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HEAD AND NECK

Tumor subsites and risk of osteoradionecrosis of the jaw in patients with oral cavity cancer: a national-based cohort study

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Abstract

Purpose The association between the tumor subsites of the oral cavity and the risk of osteoradionecrosis of the jaw (ORNJ) remains unclear. We study the correlation between oral cavity tumor subsites and the risk of ORNJ in a nationwide population-based database.

Methods We enrolled 16,701 adult patients with oral cavity cancers who were treated with radiotherapy between 2000 and 2013. The subsites of the oral tumor, treatments of oral cavity cancers, and the timing of tooth extraction were examined for their association with ORNJ in oral cancer patients.

Results 903 patients (5.40%) developed ORNJ. Of the relevant variables, pre-RT mandible surgery, tooth extraction either before or after RT, and tumor sites were associated with the risk of ORNJ. The adjusted HRs for ORNJ in the mouth floor, gums, retromolar, and buccal cancer were 2.056 (1.490–2.837), 1.909 (1.552–2.349), 1.683 (1.105–2.562), and 1.303 (1.111–1.528), respectively, compared with the risk of tongue cancer. There was no significant difference in the risk of ORNJ between the pre-RT extraction group, the during-RT extraction group, and the post-RT extraction (less than 6 months) group; the post-RT extraction (more than 6 months) group had a significantly higher risk of ORNJ.

Conclusions This study demonstrated that oral cavity tumor subsite is an independent risk factor of ORNJ after RT. Post-RT extraction (less than 6 months) group did not carry a significantly higher risk of ORNJ compared with pre-RT extraction group or during RT extraction group.

Keywords Oral cavity cancer · Osteoradionecrosis · Cohort study · Radiotherapy

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Introduction

Radiation therapy (RT) and surgery are established treatments for head and neck cancer (HNC). The methods are effective for local and regional disease control, but head-and-neck RT can have acute complications, such as mucositis, thickened secretions, mucosal infections, pain, and sensory disruptions. Furthermore, it can also have chronic effects, including tissue fibrosis, salivary gland dysfunction, increased susceptibility to mucosal infections, neuropathic pain, sensory disorders, increased susceptibility to dental caries and periodontal disease, and even osteoradionecrosis (ORN) [1].

Osteoradionecrosis is considered to be the most severe sequela of radiotherapy, and the total incidence of risk reported for osteoradionecrosis of the jaw (ORNJ) ranges from 5 to 15% [2]. Possible mechanisms of ORNJ after radiotherapy include a loss of osteoblasts relative to osteoclasts, vascular compromise, hypoxia, hypocellular change, and fibrosis [3, 4]. Osteoradionecrosis is defined by the presence of an area of exposed, devitalized, irradiated bone that fails to heal within 3–6 months in the absence of local neoplastic disease [4–6]. It can occur as a slowly progressing process or as an active progressive state that eventually leads to a pathologic fracture [7].

Many studies have explored the factors related to the risk of ORNJ in HNC patients. Some of these studies have shown that tumors located in the oral cavity are associated with a higher risk of ORNJ [2, 8]. Oral cavity cancer is the most common form of HNC, and since 1995, it has had the fourth highest incidence and mortality among cancers in males in Taiwan [9]. In a recent study, Wang et al. focused on the risk factors of ORNJ in HNC patients and revealed that buccal cancer is associated with the highest risk of ORNJ [2]. In that study, the oral cavity tumors were grouped according to the site into buccal cancers and non-buccal cancers. A correlation was not demonstrated between other tumor sites in the oral cavity and ORNJ.

Better understanding of the impact of tumor sites in the oral cavities of cancer patients would help to establish more effective approaches to improve patient outcomes. The purpose of this national cohort study was to investigate the risk factors of ORNJ in patients with oral cavity cancer. Furthermore, correlations between tumor sites in the oral cavity and the risk of ORNJ were also assessed.

Materials and methods

Ethical considerations

This study was carried out using the National Health Insurance Research Database (NHIRD). The NHIRD comprises de-identified data, and the study was performed using retrospective data, so no informed consent was requested from the patients. Kaohsiung Veterans General Hospital provided ethical approval to carry out the study within its facilities (VGHKS15-EM10-02).

Data source and population

This nationwide, population-based, retrospective study examined data collected in 2000–2013 in Taiwan in the NHIRD. The prevalence of national health insurance in Taiwan is high (up to 99%) [10]. We identified all patients who were 20 years old or more and diagnosed with oral cavity cancer (ICD-9-CM codes: 140.0–140.9, 141.1–141.9, 143.0, 143.1, 143.8, 143.9, 144.0, 144.1, 144.8, 144.9, 145.0, 145.1, and 145.9). ORNJ was defined as the exposed irradiated bone that had failed to heal over a period of 3 months in the absence of a local tumor [10]. Therefore, ORNJ cases were excluded from the analysis if they occurred within fewer than 3 months from the first day of RT.

The inclusion criteria included: (1) the presence of oral cavity cancer, (2) age of at least 20 years, (3) the receipt of a complete course of RT for oral cavity cancer (defined as a total dosage $\geq$ 60 Gy), and (4) longitudinal follow-up for more than one year after the first day of radiotherapy. The exclusion criteria were: (1) patients with missing or incomplete data, (2) patients who died within 1 year of the first day of radiotherapy, (3) patients who received head and neck radiotherapy procedures (codes 36012B or 36011B) fewer than 100 times in 75 days since the first day of RT, and (4) patients with a history of cancer.

ORNJ risk factor analysis

The outcome of interest in this study was the ORNJ incidence associated with different subsites of oral cavity cancers. Thus, we divided the enrolled patients into six groups according to tumor subsite: the lips, tongue, gums, mouth floor, buccal area, and retromolar trigone. We collected demographic data and information about major comorbidities, cancer treatments, and dental treatments that could potentially be associated with ORNJ risk. We defined the first day of RT as the index day.

The confounding factors examined included age, gender, chemotherapy (occurring within 6 months of the index day,

during RT, or within 6 months of the end of RT with cisplatin or 5-FU), pre-RT mandible surgery (within 3 months of the index day), underlying disease (diabetes mellitus (DM), hypertension, or cerebrovascular accident), socioeconomic status, hospital type (medical center, regional hospital, or other), and the timing of the dental extraction (before, during, or after RT). Intensity-modulated radiation therapy (IMRT) has rapidly replaced conventional RT and three-dimensional conformal RT since 2009 in Taiwan [11, 12]. Thus, the enrolled patients were also grouped according to whether they received RT before or after 2009 to evaluate the impact of the RT modality on the development of ORN.

Statistical analysis

All of the demographic and clinical characteristics are expressed as the means ± standard deviations (SD) or numbers (percentages) as appropriate. Independent *t*-tests and Pearson's chi-squared tests were used to determine the statistical differences between groups for continuous and discrete variables, respectively. A subdistribution hazard function was used for a competing risk analysis using ORNJ (the outcome of interest) and death (competing outcome) as events. A p value less than 0.05 was considered to indicate a statistically significant difference. We performed data processing and statistical analyses using PASW (version 20, IBM SPSS, Inc., Chicago, IL, USA).

Results

Table 1 shows the demographic and clinical data of the study population. A total of 16,701 patients were included in the study, including 903 (5.40%) that had ORNJ and 15,798 (94.6%) that did not. The mean ages of the cohorts were 51.9 and 53.0 years for patients with and without ORNJ, respectively ($p = 0.03$).

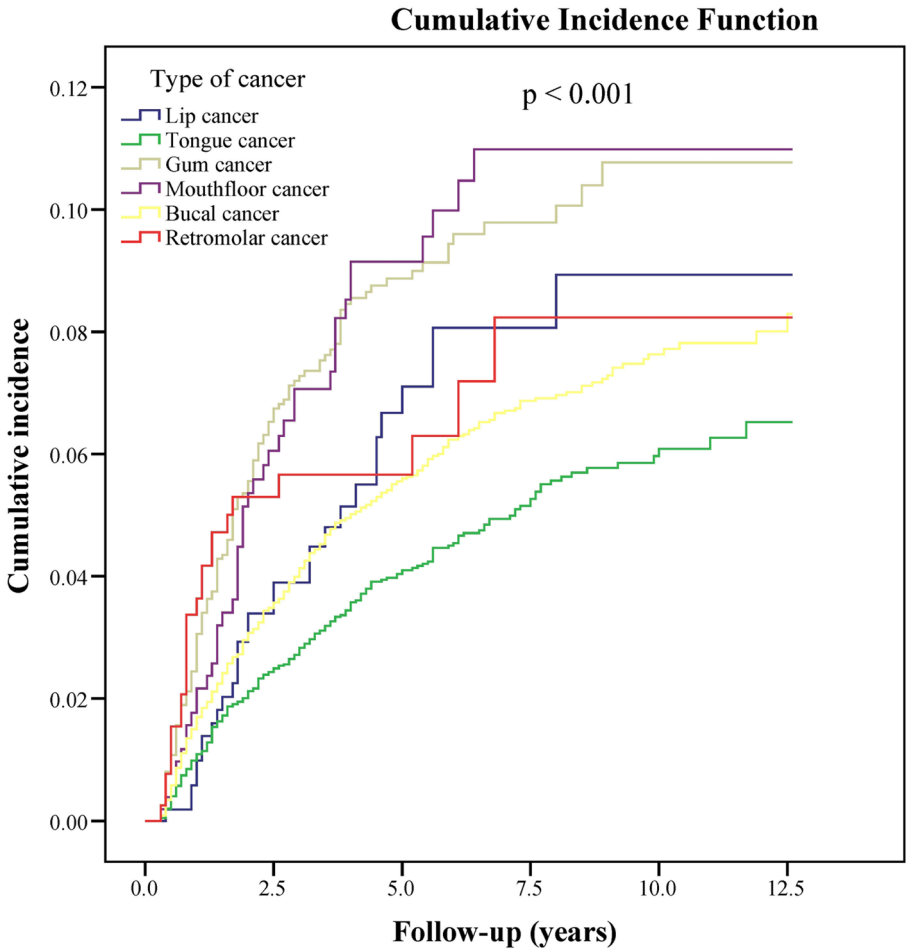
Table 1 Demographic and clinical characteristics of study patients according to ORNJ

Variable	ORNJ ($n = 903$)	Non-ORNJ ($n = 15,798$)	p value
Age (Median [range])	51.51 (20.25–86.62)	51.91 (21.49–94.38)	0.032
Gender (Male)	852 (94.4%)	14,612 (92.5%)	0.038
Received RT year			
Before 2009	626 (69.3%)	8004 (50.7%)	< 0.001
After 2009	277 (30.7%)	7794 (49.3%)	
Lip	30 (3.3%)	496 (3.1%)	0.760
Tongue	241 (26.7%)	5668 (35.9%)	< 0.001
Gum	147 (16.3%)	1713 (10.8%)	< 0.001
Mouth floor	44 (4.9%)	468 (3.0%)	0.001
Buccal	417 (46.2%)	7088 (44.9%)	0.400
Retromolar	24 (2.7%)	365 (2.3%)	0.501
Combined chemotherapy	517 (57.3%)	10,442 (66.1%)	< 0.001
Pre-RT mandible surgery	77 (8.5%)	1045 (6.6%)	0.026
DM	170 (18.8%)	2999 (19.0%)	0.907
HTN	243 (26.9%)	5025 (31.8%)	0.002
CVA	45 (5.0%)	1059 (6.7%)	0.043
SES			0.166
Low	273 (30.2%)	5089 (32.2%)	
Middle	393 (43.5%)	6977 (44.2%)	
High	237 (26.2%)	3732 (23.6%)	
Hospital type			0.155
Center	679 (75.2%)	11,413 (72.2%)	
Regional	216 (23.9%)	4225 (26.7%)	
Other	8 (0.9%)	160 (1.0%)	
Pre-RT tooth extraction	415(46.0%)	6583(41.7%)	0.011
During RT tooth extraction	107 (11.8%)	1123 (7.1%)	< 0.001
Post-RT tooth extraction (less than half year)	110 (12.2%)	876 (5.5%)	< 0.001
Post-RT tooth extraction (more than half year)	582 (64.5%)	3522 (22.3%)	< 0.001

ORNJ osteoradionecrosis of jaw, *RT* Radiotherapy, *DM* diabetes mellitus, *CVA* cerebrovascular accident, *SES* socioeconomic status

Among the patients without ORNJ, 66.1% received chemotherapy. In the ORNJ group, 69.3% of the patients received RT before 2009, and 57.3% of the group received chemotherapy ($p < 0.001$). The ORNJ group had rates of patients who were male, pre-RT mandible surgery, pre-RT tooth extraction, during-RT tooth extraction, and post-RT tooth extraction ($p < 0.05$). The non-ORNJ group had higher rates of hypertension and cerebrovascular accident ($p < 0.05$). There were no significant differences between the two groups in terms of DM, socioeconomic status, or hospital type. Figure 1 reports the cumulative incidence of ORNJ, which peaked at 0.5–1.5 years after radiotherapy for most of the subsites of oral cavity cancer.

The univariate analysis revealed that the risk factors of ORNJ included receiving RT before 2009, tumor subsites other than the tongue, pre-RT mandible surgery,



Time (years)	0	2.5	5.0	7.5	10.0	12.5
	Number of Risk					
Lip	526	375	212	117	60	21
Tongue	5909	4565	2933	1638	790	211
Gum	1860	1274	741	357	141	41
Mouth floor	512	385	240	126	65	16
Buccal	7505	5862	3839	2171	1085	314
Retromolar	389	267	154	72	29	8

Fig. 1 The incidence of ORNJ peaked from 0.5–1.5 years after radiotherapy in most of the subsites of oral cavity cancer

and tooth extraction (Table 2). The multivariate analysis with Cox regression showed that the variables validated as independent risk factors of ORNJ were gum cancer (adjusted hazard ratio (aHR): 1.909, 95% confidence interval (CI): 1.552–2.349), mouth floor cancer (aHR 2.056, 95% CI 1.490–2.837), buccal cancer (aHR 1.303, 95% CI 1.111–1.528), retromolar cancer (aHR 1.683, 95% CI 1.105–2.562), pre-RT mandible surgery (aHR 1.290, 95% CI 1.018–1.634), pre-RT tooth extraction (aHR 1.168, 95% CI 1.021–1.336), tooth extraction during RT (aHR 1.570, 95% CI 1.279–1.928), post-RT tooth extraction within 6 months after completing RT (aHR 1.741, 95% CI 1.425–2.127), and post-RT tooth extraction at least 6 months after completing RT (aHR 4.788, 95% CI 4.173–5.494) (Table 2). Figure 2 shows the competing risk survival function for ORN for the six types of cancers. We noted that lip cancer and tongue cancer had a lower risk of ORNJ than other types of oral cavity cancers, such as buccal cancer, gum cancer, retromolar cancer, and mouth floor cancer.

Discussion

In this study, we determine the tumor subsites associated with a risk of ORNJ in oral cavity cancer patients treated with RT. This nationwide population-based cohort study examined 13 years of data. We noted that pre-RT mandible surgery and tooth extraction either before or after RT were associated with an increased risk of developing ORNJ. These findings have important clinical implications. Clinically, physicians and patients should be aware of these associations. When treating oral cavity cancer patients, clinicians should be alert about the sites of tumors. Treating physicians may consider referring a patient to a dentist for additional education and pre-RT dental care.

Table 2 Univariate and multivariate analysis of the risk of Osteoradionecrosis of the jaw (ORNJ)

Variable	Number	#of ORN (%)	Univariate model		Multivariate model	
			Est. (95% C.I.)	*p* value	Est. (95% C.I.)	*p* value
Age			0.994 (0.988–1.000)	0.037		0.145
Age (> 50)	9583	502 (5.2%)	0.982 (0.861–1.119)	0.783		
Gender (Male)	15,464	852 (5.5%)	1.330 (1.003–1.764)	0.048		0.080
Received RT before 2009	8630	626 (7.3%)	1.172 (1.008–1.362)	0.038		0.912
Type of cancers						
Tongue	5909	241 (4.1%)	NA	< 0.001	NA	< 0.001
Lip	526	30 (5.7%)	1.512 (1.035–2.210)	0.033	1.360 (0.930–1.988)	0.113
Gum	1860	147 (7.9%)	2.156 (1.756–2.647)	< 0.001	1.909 (1.552–2.349)	< 0.001
Mouth floor	512	44 (8.6%)	2.157 (1.564–2.974)	< 0.001	2.056 (1.490–2.837)	< 0.001
Buccal	7505	417 (5.6%)	1.351 (1.153–1.583)	< 0.001	1.303 (1.111–1.528)	0.001
Retromolar	389	24 (6.2%)	1.686 (1.108–2.565)	0.015	1.683 (1.105–2.562)	0.015
Combined chemotherapy	10,959	517 (4.7%)	0.751 (0.658–0.857)	< 0.001		0.338
Pre-RT mandible surgery	1122	77 (6.9%)	1.407 (1.114–1.777)	0.004	1.290 (1.018–1.634)	0.035
DM	3169	170 (5.4%)	1.061 (0.898–1.254)	0.484		
HTN	5268	243 (4.6%)	0.879 (0.758–1.018)	0.085		
CVA	1104	45 (4.1%)	0.781 (0.579–1.054)	0.106		
SES						
Low	5362	273 (5.1%)				
Middle	7370	393 (5.3%)	1.038 (0.890–1.211)	0.635		
High	3963	237 (6.0%)	1.184 (0.995–1.409)	0.057		
Hospital type						
Center	12,092	679 (5.6%)	1.328 (0.661–2.666)	0.426		
Regional	4441	216 (4.9%)	1.247 (0.616–2.527)	0.539		
Other	168	8 (4.8%)				
Pre-RT tooth extraction	6998	415 (5.9%)	1.320 (1.158–1.505)	< 0.001	1.168 (1.021–1.336)	0.023
During RT tooth extraction	1230	107 (8.7%)	1.603 (1.310–1.961)	< 0.001	1.570 (1.279–1.928)	< 0.001
Post-RT tooth extraction (less than half year)	986	110 (11.2%)	2.258 (1.850–2.756)	< 0.001	1.741 (1.425–2.127)	< 0.001
Post-RT tooth extraction (more than half year)	4104	582 (14.2%)	5.074 (4.427–5.815)	< 0.001	4.788 (4.173–5.494)	< 0.001

ORNJ osteoradionecrosis of jaw, *RT* Radiotherapy, *DM* diabetes mellitus, *CVA* cerebrovascular accident, *SES* socioeconomic status

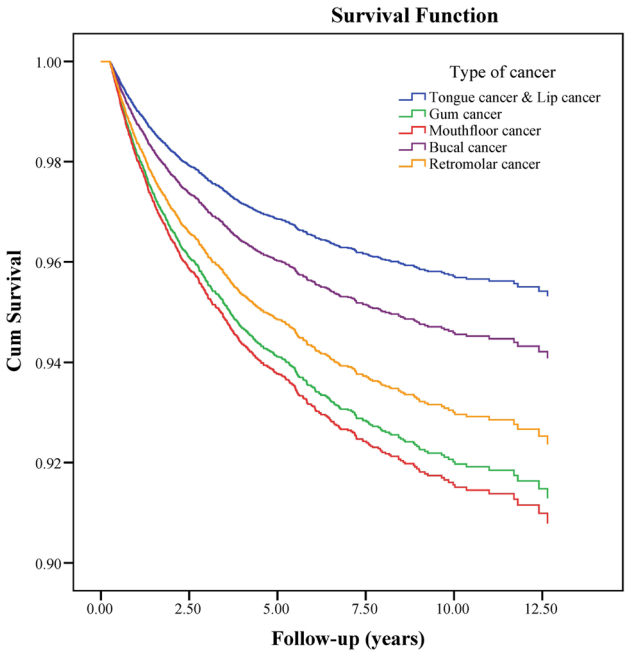


Fig. 2 The competing risk survival function for ORN for the six types of cancers showed that lip cancer and tongue cancer had a lower risk of ORNJ compared with other types of oral cavity cancers such as buccal cancer, gum cancer, retromolar cancer, and mouth floor cancer

The definition of ORNJ varies, but the most widely accepted definition is "a devitalized irradiated bone that fails to heal over a period of 3 months in the absence of local neoplastic disease" [13, 14]. However, residual or recurrent tumors can resemble ORNJ. Therefore, a diagnosis of ORNJ should be made after making sure that there is no evidence of malignancy.

The incidence of ORNJ has decreased over time in recent decades. Clayman et al. showed that the overall incidence of ORN (irrespective of dental extraction) has declined from 11.8% before 1968 to 5.4% [15]. A systemic review by Nabil and Samman reported an overall rate of ORNJ of 2% in patients with HNC from 22 randomized control trials conducted between 1985 and 2010 [14]. Many factors may responsible for this decreasing incidence of ORNJ, such as the use of IMRT, antibiotics, and oral nursing [16].

Development of ORNJ

In our cohort, the incidence of ORNJ peaked at 0.5–1.5 years after radiotherapy. This finding is consistent with that of other studies, which noted that most ORNJ events occurred within the first 2 years of treatment [17]. However, ORNJ may occur decades after treatment. For example, Wang et al. observed that ORNJ events could develop more than 12 years after irradiation [2]. Therefore, treating physicians should keep in mind that this potentially late complication warrants life-long attention [2].

Tumor sites and mandible surgery

Many studies have proposed that tumors in the oral cavity are a strong risk factor for ORNJ after radiotherapy [2, 18, 19]. The overall incidence of ORNJ was 5.4% in our study, which only evaluated patients with oral cavity cancer. Taiwan has a high prevalence of oral cavity cancer, and many patients need adjuvant radiotherapy after surgery due to the advanced stage of the disease. Accordingly, we attempted to determine the association between different oral tumor sites and the risk of ORNJ to improve treatment outcomes and patients' quality of life.

We observed that lip and tongue cancers were associated with a lower risk of ORNJ than other types of oral cavity cancers, such as buccal cancer, gum cancer, retromolar cancer, and mouth floor cancer. These findings might be explained by the inclusion of the mandible in the field of radiation [16, 20]. Many studies have noted a significantly higher risk of ORN in patients receiving high doses of radiation to the mandible [20–22]. Studer et al. suggested that high-dose RT to the mandible can result in severe acute mucositis, which can exacerbate bony exposure and lead to ORNJ [23]. Minimizing the percentage of mandibular volume exposed to 50 Gy may reduce the risk of ORN [20]. The data of actual dose and treatment volume to the mandible was not available in Taiwan national health insurance research database, and this was the key limitation of this study. Although we defined "complete RT course" as a total dosage $\geq$ 60 Gy (identified by procedure codes) to exclude those patients who did not receive a full course of radiotherapy, we were not able to know the exact applied dose or treatment volume to the mandible. However, the large-scale sample size and long-term follow-up period increase the validity of this study. Based on the observation that different tumor sites of oral cavity cancer carry different risks of ORNJ, we provided strong evidence for treating physicians to discuss the risks and benefits of a tooth extraction with oral cavity cancer patients, and the treatment plans may be tailored according to different tumor subsites.

Furthermore, we noted that mandible surgery is also an independent risk factor for ORNJ. This finding may be related to the fact that an aggressive surgical approach frequently involves the removal of arteries, which are necessary for maintaining mandibular blood flow. Therefore, this procedure may possibly increase the risk of ORNJ [19].

Timing of tooth extraction

There are no clear-cut guidelines for making decisions about pre-RT extraction or non-extraction of teeth. Teeth

with periodontal disease, advanced decay, or signs of poor dental prognosis are typically extracted prior to RT. When removing these teeth prior to RT, the patient's bone retains its normal healing capacity, which is believed to reduce the risk of ORN [21]. However, studies have presented conflicting data [16, 18, 21]. Furthermore, variations in the time interval between extraction and irradiation may lead to different levels of risk of developing ORNJ [10].

In our study, we found that pre-RT extraction, extraction during RT, and post-RT extraction were all associated with an increased risk of ORNJ. Furthermore, post-RT extraction (occurring later than 6 months after the end of radiotherapy) was associated with a significantly higher risk of ORNJ than pre-RT extraction, extraction during RT, or post-RT extraction within 6 months. This result is consistent with the findings of Kuo et al., which revealed that tooth extraction at more than half a year after radiotherapy carried a higher risk of ORNJ [10].

Curi et al. found that irradiation injuries affect the bone and surrounding soft tissues, while hypovascularity, significant cell loss, and fibrosis began at approximately 6 months after radiation and progressively worsened over time [24]. Their histopathological findings provided evidence that supports our study. We also noted that although pre-RT extraction had the lowest adjusted HR, there was no significant difference in the adjusted HRs among pre-RT extraction, extraction during RT, and post- RT extraction within 6 months. These results suggest that extracting teeth within 6 months of radiotherapy may be a better choice than waiting until later.

Furthermore, this result indicates that if patients receive pre-RT tooth extraction, it may not be necessary to delay RT for pretherapeutic dental restoration and wound healing. Our results are consistent with those of Chang et al. from 2007. They explored the impact of pre-RT dental extractions and the risk of ORNJ and concluded that pre-RT extractions do not appear to reduce the risk of ORNJ in comparison with post-RT extractions [21].

RT modalities

Some studies have concluded that IMRT is associated with a lower prevalence of ORN, a better quality of life for patients, and better survival outcomes than three-dimensional conformal RT because IMRT reduces the radiation exposure of normal regional tissues [25, 26]. In Taiwan, conventional 2DRT and 3D-CRT have rapidly been replaced by IMRT or VMAT since 2009 [11, 12]. Therefore, 2009 was defined as a cut-off year when analyzing the effect of the RT modality on ORNJ risk [11, 12]. In our study, however, RT before 2009 was not associated with a significantly higher risk of ORNJ than RT after 2009. This result might be explained by the tumor location. All the patients in this study were diagnosed with oral cavity cancer. In tumors of the oral cavity, parts of the mandible might be within the target volume either with conventional RT or IMRT [23]. Thus, the protective effect of IMRT by the exclusion of the mandible from the radiation field might not be achieved in oral cavity cancer.

Chemotherapy

For HNC patients receiving concurrent chemotherapy and RT, oral mucositis may be more severe and last longer [1]. We were curious about the impact of chemotherapy on the development of ORNJ. In this study, chemotherapy was a protective factor in the univariate analysis, but it did not remain an independent factor in the multivariate analysis. This finding is consistent with the results of previous studies by Moon et al., Kuhnt et al., and Wang et al. [2, 8, 18]. Nevertheless, further study is needed to elucidate whether induction, concomitant or adjuvant chemotherapy results in different risks of ORNJ.

Diabetes mellitus

The role of DM in the development of ORNJ is controversial. Some studies revealed that DM increases the risk of ORN through impaired microcirculation and dysfunction of the red blood cells in DM patients [27]. However, other studies showed that DM does not correlate with increased risk of ORN [28]. In our study, DM was not an independent risk factor. We performed a subgroup analysis of patients according to DM (supplementary Table 1). The DM group had significantly fewer patients who underwent tooth extraction later than 6 months. Post-RT tooth extraction later than 6 months carried the highest risk of ORNJ. Therefore, the effect of DM in the univariate analysis might have been counteracted by the lower proportion of post-RT tooth extraction later than 6 months in the DM group.

Limitations

There were some limitations to this study. Several confounding variables were not coded in the NHIRD, including tumor TNM staging, smoking status [29], betel nut chewing, alcohol intake [29], dental condition [30], irradiated volume of the mandible, and oral hygiene status. As a result, we were unable to assess the effects of these factors on the development of ORNJ. Furthermore, the types of radiation delivery techniques and radiation doses are known to be significantly associated with the development of ORN [31]. However, the actual type and dose to the mandible were not available in this study. Almost 99% of the population of Taiwan is enrolled in the NHIRD, which comprehensively collects information on all types of medical visits, laboratory test codes, procedure codes, prescription codes, and diagnostic

codes. Although the validity of the NHIRD has been proven by some studies [32, 33], coding errors are possible in the NHIRD, as with all observational studies using claims data.

Conclusion

We have identified several independent risk factors of ORNJ in oral cavity cancer patients. These risk factors included certain subsites of oral cavity cancer, pre-RT mandible surgery, and tooth extraction. Furthermore, the highest risk of ORNJ was observed in cases of post-RT tooth extraction occurring later than 6 months than with other timings of tooth extraction. Tooth extraction during RT or post-RT within 6 months might not significantly increase the risk of ORNJ compared with pre-RT extraction.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The article does not have any identifying information about participants.

References

1. Sroussi HY, Epstein JB, Bensadoun RJ, Saunders DP, Lalla RV, Migliorati CA, Heaivilin N, Zumsteg ZS (2017) Common oral complications of head and neck cancer radiation therapy: mucositis, infections, saliva change, fibrosis, sensory dysfunctions, dental caries, periodontal disease, and osteoradionecrosis. Cancer Med 6(12):2918–2931. https://doi.org/10.1002/cam4.1221
2. Wang TH, Liu CJ, Chao TF, Chen TJ, Hu YW (2017) Risk factors for and the role of dental extractions in osteoradionecrosis of the jaws: a national-based cohort study. Head Neck 39(7):1313–1321. https://doi.org/10.1002/hed.24761
3. Lyons A, Ghazali N (2008) Osteoradionecrosis of the jaws: current understanding of its pathophysiology and treatment. Br J Oral Maxillofac Surg 46(8):653–660. https://doi.org/10.1016/j.bjoms.2008.04.006
4. Marx RE (1983) Osteoradionecrosis: a new concept of its pathophysiology. J Oral Maxillofac Surg 41(5):283–288. https://doi.org/10.1016/0278-2391(83)90294-x
5. London SD, Park SS, Gampper TJ, Hoard MA (1998) Hyperbaric oxygen for the management of radionecrosis of bone and cartilage. The Laryngoscope 108(9):1291–1296
6. Marx RE, Johnson RP (1987) Studies in the radiobiology of osteoradionecrosis and their clinical significance. Oral Surg Oral Med Oral Pathol 64(4):379–390
7. Thorn JJ, Hansen HS, Specht L, Bastholt L (2000) Osteoradionecrosis of the jaws: clinical characteristics and relation to the field of irradiation. J Oral Maxillofac Surg 58(10):1088–1093. https://doi.org/10.1053/joms.2000.9562 (**discussion 1093–1085**)
8. Kuhnt T, Stang A, Wienke A, Vordermark D, Schweyen R, Hey J (2016) Potential risk factors for jaw osteoradionecrosis after radiotherapy for head and neck cancer. Radiat Oncol 11:101. https://doi.org/10.1186/s13014-016-0679-6
9. Chang TS, Chang CM, Ho HC, Su YC, Chen LF, Chou P, Lee CC (2013) Impact of young age on the prognosis for oral cancer: a population-based study in Taiwan. PLoS ONE 8(9):e75855. https://doi.org/10.1371/journal.pone.0075855
10. Kuo TJ, Leung CM, Chang HS, Wu CN, Chen WL, Chen GJ, Lai YC, Huang WC (2016) Jaw osteoradionecrosis and dental extraction after head and neck radiotherapy: a nationwide population-based retrospective study in Taiwan. Oral Oncol 56:71–77. https://doi.org/10.1016/j.oraloncology.2016.03.005
11. Zhang MX, Li J, Shen GP, Zou X, Xu JJ, Jiang R, You R, Hua YJ, Sun Y, Ma J, Hong MH, Chen MY (2015) Intensity-modulated radiotherapy prolongs the survival of patients with nasopharyngeal carcinoma compared with conventional two-dimensional radiotherapy: a 10-year experience with a large cohort and long follow-up. Eur J Cancer (Oxford, England : 1990) 51(17):2587–2595. https://doi.org/10.1016/j.ejca.2015.08.006
12. OuYang PY, Shi D, Sun R, Zhu YJ, Xiao Y, Zhang LN, Zhang XH, Chen ZY, Lan XW, Tang J, Gao YH, Ma J, Deng W, Xie FY (2016) Effect of intensity-modulated radiotherapy versus two-dimensional conventional radiotherapy alone in nasopharyngeal carcinoma. Oncotarget 7(22):33408–33417. https://doi.org/10.18632/oncotarget.8573
13. Harris M (1992) The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. Br J Oral Maxillofac Surg 30(5):313–318
14. Nabil S, Samman N (2012) Risk factors for osteoradionecrosis after head and neck radiation: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol 113(1):54–69. https://doi.org/10.1016/j.tripleo.2011.07.042
15. Clayman L (1997) Clinical controversies in oral and maxillofacial surgery: part two. Management of dental extractions in irradiated jaws: a protocol without hyperbaric oxygen therapy. J Oral Maxillofac Surg 55(3):275–281
16. Jiang Y-m, Zhu X-d, Qu S (2014) Incidence of osteoradionecrosis in patients who have undergone dental extraction prior to radiotherapy: a systematic review and meta-analysis. J Oral Maxillofac Surg Med Pathol 26(3):269–275. https://doi.org/10.1016/j.ajoms.2014.03.010
17. Glanzmann C, Gratz KW (1995) Radionecrosis of the mandibula: a retrospective analysis of the incidence and risk factors. Radiother Oncol 36(2):94–100
18. Moon DH, Moon SH, Wang K, Weissler MC, Hackman TG, Zanation AM, Thorp BD, Patel SN, Zevallos JP, Marks LB, Chera BS (2017) Incidence of, and risk factors for, mandibular osteoradionecrosis in patients with oral cavity and oropharynx cancers. Oral Oncol 72:98–103. https://doi.org/10.1016/j.oraloncology.2017.07.014
19. Curi MM, Dib LL (1997) Osteoradionecrosis of the jaws: a retrospective study of the background factors and treatment in 104 cases. J Oral Maxillofac Surg 55(6):540–544 (**discussion 545–546**)

20. Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, Tucker SL, Dong L (2013) Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. Int J Radiat Oncol Biol Phys 85(2):415–420. https://doi.org/10.1016/j.ijrobp.2012.05.032
21. Chang DT, Sandow PR, Morris CG, Hollander R, Scarborough L, Amdur RJ, Mendenhall WM (2007) Do pre-irradiation dental extractions reduce the risk of osteoradionecrosis of the mandible? Head Neck 29(6):528–536. https://doi.org/10.1002/hed.20538
22. Gomez DR, Estilo CL, Wolden SL, Zelefsky MJ, Kraus DH, Wong RJ, Shaha AR, Shah JP, Mechalakos JG, Lee NY (2011) Correlation of osteoradionecrosis and dental events with dosimetric parameters in intensity-modulated radiation therapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 81(4):e207-213. https://doi.org/10.1016/j.ijrobp.2011.02.003
23. Studer G, Studer SP, Zwahlen RA, Huguenin P, Gratz KW, Lutolf UM, Glanzmann C (2006) Osteoradionecrosis of the mandible: minimized risk profile following intensity-modulated radiation therapy (IMRT). Strahlenther Onkol 182(5):283–288. https://doi.org/10.1007/s00066-006-1477-0
24. Curi MM, Cardoso CL, de Lima HG, Kowalski LP, Martins MD (2016) Histopathologic and histomorphometric analysis of irradiation injury in bone and the surrounding soft tissues of the jaws. J Oral Maxillofac Surg 74(1):190–199. https://doi.org/10.1016/j.joms.2015.07.009
25. Peng G, Wang T, Yang KY, Zhang S, Zhang T, Li Q, Han J, Wu G (2012) A prospective, randomized study comparing outcomes and toxicities of intensity-modulated radiotherapy vs. conventional two-dimensional radiotherapy for the treatment of nasopharyngeal carcinoma. Radiother Oncol 104(3):286–293. https://doi.org/10.1016/j.radonc.2012.08.013
26. Tribius S, Bergelt C (2011) Intensity-modulated radiotherapy versus conventional and 3D conformal radiotherapy in patients with head and neck cancer: is there a worthwhile quality of life gain? Cancer Treat Rev 37(7):511–519. https://doi.org/10.1016/j.ctrv.2011.01.004
27. Renda L, Tsai TY, Huang JJ, Ito R, Hsieh WC, Kao HK, Hung SY, Huang Y, Huang YC, Chang YL, Cheng MH, Chang KP (2020) A nomogram to predict osteoradionecrosis in oral cancer after marginal mandibulectomy and radiotherapy. Laryngoscope 130(1):101–107. https://doi.org/10.1002/lary.27870
28. Goldwaser BR, Chuang SK, Kaban LB, August M (2007) Risk factor assessment for the development of osteoradionecrosis. J Oral Maxillofac Surg 65(11):2311–2316. https://doi.org/10.1016/j.joms.2007.05.021
29. Huang YF, Muo CH, Tsai CH, Liu SP, Chang CT (2019) The association with xerostomia from sialadenitis and the jaw osteonecrosis in head and neck cancer population: a nationwide cohort study. Clin Oral Invest 23(2):585–593. https://doi.org/10.1007/s00784-018-2465-3
30. Manzano BR, Santaella NG, Oliveira MA, Rubira CMF, Santos P (2019) Retrospective study of osteoradionecrosis in the jaws of patients with head and neck cancer. J Korean Assoc Oral Maxillofac Surg 45(1):21–28. https://doi.org/10.5125/jkaoms.2019.45.1.21
31. Lee IJ, Koom WS, Lee CG, Kim YB, Yoo SW, Keum KC, Kim GE, Choi EC, Cha IH (2009) Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. Int J Radiat Oncol Biol Phys 75(4):1084–1091. https://doi.org/10.1016/j.ijrobp.2008.12.052
32. Cheng CL, Kao YH, Lin SJ, Lee CH, Lai ML (2011) Validation of the national health insurance research database with ischemic stroke cases in Taiwan. Pharmacoepidemiol Drug Saf 20(3):236–242. https://doi.org/10.1002/pds.2087
33. Chen TJ, Chen YC, Hwang SJ, Chou LF (2007) International collaboration of clinical medicine research in Taiwan, 1990–2004: a bibliometric analysis. J Chin Med Assoc 70(3):110–116. https://doi.org/10.1016/s1726-4901(09)70340-5