating clinician using defined criteria [7].

Statistical analysis

Raw data for all patients were entered into Excel files (Microsoft, Redmond, WA, USA) before being uploaded into IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). Two-sided Fisher's exact test was used to investigate correlations between registered variables and development of osteoradionecrosis. Differences at $P < 0.05$ were considered statistically significant.

Ethical considerations

The study was approved by a regional ethics committee (local approval number 202643) and was conducted in accordance with the Declaration of Helsinki. All patients were given written information about the study and had the opportunity to withdraw their participation, but none did. Registered data were anonymized after registration and stored on a password-protected computer, only accessible to the co-authors of the study.

Table 1 Patient and tumor characteristics in relation to the development of osteoradionecrosis

	No ORN	ORN	*P*-value
RT	25	1	0.658
Surgery + RT	44	5	
Males	53	5	1
Females	16	1	
<50 years	10	1	1
>50 years	58	6	
Right tonsil	27	2	1
Left tonsil	42	4	
HPV-positive	37	2	0.4186
HPV-negative	32	4	
Smokers	24	4	0.1881
Non-smokers	45	2	

ORN, osteradionecrosis; RT, radiotherapy; HPV, human papillomavirus. Right tonsil, tumor of the right tonsil; Left tonsil, tumor of the left tonsil

Table 2 Tooth extractions in relation to the development of osteoradionecrosis

	No ORN	ORN	*P*-value
Pre RT:			
Molars extracted	30	6	0.0097**
Molars not extracted (including edentulous)	39	0	
Pre RT and molars present:			
Molar extracted	30	6	0.0354*
Molars not extracted (excluding edentulous)	26	0	
Molars in radiation field	56	6	0.5822
Molars not in radiation field	13	0	
<5 molars in radiation field	32	1	0.3766
>5 molars in radiation field	38	4	
Need for extraction after RT	17	3	0.3327
No need for extraction after RT	52	3	
HBO after RT	6	3	
No HBO after RT	63	3	

*$P < 0.05$, **$P < 0.01$. HBO, hyperbaric oxygen therapy; ORN, osteradionecrosis; RT, radiotherapy

Results

Patient and tumor characteristics

A total of 75 patients were included. The majority were male (77.3%) and above 50 years old (85.3%) when first diagnosed with oropharyngeal cancer. Only radiotherapy was performed for 34.6% of the patients, whereas surgery and radiotherapy were performed for 65.4%. HPV-positive tumors were registered in 52%, and 37% stated that they had smoked daily (Table 1).

Development of osteoradionecrosis

Of the 75 patients, 62 had molars present in the >50 Gy radiation field prior to RT. Among those patients, extraction of molars was performed in 36 and not performed in 26. Of the 36 patients who underwent tooth extractions, six developed ORN (Table 2). Teeth were extracted due to apical periodontitis in five patients (two developed ORN), marginal periodontitis in nine (none developed ORN) or large dental restorations in 11 (one developed ORN). In the remaining 11 patients the teeth had no pathology, but were extracted because they were present in an area scheduled to receive high-dose radiation (>50 Gy). Three of these patients developed ORN. The total incidence of osteonecrosis after radiotherapy was 8%, and was higher among patients who underwent both surgery and radiation therapy (10.2%) than among those who underwent only radiotherapy (3.8%). However, this difference was not statistically significant. The mandible was most frequently affected (83.3%). For patients with molars present in the radiation field that were extracted prior to radiotherapy, the incidence of ORN was 16.7%. Almost one third of the patients (32.3%) required tooth extraction after radiotherapy, but most of the teeth were outside the radiation field. In total, nine patients were given hyperbaric oxygen therapy (HBO) after radiation therapy. HBO was administered due to ORN (three patients) or to prevent ORN due to planned tooth extractions in the radiation field (six patients). None of the patients who underwent tooth extractions after radiotherapy developed ORN. If present, extraction of molars in the radiation field before radiotherapy significantly increased the risk of developing ORN ($P = 0.0354$). For patients who underwent tooth extraction before radiotherapy, the risk of having to extract additional teeth after radio-

Table 3 Indications for tooth extraction after radiotherapy

	Molars extracted before RT	Molars not extracted before RT	*P*-value
Molars extracted post RT	15	5	0.00001***
Molars not extracted post RT	5	50	

***$P < 0.001$. RT, radiotherapy

therapy was also significantly increased ($P < 0.001$) (Table 3). The average time between tooth extraction and the start of RT was 29.6 days for patients who developed ORN (range 12-84 days), and 31.5 days for those who did not develop ORN following tooth extraction (range 1-106 days). The time between tooth extraction and the start of RT did not differ significantly between the two groups. Active smokers had a higher incidence of ORN (16.7%) than non-smokers (4.5%), and patients with HPV-negative tumors had a higher incidence of ORN (12.5%) than patients with HPV-positive tumors (5.4%). However, these differences were not statistically significant. No statistically significant correlations between gender, age or tumor location could be identified (Table 1).

Discussion

This study of patients with oropharyngeal cancer showed that extraction of teeth before administration of high-dose radiation to the affected area increased the subsequent risk of developing ORN. The primary limitation of the study was its retrospective nature, and the fact that evaluations were performed by different clinicians who were not calibrated in advance. However, standard criteria for ORN [7] were applied and records of insufficient quality were excluded from the study.

Dental examinations and necessary dental treatment are performed for all head and neck cancer patients scheduled for RT. Revisions has been made to the treatment protocol for oropharyngeal cancer, which previously involved primary surgery followed by RT. It has been shown that surgical therapy combined with RT has no survival benefit, and only decreases health-related quality of life compared to RT alone [15]. Primary RT has therefore been established as the standard treatment protocol, and this shortens the time from establishment of cancer diagnosis to the start of RT. Tooth extractions performed during or before tumor resection would result in a longer healing time before the start of RT, which could influence the incidence of osteoradionecrosis as full bony healing of the dental alveolus takes between 3 and 12 months [17]. Here, however, no correlation between healing time from tooth extraction to the start of RT and the development or ORN could be identified. In fact, patients who underwent both surgery and RT had a higher incidence of ORN (10.2%) than those who received radiotherapy alone (3.8%). Patients whose molars were extracted prior to RT had a significantly higher risk of developing ORN ($P < 0.01$) than patients whose molars were not extracted. These results were also valid after adjusting for edentulous patients ($P < 0.05$). A systematic review has previously identified tooth extraction as a risk factor for development of ORN [8], but has identified a risk of ORN if tooth extractions are performed after RT. In the present study, none of the patients whose teeth had to be extracted after RT developed ORN. As the follow-up time was limited to 5-10 years, tooth extraction in the radiation field may therefore have become necessary later, with possible indications for extensive and costly HBO treatment to prevent the development of ORN. In the present dataset, 6 patients had HBO treatment prior to tooth extraction after RT, which potentially could have been prevented had the teeth been extracted prior to RT. However, none of these patients developed ORN.

The reported incidence of ORN following RT to the head and neck area has varied. A systematic review investigating the timing of dental extractions in patients undergoing RT, which included 21 studies and 36, 294 patients, reported an overall ORN incidence of 5.5% for extractions prior to RT and 5.3% for extractions after RT [18]. Another systematic review reported that the incidence of ORN after tooth extractions following RT was 7%, which was reduced to 4% if HBO was administered and to 6% if the patients were given antiobiotics [11]. In the present study, for patients whose teeth were extracted before radiotherapy, the risk of having to extract additional teeth after RT was significantly increased, although these patients did not develop ORN.

Survival rates after oropharyngeal cancer are influenced by several factors including the HPV status of the tumor, smoking habits, TNM stage, and the age of the patient. Overall, HPV-positive tumors have a better prognosis than HPV-negative tumors [3,4]. TNM stage predicts survival only among HPV-negative patients, and a higher patient age has a negative effect on survival, in particular for patients with HPV-positive tumors [19]. Survival rate also influences the risk of developing ORN, as longer life expectancy and side effects of radiation therapy including xerostomia and decreased mouth opening may influence the patient's ability to maintain adequate oral hygiene. One might therefore argue that increased life expectancy warrants a more radical approach to tooth extraction, as these patients might be more likely to develop dental problems later in life. Based on the present data, however, within a perspective of 5-10 years, no increased risk of ORN could be identified if teeth were not extracted.

Extraction of teeth in the radiation field prior to radiotherapy increased the risk of developing ORN. For patients with good oral hygiene and absence of dental disease, avoiding tooth extraction in the radiation field could reduce the risk of complications.

Conflict of interest

The authors have no competing interests to declare.

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