Title:

Timing of development of osteoradionecrosis post head and neck radiotherapy

Abstract

Introduction

Risk factors for developing osteoradionecrosis (ORN) are well known, but less is known about factors influencing the interval between radiotherapy and the onset of ORN. Also, it is unknown if there is any specific period post-radiotherapy with a reduced probability of ORN when irradiated teeth require extraction.

Purpose

The primary aim of this study was to identify factors influencing the interval in developing ORN in the following subgroups of patients: 1) patients who spontaneously developed ORN, 2) surgical-intervention related ORN with a particular focus on patients after mandibulectomy. The secondary aim was to attempt to identify a possible time for safer dental intervention after primary treatment.

Materials and methods

The authors retrospectively analysed 1608 head and neck cancer (HNC) patients treated in a single centre. Time intervals were measured from the end of radiotherapy to the development of ORN and further analysed in the subgroups listed above.

Results

141 patients (8.8 %) developed Intra-oral ORN. Median time from radiotherapy to ORN development in the whole cohort was 9 months. Median interval for spontaneous ORN was 8 months, 6.5 months for intervention-related ORN, and 15 months for patients post-mandibulectomy. In patients who required dental extraction pre-radiotherapy, median interval of ORN onset was 5 months.

Conclusion

In our study, a slightly higher proportion of patients with intervention developed ORN earlier in comparison with spontaneous ORN. The period from 12-18months after radiotherapy was identified as with the highest probability of developing ORN in patients after mandibulectomy. A time for safer dental intervention after primary treatment was not identified.

Key words: radiotherapy; osteoradionecrosis; head and neck cancer; time factor; dental intervention.

Introduction

More than 600,000 patients with head and neck cancer (HNC) are diagnosed each year worldwide. The incidence is growing due to increasing number of patients with human papilloma virus related oropharyngeal cancer. This subgroup has a better prognosis, with many expected long-term survivors who may be left with severe late toxicities from the treatment of their cancer [1].

Osteoradionecrosis (ORN) of the mandible is a recognised late toxicity of HNC radiotherapy (RT). From recently published large studies, the incidence of ORN ranges from 5.4 to 13% and the risk factors for ORN development have been identified [2,3,4,5].

Over the last 20 years, several large analyses of risk factors for development of ORN after RT for HNC have been published. As the outcome of conservative treatment of ORN is suboptimal, precise identification of risk factors is essential to reduce the incidence of this serious toxicity. Most of studies focused on identification of dose/mandibular volume ratio with an objective to introduce the effective mandibular dose/volume constrains. The clarification of timing of appearance of ORN has not been systematically analysed, usually only median interval between RT and diagnosis of ORN is mentioned. The knowledge of the timing of ORN occurrence is important especially in two clinical situations. Firstly, to identify the risk period for development of ORN with an objective to focus on this toxicity during the follow-up clinics. Secondly, to identify the period with lower probability of development of ORN for the situation when the intervention affecting the integrity of the jaw is required – what is the best time for dental extraction after radiotherapy or what is the best time for insertion of dental implants. As the last comprehensive analysis of timing was the study by Marx in 1987 [23], authors of this study felt that timing analysis of our large clinical material could contribute to knowledge of this toxicity.

Purpose

The primary aim of this study was to identify factors influencing the interval in developing ORN in the following subgroups of patients: 1) patients who spontaneously developed ORN, 2) intervention related ORN with a particular focus on patients after mandibulectomy. The secondary aim was to attempt identifying a possible time for safer dental intervention after primary treatment.

Material and method

Patient selection

From January 2010 to December 2020, the records of 1608 HNC patients treated at our centre with radical or adjuvant (chemo)RT were reviewed retrospectively. All patients were treated with intensity modulated radiotherapy (IMRT) daily fractionated with a dose range from 60Gy to 66Gy in 30 fractions over six weeks (standard primary radiotherapy regimen used was 65-66Gy in 30 daily fractions and adjuvant radiotherapy regimen was 60-63Gy in 30 daily fractions).

The analysis of risk factors for development of ORN of an initial cohort consisting of 935 patients has already been published [5].

Primary treatment

All patients received primary (n = 910; 57%) or adjuvant (n = 698; 43%) radiotherapy either with or without concurrent chemotherapy. Cisplatin was used in 789 patients, cetuximab in 65 patients, RT alone was administered in 754 patients. No patients had brachytherapy.

Before RT, all patients received a comprehensive dental evaluation by restorative dental team. Patients with poor dentition underwent dental extractions prior to start of RT.

After completion of RT, patients were followed at three monthly intervals for 2 years, then every six months for the next three years by the ENT or oral-maxillofacial surgical teams.

In all patients who developed ORN, their RT treatment plans were retrieved and RT dose mapping for the anatomical origin of ORN was performed. Datasets from treated patients were transferred from their respective planning systems (Oncocentra Masterplan, Accuray Tomotherapy or Raystation) to Raystation V7.0 with the relevant diagnostic CT at the time of ORN development. The treatment plans were reconstructed and the exact dose in the origin of each site of ORN was established by a radiation oncologist +/- with a help from a maxillofacial surgeon.

Definition of ORN and time to ORN development

ORN was defined as “exposed irradiated bone that fails to heal over a period of 3 months without evidence of persisting or recurrent tumour” [3].

To determine the extent of ORN, Notani *et al* [6] classification was used as follows:

Class I – ORN confined to dentoalveolar bone.

Class II – ORN limited to dentoalveolar bone or mandible above the inferior dental canal, or both.

Class III – ORN involving the mandible below the inferior dental canal or pathological fracture, or skin fistula.

Notani classification could not be established in patients with mandibular surgery as the inferior dental canal could not be identified and in those patients with maxillary ORN.

Statistical analysis

Because of positive skew distribution, median value was chosen to analyse the impact of various variables on interval between RT and the event. Statistical analysis was performed in GraphPad Prism 9 (GraphPad, Boston, USA) and STATISTICA software (TIBCO STATISTICA 14.1.0, Palo Alto, USA). Kaplan-Meier survival curves were

created using the date of last fraction of RT as the start date until date of development of ORN. Variables with $p<0.25$ from univariate analysis were entered into multivariable Cox regression analysis to determine an adjusted influence of variables on outcome. Variables with $p<0.05$ were considered statistically significant in the multivariable model. The results of multivariate Cox regression model were expressed as hazard ratios (HR) with 95% confidence intervals and p-values. It was felt that the distribution of ORN in time was best visualized by using histograms.

Results

Patient demographics

Of a total 1608 patients, there were 1194 males and 414 females. The median age of the patient cohort was 61 years (range: 15 – 92 years).

Median follow-up for the whole group was 36 months (range: 0 – 146 months), median follow-up of surviving patients was 45 months (range: 18 – 146 months). In total, 1094 patients are alive, 514 patients had died. Out of those patients who died, 279 died from their cancer, the rest from other causes. Disease recurred, or metastatic disease developed in 305 patients. Smoking status was available for 1447 patients. Out of these, 483 never smoked, 399 were current smokers, 565 were past smokers.

Incidence of ORN

Intraoral ORN developed in 141 patients (8.8 %), at a median time of 9 months (mean 17.8 months, range: 1-107 months). Median age of patients with ORN was 58 years (range: 36 – 86 years). There were 106 males and 35 females. Multiple areas of ORN developed in 6 patients, all developed simultaneously, and the most advanced site was included in the analysis. Smoking status was available in 135 patients. Out of these, 35 never smoked, 62 were current smokers, 38 were past smokers.

Notani classification was applicable in 117 patients with jaw ORN with no previous surgery to the mandible: Notani class I (n = 45), Notani class II (n = 19) and Notani class III (n = 53).

The analysis of the interval between completion of RT and development of ORN was performed for all 141 patients with ORN and for the 96 patients with more advanced ORN grades as a separate subset (excluding patients with Notani class I).

The analysis of the interval between completion of RT and development of ORN of all Notani classes

In 141 patients with intraoral ORN of all grades, 133 developed in the mandible, 8 in maxilla. RT alone was used in 46 patients, 85 patients were treated with combination of RT and cisplatin and 10 patients with combination of RT and cetuximab. The median received dose of RT at the origin of ORN was 61.5 Gy (range: 18.5 – 67.9 Gy).

Out of 141 patients with ORN, a surgical or dental intervention to the maxilla/mandible bone was performed between the cancer diagnosis and development of ORN in 104 patients, and in the remaining 37 patients there was no surgical or dental intervention (for this analysis, intervention was defined as; bone surgery, dental extraction, or dental implant). Development of ORN was related to the intervention site in 99 patients, in 5 patients the ORN developed in bone outside the intervention area. Out of these 99 interventions, 72 were dental extractions (51 performed before and 21 after RT), 2 dental implant insertions (both after RT). There were also 25 bone surgeries, which were performed before RT as a part of primary treatment – 11 mandibulectomies, 7 mandibulotomies, 3 maxillectomies and 4 partial bone resections (usually rim resections as a part of primary tumour resection). In total, 76 interventions related to ORN were performed before and 23 after the RT (21 dental extractions and 2 implant insertions).

In 141 patients with ORN, median follow-up was 53 months (range: 5 – 146 months). The median follow-up in surviving patients with ORN was 57.5 months (range: 18 – 148 months). Table 1 summarises the distribution of ORN in time for all patients.

Table 1: The distribution of ORN in time for 141 patients with Notani class I, II, III

Characteristics / interval end of RT to diagnosis of ORN	**Patients (n)**	**Median (months)**	**Mean (months)**	**Range (months)**
Whole group	141	9	17.8	1 - 107
Impact of gender				
Male	106	7	16.4	1 - 107
Female	35	15	22	1 - 58
Impact of age				
≤60years	86	7	15.8	1 - 88
>60years	55	10	20.9	2 - 107
Spontaneous versus intervention related				
Spontaneously developed	42	8	20.7	1 - 107
Related to all interventions (pre- and post-RT)	99	10	16.5	1 - 77
Related to intervention before RT	76*	6.5	11.4	1 - 46
Impact of type intervention (pre-RT)				
Dental extraction	51**	5	8.6	1 - 46
Any surgery	25***	12	17	1 - 46
Mandibulotomy	7	5	7.4	1 - 22
Mandibulectomy	11***	15	18.5	3 - 42
Maxillectomy	3	30	26.4	1 - 46
Bone resection (usually rim resection)	4	24.5	22.8	9 - 33
Impact of systemic treatment				
RT only	46	7	15	1 – 60
RT and cisplatin	85	8	18.6	1 - 107
RT and cetuximab	10	25.5	24	6 - 42
Dose of RT at ORN site				
< 60Gy	53	7	16.5	1 - 107

≥ 60Gy	88	11	18.6	1 – 88
Impact of smoking				
Non smokers	35	11	23.8	2 - 88
Active smokers	62	6	11.7	1 - 58
Past smokers	38	9	19.2	1- 107
Impact of dental extraction after RT (no other intervention)				
Dental extraction after RT	21	32	35.3	2 - 77

*In 5 patients ORN developed outside the area affected by any intervention. ** In 4 patients ORN developed outside the extraction site. *** In 1 patient ORN developed outside the area affected by surgical intervention.

The analysis of the interval between completion of RT and development of ORN for advanced ORN (Notani class I excluded)

Out of 96 patients with advanced ORN (excluding Notani class I), 8 developed in maxilla and 88 in the mandible. In this group of patients, 37 received RT alone; 53 received RT and cisplatin and 6 patients received RT and cetuximab. Median dose of RT at the site of ORN was 62Gy (range: 18.5 – 67.9 Gy).

In this group of patients with advanced intraoral ORN, surgical or dental intervention between the diagnosis and development of ORN was performed in 71 patients and in the remaining 25 patients there was no surgical or dental intervention. Out of 71 interventions, 44 were dental extractions, 2 dental implants insertions and 25 bone surgeries – 6 mandibulotomies, 12 mandibulectomies, 3 maxillectomies and 4 bone resections. Of these 71 patients with an intervention, development of ORN was related to the intervention site in 67 patients, in 4 patients the ORN developed outside the intervention site.

In 96 patients with advanced intraoral ORN, median follow-up was 54.5 months (range: 11 – 146 months), median follow-up in surviving patients with ORN was 61 months (range: 18 – 146 months). Table 2 summarises the distribution of ORN in time for patients with advanced ORN.

Table 2: The distribution of ORN in time for 96 patients with advanced ORN (Notani class I excluded)

Characteristics / interval end of RT to diagnosis of ORN	**Patients (n)**	**Median (months)**	**Mean (months)**	**Range (months)**
Whole group	96	10.5	19.2	1 - 107
Impact of gender				
Male	71	9	18.6	1 - 107
Female	25	15	20.8	2 - 58
Impact of age				
≤60years	60	9.5	15.8	1 - 77
>60years	36	12	24.8	2 - 107
Spontaneous versus intervention related				

Spontaneously developed	29	8	20.3	1 - 107
Related to all interventions (pre- and post-RT)	67*	12	18.7	1 - 77
Related to intervention before RT	49*	9	14	1 - 46
Impact of type intervention (pre-RT)				
Dental extraction	25**	6	10.6	2 - 46
Any surgery	25***	12	17.2	1 - 46
Mandibulotomy	6	5.5	7.8	1 - 22
Mandibulectomy	11***	15	18.5	3 - 42
Maxillectomy	3	30	26.3	3 - 46
Bone resection (usually rim resection)	4	24.5	22.8	9 - 33
Impact of systemic treatment				
RT only	37	9	15.6	1 - 60
RT and cisplatin	53	10	21.2	2 - 107
RT and cetuximab	6	25.5	21	6 - 42
Dose of RT at ORN site				
< 60Gy	29	9	20.2	1 - 107
≥ 60Gy	67	11	18.7	2 – 88
Impact of smoking				
Non smokers	25	18	23.8	2 - 77
Active smokers	42	7	11.4	1 - 58
Past smokers	23	16	23.7	3 - 107
Impact of dental extraction after RT (no other intervention)				
Dental extraction	16	32	33.6	2 - 77

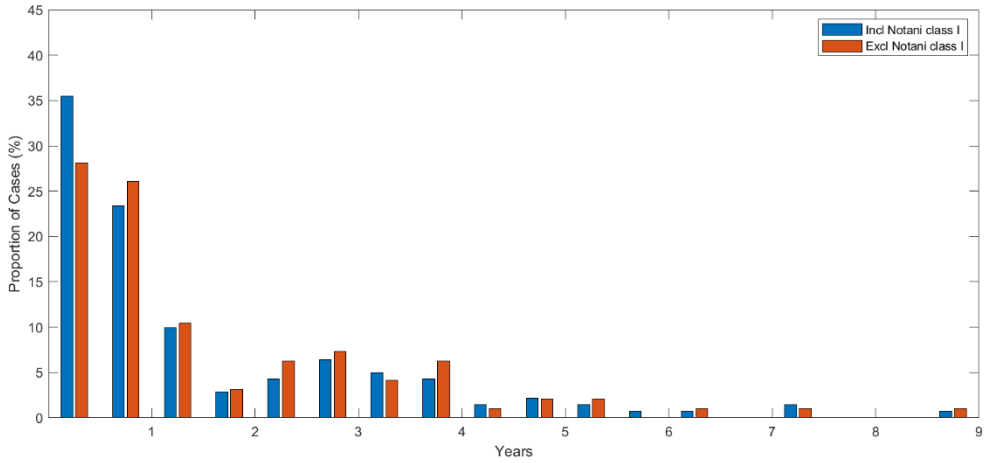
*In 4 patients ORN developed outside the area affected by intervention. **In 3 patients ORN developed outside the extraction site. ***In 1 patients ORN developed outside the area affected by surgical intervention.

Pattern of timing in development of ORN in the whole group of patients

The distribution of ORN in time for all ORN (n = 141, in blue colour) and for more advanced ORN (Notani class I excluded, n = 96, in brown colour) is demonstrated in figure 1. For ORN Notani class I-III, 35.5% developed within the first 6 months after RT and a further 23.4% between 6 and 12 months after RT. Then the rate considerablydecreased and after 5 years we observed few random cases of ORN.

In the subgroup of 96 patients with exclusion of Notani class I (in brown colour), the pattern was similar, 28.1% episodes of ORN developed within the first 6 months after RT, and a further 26.0% between 6 and 12 months after RT. Overall, the probability of developing ORN is at its highest within the first 12 months and it then subsides with increasing time.

Figure 1: Distribution of ORN in time for the whole group of 141 patients (141 patients = 100%, blue) and for 96 patients with advanced ORN (96 patients = 100%, Notani class I excluded, brown)



The difference in pattern of timing between patients with spontaneously developed ORN and pre-RT intervention related ORN

Whilst comparing spontaneously developed ORN (n = 42) with pre-RT intervention related ORN (n = 76), figure 2A demonstrates the difference in distribution of ORN for all Notani classes and figure 2B illustrates the pattern of timings of ORN development in advanced cases (excluding Notani class I). Our results show high incidence of ORN development in the first year for both spontaneous and pre-RT intervention related ORN. The first-year incidence was 62.2% for spontaneous and 69.1% for intervention related ORN in the analysis including all Notani classifications (figure 2A). The pattern is similar in more advanced ORN (exclusion of Notani class I) with results showing a high first year incidence 68.0% for spontaneous and 58.5% for intervention related ORN. There were no spontaneously developed advanced ORN during the second year. After five years of follow-up, ORN developed only in one patient in each group.

Figure 2: Distribution of ORN over time for spontaneously developed ORN (blue) and intervention related ORN (brown). **Figure 2A** represents all Notani classes ORN (42 patients with spontaneous ORN = 100% and 76 patients with ORN related to intervention before RT = 100%) and **figure 2B** more advanced ORN (Notani class I excluded, 29 patients who spontaneously developed ORN = 100%) compared with patients with 49 interventions related ORN (Notani class I excluded, 49 = 100%).

Figure 2A

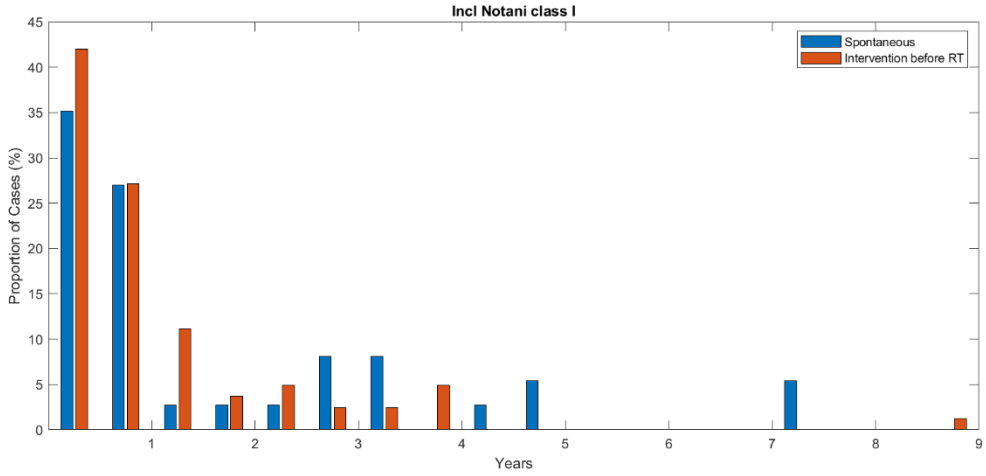
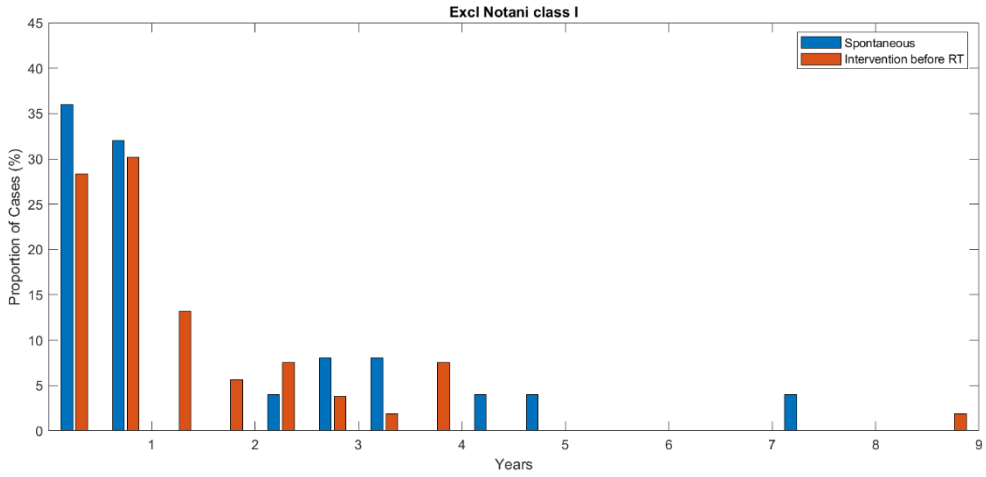


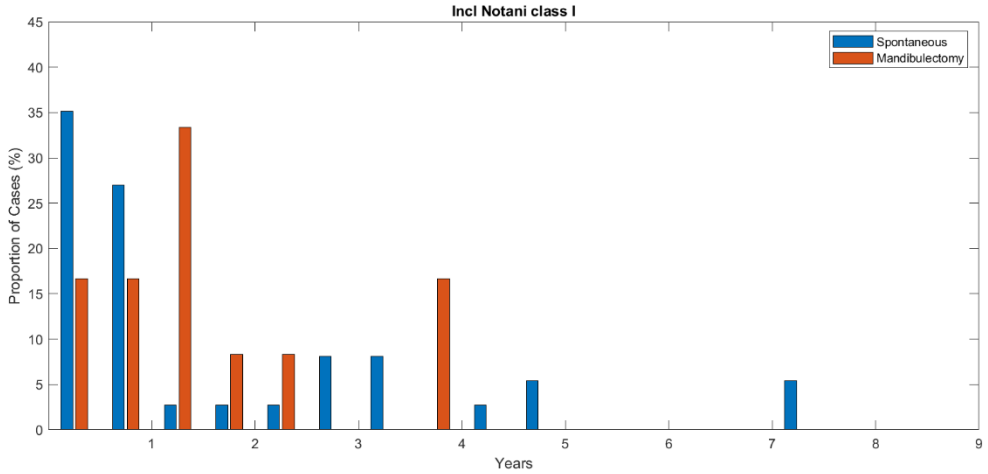
Figure 2B



Pattern of timings in development of ORN in subgroup of patients after mandibulectomy as a part of primary treatment

In patients after mandibulectomy and reconstruction, the onset of ORN was delayed as seen in figure 3. The difference in distribution of ORN over time in 15 patients after mandibulectomy and 42 patients with spontaneously developed advanced ORN is demonstrated. After mandibulectomy, 16.7% ORN developed within the first 6 months, and 16.7% developed between 6 and 12 months after RT. However, between 12 and 18 months 33.3% of ORN developed. After 48 months no case of ORN was observed in patients after mandibulectomy.

Figure 3: Distribution of ORN in time in 11 patients after mandibulectomy as the part of primary treatment (brown colour) in comparison with 42 patients with spontaneously developed advanced ORN (blue colour).



Pattern of timing in development of ORN after extraction of irradiated teeth (post-RT).

As seen on figure 4, ORN developed after post-RT dental extraction (with no other intervention) in 21 patients. Out of these, 28.6% developed within 18 months after RT. There was no case of ORN between 18 and 24 months. Then there was a continued incidence of ORN development until 7 years. More advanced ORN showed a similar pattern. The median interval between extraction and development of ORN was 2.5 months (mean 4.3 months, range 0 – 16 months). In one patient who developed ORN within 3-6 months of intervention, the exact date of extraction could not be identified.

Figure 4: Distribution of ORN in time in patients with dental extraction after RT). Figure 4A represents all ORN (21 patients = 100%) and figure 4B more advanced ORN (Notani class I excluded, 16 patients = 100%).

Figure 4A

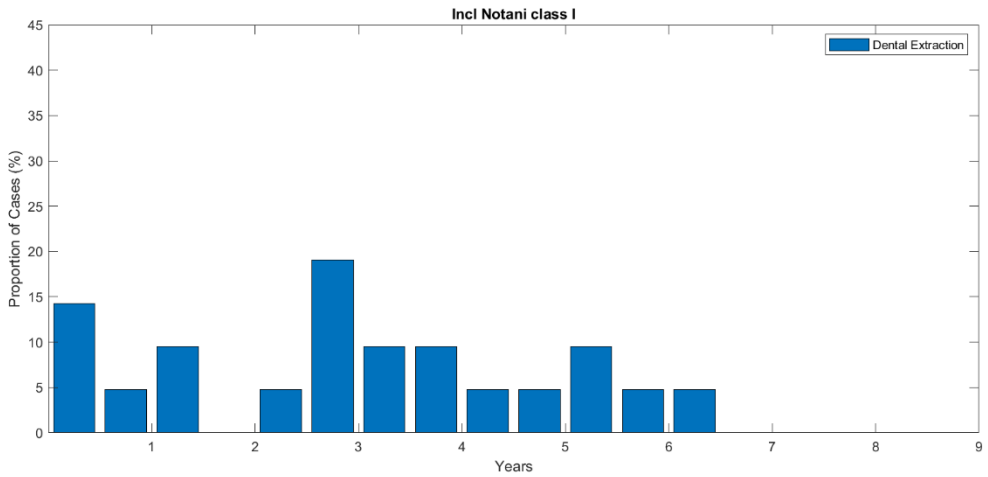
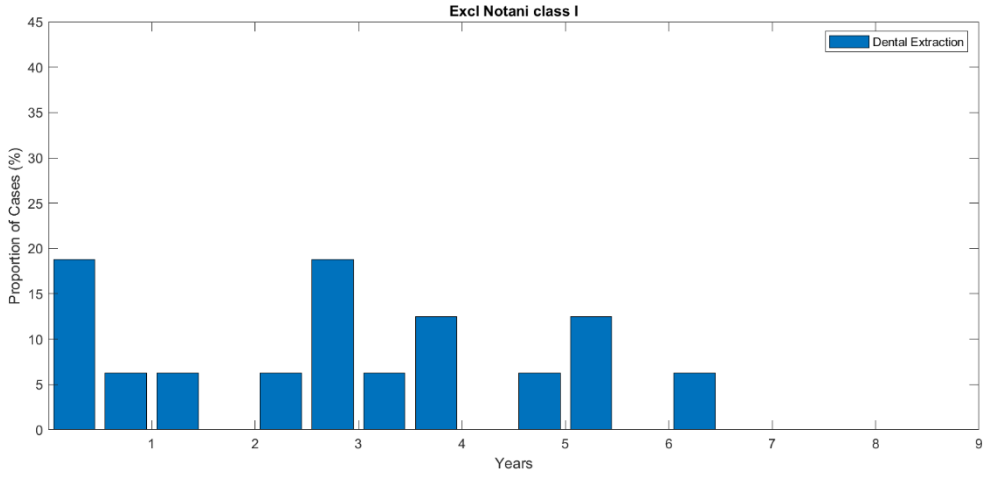


Figure 4B



Statistical analysis of the impact of various risk factors on timing of the development of ORN

The impact on the timing of development of ORN was analysed for following variables: gender, age, smoking status, dental extraction before RT, mandibulotomy, mandibulectomy, partial bone (rim) resection, addition of systemic treatment – cisplatin and cetuximab, dose in the origin of ORN. The outcome is summarised in table 3.

Table 3: Univariable/multivariable analysis of the impact of risk factors influencing the timing of ORN. *Median = time between the 1st day of RT and onset of the event (in months).

Characteristics	**Variable**	**n**	***Median**	**Variable**	**n**	**Median**	**Univariable analysis**	**Multivariable analysis**
							p-value	**p-value HR (95% CI)**
Gender	Male	106	7	Female	35	15	0.18	p=0.11 HR=1.4 [0.92-2.14]
Age	≤60years	86	7	>60years	55	10	0.14	p=0.18 HR=0.76 [0.51-1.13]
Smoking status	Active smokers	62	6	Non smokers	35	11	**0.006**	**p=0.042** **HR=1.62 [1.016-2.6]**
	Past smokers	38	38	Non smokers	35	11	0.46	
Intervention before RT	Dental extraction	51	5	Spontaneous	42	8	**<0.001**	p=0.27 HR=3.86 [0.34-43.41]
	Mandibulotomy	7	5	Spontaneous	42	8	0.070	p=0.35 HR=0.50 [0.11-2.18]
	Mandibulectomy	11	15	Spontaneous	42	8	0.79	
	Bone resection	4	24.5	Spontaneous	42	8	0.711	
Systemic treatment	Cisplatin	85	8	RT only	46	7	0.287	
	Cetuximab	10	25.5	RT only	46	7	0.237	**p=0.02** **HR=0.42 [0.20-0.90]**
**Dose of RT	≥60Gy	55	10	<60Gy	86	7	0.516	

*Median = time between the 1st day of RT and onset of the event (in months).

**Dose of RT = dose of RT in the origin of ORN (in Gy).

Active smoking and dental extraction before RT were identified as significant variables in univariable analysis. Smoking remained significant in multivariable analysis, but dental extraction before RT lost its significance in multivariable analysis. Active smokers had a significantly shorter median time to ORN onset (6 months) compared to non-smokers (11 months) in both univariable (p=0.006) and multivariable analysis (p=0.042; HR=1.62 [1.016-2.6]). Past smokers did not significantly differ from non-smokers.

Addition of cetuximab was included into multivariable analysis, as univariable analysis showed p=0.234 and it was identified as significant p=0.02; HR=0.42 [0.20-0.90]. In ten patients treated with cetuximab, the ORN developed in median 25.5 months, significantly later than in 46 patients treated with RT alone (median 7 months).

Discussion

In most publications analysing the risk factors for ORN, authors present the median interval between the completion of the treatment and the development of ORN. Table 4 summarises the median interval values from RT to occurrence of ORN in several large series of ORN patients published recently.

Table 4: Median interval between RT and development of ORN

Study	Sample size (n)	Period of treatment	ORN (%)	Interval RT – ORN (median months)
Kubota et al [7]	616	2008 - 2018	7.5	27
Tsai et al [2]	402	2000 - 2008	7.5	8
Owosho et al [8]	1023	2004 - 2013	4.3	19.1
Reuther at al [9]	830	1969 - 1999	8.2	13
Kovarik et al [5]*	935	2010 - 2019	9.7	8
Moon et al [10]	252	2009 - 2015	5.5	8
Aarup-Kristensen et al [3]	1224	2007 - 2015	4.6	10.9
Kabir et al [11]	620	2011 - 2016	2.2	9
Kuhnt at al [12]	776	2003 - 2013	12.4	9
Chang at al [13]	413	1987 - 2002	8.9	9
van Dijk at al [14]	1259	2005 - 2015	13.7	17
Möring at al [15]**	227	2010 - 2018	20.3	13.6
Lee at al [16]	198	2014 - 2020	6.8	15.6
Caparrotti at al [17]	1196	2005 - 2014	6	10.8
Studer at al [18]	715	2002 - 2013	5	20***
Current study	1608	2010 – 2020	8.8	9

* The authors of this current study published an initial report on risk factors for development of ORN in a cohort of 935 patients [reference 5]. ** Oral cavity only. ***Mean interval (median not reported).

Impact of systemic treatment on timing of ORN

Reuther et al [9] analysed the impact of the addition of chemotherapy on the timing of ORN. He reported a correlation between pre-surgical RT with chemotherapy and the time until ORN developed: the interval was 9 months for the combination treatment compared to 14 months for RT alone ($p = 0.03$). In our series, we recorded an 8-month interval from the last day of chemo-radiotherapy to the development of ORN versus 7 months in the radiotherapy only group. Our result differs from that which, Reuther et al observed. We are unable to explain the long interval (25.5 months) for development of ORN in the group of 10 patients treated with a combination of RT and cetuximab. Such an observation has not been published before; however, the unusual impact of cetuximab on dental loss has been reported. Kovarik et al [19] recorded a significant increase of dental loss in HNC patients treated combination of RT and cetuximab ($p < 0.0001$). It seems to be that an alteration of epidermal growth factor receptor may unpredictably affect the late effects of the treatment [20]. The authors suggest interpreting such an observation with caution as the group of patients was small ($n = 10$).

Impact of the RT dose on the timing of ORN

Although the impact of received dose of RT on the incidence of ORN is well recognised, literature analysing the impact of the dose on the timing of ORN is sparse. It is generally presumed that higher doses of RT are associated with an earlier development of ORN [21]. However, our data does not support such a statement. The median interval between the end of RT and the development of ORN was 7 months for patients where the dose at the origin of ORN was < 60Gy versus 11 months for ≥ 60Gy. We are unable to explain this phenomenon. Reuther at al [9] analysed the impact of the dose of RT on timing of ORN but was unable to identify any correlation between the dose and time until development of ORN.

Impact of gender on the timing of ORN

The authors are unable to explain the difference in the time to the development of ORN between males (median 7 months) and females (median 15 months). Such an observation has not been described in the literature. A possible explanation could be the difference in the level of post RT oral hygiene and dental care.

Impact of the intervention on the timing of ORN

Thorn et al [22] analysed a group of 80 patients with ORN and observed that 74% of ORN developed within the first 3 years after RT with most of the remaining 26% of late-onset ORN cases being intervention related. Thorn et al concluded, that most ORN develop in first few years, including almost all the spontaneously developed ORN. Procedure-induced ORN may evolve any time after RT. In our study, the incidence of ORN development in both groups was quite similar. Most ORN cases were seen within first 24 months after treatment. The few late incidences were more common in the spontaneous development group.

Reuther et al [9] analysed 68 patients with ORN; in 34, a tooth extraction was associated with the occurrence of ORN. Extraction was performed before RT in 16

patients, 18 patients underwent tooth extractions after RT (median 9 months). The median time interval between RT and occurrence of ORN was 13 months. After the analysis of dental status, Reuther et al concluded, that there was no correlation between the timing of dental extraction and the time to occurrence of ORN.

Owosho et al [8] analyzed 1023 patients, ORN developed in 44 of them (4.3%). The incidence of ORN development in patients with oral cavity anatomical site was 4% (12/299) and 4.4% (32/724) in patients with primary oropharyngeal carcinoma. The authors made an interesting observation – there was no difference in incidence of procedure-related ORN (no history of trauma or dentoalveolar procedure) between oropharyngeal and oral cavity origin. The only difference was timing of appearance of ORN. The median time from the last fraction of radiotherapy to the diagnosis of ORN was 19.1 months for the whole group, but 36.1 months for patients with oral cavity primary and 14.6 months for patients with oropharyngeal primary and this difference was significant (p 0.03). This result correspondences with our observation as well.

Published in 1983, Marx [23] analysed 536 cases of ORN, 365 related to external beam RT, 124 related to brachytherapy and 47 combined external beam and brachytherapy. Out of 402 cases of ORN related to external beam RT, 3 were orthovoltage delivery (<500 kV). Out of 399 remaining cases, 312 were treated with megavoltage photon sources (> 1 MV), and 7 with neutron beam. Marx analysed 209 spontaneous and 327 procedure related ORN. Of these, 274 were related to dental extraction. Extraction was performed before RT in 57 cases, 10 during RT and after RT 207 cases. In 48 cases, ORN was related to non-dental oral interventions. Marx's bimodal peak of incidence of intervention related ORN has not been observed by other authors [9,21]. The significant inhomogeneity in the type of RT treatment – the use of brachytherapy in 32% of patients could bias interpretation of this data for patients treated with external beam radiotherapy. Our observations differ from Marx analysis in that the incidence of intervention related ORN decreased synchronously with spontaneously developed ORN and the bimodal peak of incidence of intervention related ORN was absent. Also, it is important to note that this study was published in 1987 and use of combination of various radiotherapy techniques is obsolete now during the modern IMRT era.

Pattern of timing in development of ORN in subgroup of patients after mandibulectomy as a part of primary treatment

Reuther et al [9] observed a correlation between the extent of surgery and the time to occurrence of ORN. More extensive surgical therapy was associated with an earlier appearance of the development of ORN (p = 0.002). Our data does not support this observation. Median time to the onset of ORN was 15 months after mandibulectomy with fibular reconstruction. This could be because of modern reconstruction techniques using well vascularised fibular flaps.

Procedure-induced ORN

Beumer et al [21] reviewed 16 patients with ORN which developed after 72 post-RT dental extractions. Out of these, 13 were in mandible and 3 in maxilla. Out of the 13 incidents of mandibular ORN, 11 developed after external beam RT alone, and 2 after the insertion of interstitial implants. Beumer et al analysed the impact of the timing of extraction and concluded, that the risk of ORN was not related to the interval between RT and extraction.

We analysed a group of 21 ORN patients who underwent dental extraction post RT treatment. Any specific period which correlated with a lower probability for the development of ORN was not identified. In the period between 18 and 24 months after the primary treatment we observed a drop in the number of events, however, this could be a random error due to the low number of patients.

Development of ORN outside mandible is uncommon. In our study, there were 8 cases of ORN involving the maxilla. We recently published a detailed analysis of development of extra mandibular osteoradionecrosis (13 patients in total); the median interval of ORN development was 7.5 months but the median interval from end of radiotherapy to the development of ORN in temporal bone was 41 months [24].

Strengths and limitations of current study

The strengths include: the large number of patients reviewed; the clinical data is homogeneous from a single centre; there was precise dose mapping performed on all cases of ORN; in the sub group of patients with post radiotherapy dental extraction, there was no other confounding intervention performed which could have affected the integrity of bone. Concerning the weaknesses of our study, it is a retrospective study which carries potential selection bias itself. However, every effort was made to minimise the selection bias.

Clinical recommendations based on current study:

1. The period from 12 to 18 months after RT was identified as the interval with the highest probability of developing ORN in patients after mandibulectomy. A close clinical monitoring with a particular focus on risk of ORN development is recommended. A baseline and follow-up OPG might help identifying the ORN at relatively early stage.
2. In a sub group of 21 patients in whom ORN was related to dental extraction post-RT and there was no defined timeframe for safer dental intervention post-RT. Therefore, clinically waiting for an extra ‘safe’ period before dental extraction post-RT might not be beneficial.

Conclusion

Information about factors influencing the interval between the completion of RT and onset of ORN is sparse. Our study provides valuable information on the time periods under scrutiny. Our results differ from previous studies reviewing the time interval between RT and development of ORN. There was a slightly higher proportion of patients with intervention developed ORN earlier in comparison with spontaneous ORN, although the trend was similar, and a previously described bimodal peak of

incidence of intervention related ORN was absent. The period from 12 to 18 months after RT was identified as the interval with the highest probability of developing ORN in patients after mandibulectomy. In a sub group, we analysed 21 patients in whom ORN was related to dental extraction post-RT and there was no defined timeframe for safer dental intervention post-RT.

References

1. Baxi SS, Pinheiro LC, Pati SM, Pfister DG, Oeffinger KC, Elkin EB. Causes of death in long term survivors of head and neck cancer. Cancer 2014;120:1507-13.

2. Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, Tucker SL, Dong L. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2013 Feb 1;85(2):415-20. Doi: 1016/j.ijrobp.2012.05.032. Epub 2012 Jul 12.

3. Aarup-Kristensen S, Hansen CR, Fornber L, Brink C, Eriksen JG, Johansen J. Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations. Acta Oncologica https://doi.org/10.1080/0284186X.2019.1643037

4. Caparrotti F, Huang SH, Lu L, Bratman SV, Ringash J, Bayley A, Cho J, Giuliani M, Kim J, Waldron J, Hansen A, Tong L, Xu W, O'Sullivan B, Wood R, Goldstein D, Hope A. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. Cancer. 2017 Oct 1;123(19):3691-3700. doi: 10.1002/cncr.30803. Epub 2017 Jun 13. PMID: 28608925.

5. Kovarik JP, Voborna I, Barclay S, Iqbal MS, Cunnell M, Kelly C, Willis N, Kennedy M, Kovarik J. Osteoradionecrosis after treatment of head and neck cancer: a comprehensive analysis of risk factors with a particular focus on role of dental extractions. Br J Oral Maxillofac Surg. 2022 Feb;60(2):168-173. doi: 10.1016/j.bjoms.2021.03.009. Epub 2021 Mar 27. PMID: 34857411.

6. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K, Nakamura M. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. Head Neck. 2003 Mar;25(3):181-6. doi: 10.1002/hed.10171. PMID: 12599284.

7. Kubota, H., Miyawaki, D., Mukumoto, N. *et al.* Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma. *Radiat Oncol* **16**, 1 (2021). https://doi.org/10.1186/s13014-020-01701-5.

8. Owosho AA, Tsai CJ, Lee RS, Freymiller H, Kadempour A, Varthis S, *at al*. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated ith intensity-modulated radiation therapy: The Memorial Sloan Kettering Cancer Center Experience.

Oral Oncol. 2017 January; 64:44-51. Doi:10.1016/j.oraloncology.2016.11.015.

9. Reuther T, Schuster T, Mende U, Kübler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients--a report of a thirty year retrospective review. Int J Oral Maxillofac Surg. 2003 Jun;32(3):289-95. doi: 10.1054/ijom.2002.0332. PMID: 12767877.

10. Moon DH, Moon SH, Wang K, Weissler MC, Hackman TG, Zanation AM, *at al*. Incidence of, and risk factors for, mandibular osteoradionecrosis in patients with oral cavity and oropharynx cancers.
Oral Oncol. 2017 Sep; 72:98-103. Doi: 10.1016/j.oraloncology.2017.07.014. Epub 2017 Jul 16.

11. Kabir R, Durand R, Roberge D, Dufresne E, Nguyen-Tân PF. Incidence of osteoradionecrosis of the jaws: a retrospective study of 620 patients with head and neck cancer. Gen Dent. 2022 Jul-Aug;70(4):72-77. PMID: 35749251.

12. Kuhnt T, Stang A, Wienke A, Vordermark D, Schweyen R, Hey J. Potential risk factors for jaw osteoradionecrosis after radiotherapy for head and neck cancer. Radiat Oncol. 2016 Jul 30;11:101. doi: 10.1186/s13014-016-0679-6. PMID: 27473433; PMCID: PMC4967325.

13. Chang DT, Sandow PR, Morris CG, Hollander R, Scarborough L, Amdur RJ, Mendenhall WM. Do pre-irradiation dental extractions reduce the risk of osteoradionecrosis of the mandible? Head Neck. 2007 Jun;29(6):528-36. doi: 10.1002/hed.20538. PMID: 17230555.

14. van Dijk LV, Abusaif AA, Rigert J, Naser MA, Hutcheson KA, Lai SY, Fuller CD, Mohamed ASR; on behalf on the MD Anderson Symptom Working Group. Normal Tissue Complication Probability (NTCP) Prediction Model for Osteoradionecrosis of the Mandible in Patients With Head and Neck Cancer After Radiation Therapy: Large-Scale Observational Cohort. Int J Radiat Oncol Biol Phys. 2021 Oct 1;111(2):549-558. doi: 10.1016/j.ijrobp.2021.04.042. Epub 2021 Jun 10. PMID: 33965514; PMCID: PMC8906058.

15. Möring MM, Mast H, Wolvius EB, Verduijn GM, Petit SF, Sijtsema ND, Jonker BP, Nout RA, Heemsbergen WD. Osteoradionecrosis after postoperative radiotherapy for oral cavity cancer: A retrospective cohort study. Oral Oncol. 2022 Oct;133:106056. doi: 10.1016/j.oraloncology.2022.106056. Epub 2022 Aug 4. PMID: 35933938.

16. Lee CT, Litwin S, Yao CMKL, Liu JC, Ridge JA, Galloway TJ. Osteoradionecrosis rate in oropharynx cancer treated with dose volume histogram based constraints. Radiother Oncol. 2022 Nov;176:215-221. doi: 10.1016/j.radonc.2022.10.011. Epub 2022 Oct 15. PMID: 36252636.

17. Caparrotti F, Huang SH, Lu L, Bratman SV, Ringash J, Bayley A, Cho J, Giuliani M, Kim J, Waldron J, Hansen A, Tong L, Xu W, O'Sullivan B, Wood R,

Goldstein D, Hope A. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. Cancer. 2017 Oct 1;123(19):3691-3700. doi: 10.1002/cncr.30803. Epub 2017 Jun 13. PMID: 28608925.

18. Studer G, Bredell M, Studer S, Huber G, Glanzmann C. Risk profile for osteoradionecrosis of the mandible in the IMRT era. Strahlenther Onkol. 2016 Jan;192(1):32-9. doi: 10.1007/s00066-015-0875-6. Epub 2015 Aug 12. PMID: 26265308; PMCID: PMC4705130.

19. Kovarik JP, Voborna I, Barclay S, Nicol A, Kelly C, Kovarik PD, Iqbal MS, Kovarik J. Dental loss after radiotherapy for head and neck cancer. Br Dent J. 2021 Oct;231(8):473-478. doi: 10.1038/s41415-021-3536-4. Epub 2021 Oct 22. PMID: 34686814.

20. Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. Support Care Cancer 2017;25:1713-1739.

21. Beumer, J., III, Harrison, R., Sanders, B. and Kurrasch, M. (1983), Postradiation dental extractions: A review of the literature and a report of 72 episodes. Head Neck, 6: 581-586. https://doi.org/10.1002/hed.2890060107

22. Thorn JJ, Hansen HS, Specht L, Bastholt L. Osteoradionecrosis of the jaws: clinical characteristics and relation to the field of irradiation. J Oral Maxillofac Surg. 2000 Oct;58(10):1088-93; discussion 1093-5. doi: 10.1053/joms.2000.9562. PMID: 11021701.

23. Marx RE. Osteoradionecrosis: a new concept of its pathophysiology. J Oral Maxillofac Surg. 1983 May;41(5):283-8. doi: 10.1016/0278-2391(83)90294-x. PMID: 6572704.

24. Kovarik PDE, Patil R, Cvek J, Kelly C, Jackson M, Mackenzie L, West N, Willis N, Kovarik JP, Banks R, Kennedy M, Adams J, Iqbal MS. Extra-mandibular Osteoradionecrosis after the Treatment of Head and Neck Cancer. Clin Oncol (R Coll Radiol). 2023 Sep;35(9):e498-e505. doi: 10.1016/j.clon.2023.06.013. Epub 2023 Jun 27. PMID: 37433701.