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Jaw osteoradionecrosis and dental extraction after head and neck radiotherapy: A nationwide population-based retrospective study in Taiwan

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SUMMARY

Objectives: Osteoradionecrosis of the jaws (ORNJ) is painful for patients and relatively difficult to treat clinically. The high risk of ORNJ for post radiotherapy R/T dental extraction is known; however, many patients still have to have teeth extracted after head and neck R/T. The objective of the present study is to review post R/T dental extraction and determine the ORNJ risk.

Materials and methods: We preformed a retrospective cohort study of 1759 patients with head and neck cancer s/p R/T from a random sample of 1,000,000 insurants in the National Health Insurance Research Database during 2000–2013 in Taiwan.

Statistical methods included two-proportion *Z*-test.

Results: We evaluated two cohorts: 522 patients with post R/T dental extraction and 1237 patients without post R/T extraction. Overall moderate-to-severe ORNJ after R/T was 2.22% (39/1759), and a total of 39 ORNJ cases were noted during an average of 3.02 years (range: 0.62–8.89 years, ±2.07).

ORNJ prevalence in the overall post R/T extraction-exposed cohort (5.17%, 27/522) was significantly greater than that in the unexposed cohort (0.97%, 12/1237).

In a group of patients with ⩽5 post R/T dental extractions (n = 373), the ORNJ risk was 2.4% (ORNJ case n = 9); in a group of patients with >5 dental extractions (n = 149), the ORNJ risk was 12.1% (ORNJ case n = 18) (Z-score = 4.5062; p-value < 0.0001).

In the extraction-exposed cohort, the ORNJ risk is higher if the index day to first extraction day was ⩽0.5 year (n = 103) compared with the group with the index day to first extraction day >0.5 year (n = 419) (Z-score = −2.1506; p-value = 0.0315).

Conclusion: A tooth extraction time less than half a year after R/T or during the head and neck R/T period, and extraction tooth number ⩽5 would significant lower the ORNJ prevalence.

Introduction

Head and neck radiotherapy (R/T) combined (or not combined) with chemotherapy with/without surgery is the most effective way to ease the condition of head and neck cancers [1,2]. According to Chi et al., if head and neck R/T is applied, intensity-modulated radiation therapy (IMRT) or three-dimensional conformal radiation therapy (3D-CRT) is recommended [3].

Although R/T can kill the cancer cells effectively and decrease the size of tumor [3,4], it may also cause rapid or chronic change on oral mucosa, salivary glands, taste, dentition, periodontal tissue, bone, muscle, and joints [5,6].

Any kind of head and neck R/T has its own complications. The common complications are mucositis, taste disturbance, opportunistic infections, xerostomia and salivary hypofunction, trismus, radiation caries, osteonecrosis of jaw, and progressive periodontal destruction [5]. Among these, osteoradionecrosis of the jaws

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(ORNJ), also known as osteoradionecrosis (ORN), is painful for patients and relatively difficult to treat clinically [7].

In 1983, the definition of ORN described by Marx is "exposed necrotic bone >1 cm in an area of previous irradiation that failed to heal after 6 months" [8]. Currently, the most widely accepted definition of ORN is "irradiated bone that becomes devitalized and exposed through overlying skin or mucosa without healing for more than three months, without recurrence of cancer" [9].

Some factors affect the grade of ORN, such as tumor size and location, location and dosage of R/T, types of mandible resection, traumatic history of jaw, dental extraction history, infection, immune disease, and nutrition [10].

Jawad's research in 2015 suggests avoiding post R/T dental extraction to reduce ORNJ [11]. Nabil's systematic review in 2011 found that after head and neck R/T, dental extraction results in 7% ORN [12]. The high risk of ORNJ for post R/T dental extraction is known; however, many patients still have to have teeth extracted after head and neck R/T because of unrestorable caries, poor periodontal condition, tooth fracture, odontogenic infection, etc.

The aim of the present study is to address key questions in post R/T dental extraction and ORNJ risk. For example, in post head and neck R/T, how to decrease the ORNJ risk as low as possible? When to extract teeth (how many years after R/T)? Does an increase in the number of extracted teeth increase the ORNJ risk?

Materials and methods

Data source and study cohort

The nationwide, population-based retrospective study used the database of the National Health Insurance Research Database (NHIRD) from 2000 to 2013 in Taiwan. The data of Taiwan NHIRD are generally accurate and reliable [13]. The prevalence of National Health Insurance is high, up to 99%.

During 2000–2013, 2970 adult head and neck cancer patients (aged $\geqslant$ 18 years) with head and neck R/T were identified from the random sample of 1,000,000 insurants of the NHIRD (a subset of the NHIRD).

The exclusion criteria were patients with cancer history, ORNJ history, unclear data, follow-up period less than 6 months, and the procedure codes (36012B or 36011B) <100 times in 75 days (since the day R/T began) (Fig. 1). According to the International Classification of Diseases, Ninth Revision, clinical modification (ICD-9-CM), diagnostic codes of head and neck cancer (ICD-9 140-149,161), and R/T procedure codes (36012B or 36011B) were used.

In our study, index day was the day head and neck R/T began.

Identification of ORNJ cases

After head and neck R/T, patients who had dental extraction were screened from those who had no dental extraction to create the post R/T dental extraction-exposed and unexposed cohorts. In Taiwan, we lack a code for "osteoradionecrosis of the jaws (ORNJ)" in ICD-9; the codes related to ONJ in our study were based on Yuh and Chang's definition [13], with small adjustments to the diagnosis codes. ICD-9 diagnostic codes, including inflammatory conditions, chronic osteomyelitis, non-healing surgical wounds, alveolitis, and oral aphthae (i.e., 526.4, 526.5, 528.2, 730.1, 730.10, 730.18, 998.83, 730.00, 730.08), and treatment procedure codes, including facial bone debridement, such as sequestrectomy, saucerization, resection, debridement, local excision, ostectomy, and other oral cavity operations because of previous reasons (i.e.,64005B, 92025B, 92026B, 92204B, 92205B, 92207B, 92041C, 92042C, 64104B, 64105B, 64106B, 65038B, 65039B, 83015C, 92209B, 92210B, 92211B, 92212B, 92213B, 92214B, 92215B, 59013B, 64101B, 64102B, 64108B, 64110B, 64111B). In the present study, we focused on ORNJ with moderate-to-severe symptoms, which are grades 2–4 of Tsai's classification [14].

Statistical method

Information on age, sex, systemic diseases, and with/without bisphosphonate treatment, with/without chemotherapy, post R/T tooth extraction number, and first extraction time after R/T of the examined patients were potential confounding factors for evaluating the risk of ORNJ.

PASW20 (IBM SPSS, Inc., Chicago, IL, USA) software was used for data processing and statistical analyses. To assess the potential confounding factors that might increase the risk of ORNJ, the 2-proportion Z test was used to examine the distributions of the categorical variables, including information on age, gender, systemic diseases, chemotherapy, post R/T tooth extraction number, and first extraction time after R/T. The results were judged as significant at $p < 0.05$ (see Table 1).

To further investigate the relationship between post R/T extraction tooth number and the proportion of ORNJ, a rigid line plot was processed and drawn (Fig. 2).

Results

The study population included 522 head and neck cancer patients in the post R/T extraction-exposed cohort compared with 1237 head and neck cancer patients without post R/T extraction.

In the present study, overall moderate-to-severe ORNJ after head and neck R/T was 2.22% (39/1759), and a total of 39 ORNJ cases (Tables 2 and 3) were noted during an average of 3.02 years (range: 0.62–8.89 years, ±2.07). The incidence of post-extraction ORNJ was 5.17% (27/522) during an average of 3.25 years (range: 0.62–8.89 years, ±2.24), and index day to first extraction day averaged 2.7 years (range: 0.24–7.93 years, ±1.97) (Fig. 1). The prevalence of ORNJ in the overall post R/T extraction-exposed cohort (5.17%, 27/522) was significantly greater than that in the unexposed cohort (0.97%, 12/1237). The estimated risk of ORNJ was significantly increased in the post R/T extraction-exposed cohort compared with the unexposed cohort (Z-score = 5.4661; 95% confidence interval [CIs]: ~0.0269–0.0571); $p < 0.0001$). In the post R/T non-extraction comparison cohort, 12 ORNJ cases were found, index day to ORNJ diagnosed day averaged 2.51 year (range: 0.69–5.84 years, ±1.58).

Age, gender, and systemic disease (e.g., diabetes mellitus, cerebral vascular accident, immune disease, dementia, combined chemotherapy) of the patients in the post R/T extraction-exposed cohort were not significantly different from the post R/T no-extraction cohort (Tables 4 and 5). In a group of patients with $\leqslant$5 post R/T dental extractions (n = 373), the ORNJ prevalence was 2.4% (ORNJ case n = 9); in a group of patients with >5 dental extractions (n = 149), the ORNJ prevalence was 12.1% (ORNJ case n = 18) (Z-score = 4.5062; 95% CIs: ~0.0546–0.1388; $p < 0.0001$) (Tables 4 and 5).

When we analyzed the timing for post R/T dental extraction, we found 64 patients received dental extraction within 75 days after R/T, but no ORN conditions were noted during 3.65 years (ranging from 0.54 to 13.97 years) of follow-up. In contrast, the ORN prevalence was 0.97% for patients who received R/T within a half year, and 6.21% more than a half year from the index day. In the post R/T extraction-exposed cohort group, the index day to first extraction day was $\leqslant$0.5 year (n = 103); the ORNJ prevalence is lower than the group in which the index day to first extraction day was >0.5 year (n = 419) (Z-score = −2.1506; 95% CIs: ~−0.1002 to −0.0046; p = 0.0315) (Table 5).