Chronic rhinosinusitis after radiotherapy in patients with head and neck cancer: a population-based cohort study in Taiwan

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Background: Chronic rhinosinusitis (CRS) is a common post-radiotherapy (RT) side effect in patients with nasopharyngeal cancer (NPC). However, whether RT is a risk factor for CRS in patients with other types of head and neck cancer remains unclear. This study investigated the association, if any, between CRS and RT in patients with head and neck cancer.

Methods: This retrospective cohort study included the data of patients newly diagnosed as having head and neck cancer between January 1, 2005, and December 31, 2008, from the 2005 Longitudinal Health Insurance Database. Patients were categorized into the following groups according to the treatment regimens received: RT alone (RT-alone), RT combined with other treatments (any-RT), and treatments without RT (no-RT). The outcome was the occurrence of CRS after treatment.

Results: Of the 701 patients, 7% experienced CRS within 5 years after initial treatment. Patients were divided into subgroups according to different treatment policies, and the RT-alone group, any-RT group, and no-RT group had 5-year incidence of CRS of 12%, 9.3%, and 4.5%, respectively. Patients in the RT-alone and any-RT groups exhibited an increased risk of CRS compared with patients in the no-RT group (hazard ratio: 6.76 and 2.91; 95% confidence interval: 2.60 to 17.5 and 1.60 to 5.31, respectively).

Conclusion: This is the first nationwide population-based cohort study to evaluate the risk of posttreatment CRS in patients with head and neck cancer. Our findings indicate that RT is a major risk factor for CRS. Thus, physicians should consider this potential risk in patients with head and neck cancer after RT.

Key Words:
chronic rhinosinusitis; head and neck cancer; radiotherapy; nationwide population-based cohort study; cancer; rhinosinusitis; surgery

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Chronic rhinosinusitis (CRS) is a common posttreatment side effect among patients with nasopharyngeal cancer (NPC).[1] The incidence of CRS can be up to 16.7%, as reported by single-institution research.[2] Studies have also revealed that the pathophysiology of postirradiation CRS could be attributed to radiation-induced damage to cilia and mucus-secreting cells.[3,4] However, these studies have focused on NPC only. In addition to radiotherapy (RT), chemotherapy (CT), and surgery, which are treatments commonly combined with RT, can disrupt the sinonasal cavity, and thus, cause CRS.[1] Therefore, studies have yet

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to determine whether the high CRS incidence observed in patients with head and neck cancer represents long-term treatment (particularly RT) toxicity or only reflects the increased prevalence of traditional risk factors in this population.

To address the aforementioned research gap, this nationwide cohort study investigated whether RT is the risk factor for CRS in patients with head and neck cancer.

Patients and methods

National health insurance research database

The National Health Insurance (NHI) program, established on March 1, 1995, is a universal health insurance plan that currently provides coverage for all types of health care services to more than 99% of the 23.5 million residents of Taiwan.[5,6] The National Health Insurance Research Database (NHIRD) contains comprehensive medical data, including records of registration, ambulatory and inpatient care, catastrophic illnesses, and drug prescriptions.[6,7] All patient data used in this study were obtained from the Longitudinal Health Insurance Database 2005 (LHID2005), a subset of the NHIRD. The LHID2005 contains detailed information of 1 million patients selected randomly from the 2005 Registry of Beneficiaries of the NHIRD by using a systematic sampling method; moreover, this subset contains all claims data recorded between 1996 and 2013.[8] The data in the LHID2005 exhibit an identical distribution in sex and age as those in the NHIRD, indicating that the LHID2005 is a true representation of the overall patient landscape.[9,10]

This study was approved by the Institutional Review Board of St. Martin De Porres Hospital (approval No. 17B-028). The diagnostic and procedure codes in this study were defined by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Procedure Coding System (ICD-9-PCS).

Study design and sample cohort generation

This research was designed to investigate the relationship between RT and the subsequent development of CRS in a cohort of patients with head and neck cancer. To create our cohort, patients (aged ≥20 years) diagnosed as having various types of head and neck cancer between January 1, 2005, and December 31, 2008, with the exception of sinonasal cancer, were selected from the LHID2005. Sinonasal cancer was excluded because it could directly engender anatomic destruction of sinuses and lead to a relatively high incidence of rhinosinusitis, which would confound the results. Patients who received no treatments after diagnosis were not included in our cohort. Patients previously diagnosed as having CRS (ICD-9-CM code: 473 or 471.9) and patients with preexisting head and neck cancer between 1995 and 2005 were also excluded. The patient enrollment process in this study is presented in Figure 1. All patients in this study were investigated until the end of the study period

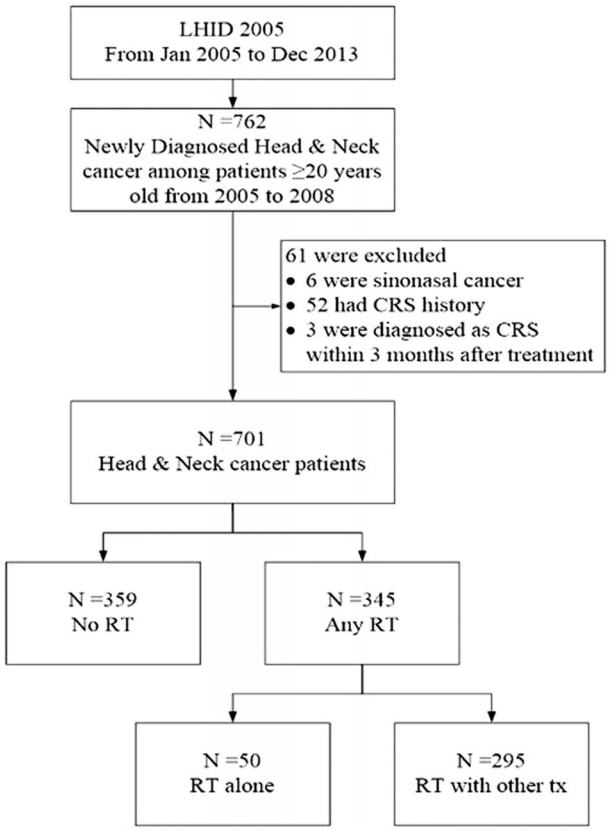

FIGURE 1. Flow diagram of identification and enrollment of the study patients. CRS = chronic rhinosinusitis; LHID = Longitudinal Health Insurance Database; RT = radiotherapy; tx = treatment.

(December 31, 2013) or their voluntary withdrawal from the NHI program before.[5,11] The diagnosed head and neck cancer was subgrouped according to the original recorded cancer sites: oral cancer (ICD-9-CM codes: 140 to 145), laryngeal cancer (ICD-9-CM code: 161), oropharyngeal cancer (OPC) (ICD-9-CM code: 146), hypopharyngeal cancer (ICD-9-CM code: 148), and NPC (ICD-9-CM code: 147).

Patients were categorized into the following groups according to the treatment regimen received: no RT (no-RT), any RT (any-RT), and RT alone (RT-alone). The any-RT group comprised patients who received RT as well as either surgical treatment or CT or both. According to these criteria, "any-RT" was defined as patients who underwent treatment with "RT alone," "surgery with RT," "surgery with CT and RT," or "CT with RT."

Outcome and covariate measurement

The primary outcome used in this study was the new diagnosis of CRS (ICD-9-CM code: 473 or 471.9), which is defined as persistent sinonasal inflammation for a period of 12 weeks or longer according to the American Rhinology Society.[12] To eliminate any preexisting conditions that would have skewed our statistics, CRS that occurred before treatment or within the first 3 months after treatment was not included. Patients who made at least 2 outpatient service claims or who were hospitalized at least once and

TABLE 1. Characteristics of subgroup with different treatment regimens (RT alone, no RT, and any RT)

Characteristics	RT alone n (%)	No RT n (%)	*p* (RT alone vs no RT)	Any RT n (%)	*p* (any RT vs no RT)
Chronic rhinosinusitis	6 (12)	16 (4.5)	0.027*	32 (9.3)	0.011*
Patient factors					
Age			0.000*		0.632
20–40 years	6 (12)	54 (15.1)		60 (17.5)	
40–60 years	19 (38)	221 (61.7)		210 (61.2)	
>60 years	25 (50)	83 (23.2)		73 (21.3)	
Sex (male)	41 (82)	322 (89.9)	0.096	303 (88.3)	0.494
Origin of head and neck cancer			0.000*		0.000*
Oral cancer	15 (30)	321 (89.1)		158 (46.1)	
Laryngeal cancer	7 (14)	12 (3.4)		20 (5.8)	
Oropharyngeal cancer	8 (16)	5 (1.4)		38 (11.1)	
Hypopharyngeal cancer	9 (18)	17 (4.7)		42 (12.2)	
Nasopharyngeal cancer	11 (22)	5 (1.4)		92 (26.8)	
Comorbidity					
DM	10 (20)	39 (10.9)	0.100	47 (13.7)	0.300
Allergic rhinitis	5 (10)	21 (5.9)	0.347	35 (10.2)	0.037*
Asthma	3 (6)	9 (2.5)	0.172	8 (2.3)	1.00

*Significant at $p < 0.05$.
DM = diabetes mellitus; RT = radiotherapy.

received a subsequent CRS diagnosis by an otolaryngologist during the designated period were defined as CRS-positive.

For patients who underwent RT, the first date of RT treatment was defined as the index date. For patients who did not undergo RT, the index date was the date of surgery or the start date of CT.

To increase the representative accuracy of our study, the following comorbid diseases were considered in this study: diabetes mellitus (DM) (ICD-9-CM code 250), asthma (ICD-9-CM codes 493), and allergic rhinitis (ICD-9-CM codes 477). To control for age-related CRS occurrence, patients were further divided into 3 age groups: (1) 20 to 40, (2) 40 to 60, and (3) >60 years.

Statistical analysis

To compare the characteristics and comorbidities of the patients in the different treatment groups (RT-alone, any-RT, and no-RT), descriptive statistics were used and variables were analyzed using the Pearson chi-squared test. The log-rank test was used to evaluate and statistically differentiate the cumulative incidence of CRS in the different groups. Hazard ratios (HRs) for CRS occurrence in each group were estimated using a Cox proportional hazards model. Potential confounding factors, including allergic rhinitis, DM, and asthma, were considered and analyzed using a Cox proportional hazards model to confirm the consistency of CRS risk. All statistical analyses were conducted using SAS 9.4 (SAS Inc., Cary, NC), and a 2-sided p value of <0.05 was considered statistically significant.

Results

Demographic characteristics

After the exclusions outlined in Figure 1, this study included the data of 701 patients with head and neck cancer, the majority of whom were men (n = 625, 89%) and aged between 40 and 60 years (n = 431, 65%). The most common tumor sites recorded in the database were the oral cavity (n = 479, 68%), nasopharynx (n = 97, 14%), and hypopharynx (n = 59, 8%). Of the patients, 7% (n = 50) belonged to the RT-alone group, 51% (n = 359) to the no-RT group, and 49% (n = 345) to the any-RT group. Moreover, 48% of the patients (n = 340) underwent CT. Among the patients in the cohort, those diagnosed as having NPC (n = 92, 94.8%) and OPC (n = 38, 88.4%) were most commonly prescribed RT. Less than 10% of the patients had received diagnoses of the comorbid diseases allergic rhinitis (n = 56, 8%) and asthma (n = 17, 2.4%), but 12% (n = 86) of the patients were diagnosed as having DM; these may be CRS risk factors.

Table 1 presents comparisons of the characteristics of the patients within the different treatment groups. The 5-year

TABLE 2. Cox proportional hazards analyses the risk of chronic rhinosinusitis between RT alone and no RT groups

Variable	HR	*p*	95% CI
Treatment			
No RT	1.00	–	–
RT alone	6.76	0.000*	2.60–17.5
Patient factors			
Age			
20–40 years	1.31	0.656	0.40–4.29
40–60 years	0.73	0.526	0.27–1.96
>60 years	1.00	–	–
Sex			
Male	1.00	–	–
Female	1.60	0.395	0.54–4.73
Origin of head and neck cancer			
Oral cancer	0.35	0.021*	0.14–0.85
Laryngeal cancer	0.90	0.906	0.12–6.59
OPC	4.19	0.054	0.98–17.97
HPC	0.05	0.522	0.00–554
NPC	6.95	0.000*	2.35–20.53
NPC and OPC	6.54	0.000*	2.56–12.72
Comorbidity			
DM	1.26	0.204	0.37–4.25
Allergic rhinitis	2.02	0.259	0.60–6.81
Asthma	5.60	0.021*	1.30–24.21

*Significant at $p < 0.05$.
CI = confidence interval; DM = diabetes mellitus; HR = hazard ratio; HPC = hypopharyngeal cancer; NPC = nasopharyngeal cancer; OPC = oropharyngeal cancer; RT = radiotherapy.

TABLE 3. Cox proportional hazards analyses the risk of chronic rhinosinusitis between any RT and no RT groups

Variable	HR	*p*	95% CI
Treatment			
No RT	1.00	–	–
Any RT	2.91	0.001*	1.60–5.31
Chemotherapy			
No chemotherapy	1.00	–	–
With chemotherapy	1.58	0.114	0.90–2.80
Patient factors			
Age			
20–40 years	2.00	0.117	0.84–4.78
40–60 years	1.05	0.908	0.47–2.32
>60 years	1.00	–	–
Sex			
Male	1.00	–	–
Female	2.09	0.032*	1.07–4.10
Origin of head and neck cancer			
Oral cancer	0.29	0.000*	0.17–0.52
Laryngeal cancer	0.09	0.888	0.22–3.72
OPC	2.48	0.055	0.98–6.28
HPC	0.05	0.230	0.00–7.14

*Significant at $p < 0.05$.
HPC = hypopharyngeal cancer; HR = hazard ratio; NPC = nasopharyngeal cancer; OPC = oropharyngeal cancer; RT = radiotherapy.

incidence rates of CRS in the RT-alone, no-RT, and any-RT groups were 12%, 4.5%, and 9.3%, respectively, revealing significant differences between the RT-alone and no-RT groups ($p = 0.027$) and between the RT-alone and any-RT groups ($p = 0.011$). A comparison of the RT-alone and no-RT groups also revealed statistically significant differences in age and cancer site. In a second comparison of the any-RT and no-RT groups, covariates such as cancer site and allergic rhinitis differed significantly.

The effects of different treatment regimens and covariates on CRS were assessed using the Cox proportional hazards model. The results are presented in Tables 2 and 3.

The results revealed a significant crude relationship between treatment regimen and CRS: the HR for CRS in patients in the RT-alone group was 6.76 times higher than that in patients in the no-RT group (HR 6.76; 95% confidence interval [CI], 2.60 to 17.5; $p < 0.001$), as presented in Table 2. After NPC, oral cancer, and asthma were controlled in the multivariate model, the adjusted cause-specific HR for CRS was 4.77 (HR 4.77; 95% CI, 1.24 to 18.3; $p = 0.023$). Figure 2 illustrates the representative cumulative incidence of CRS in the RT-alone and no-RT groups.

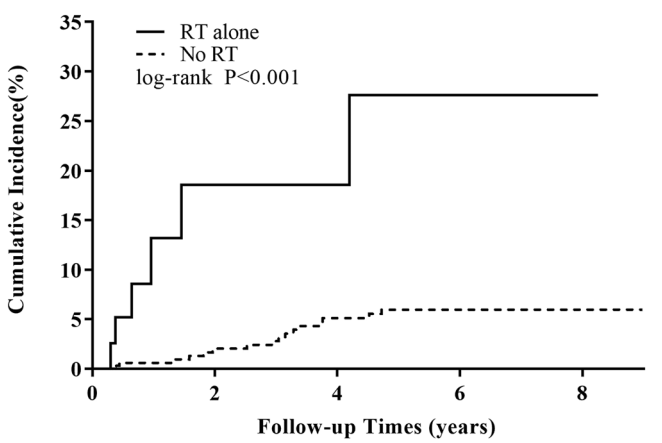

FIGURE 2. The cumulative incidence functions of chronic rhinosinusitis for RT alone and no RT. RT = radiotherapy.

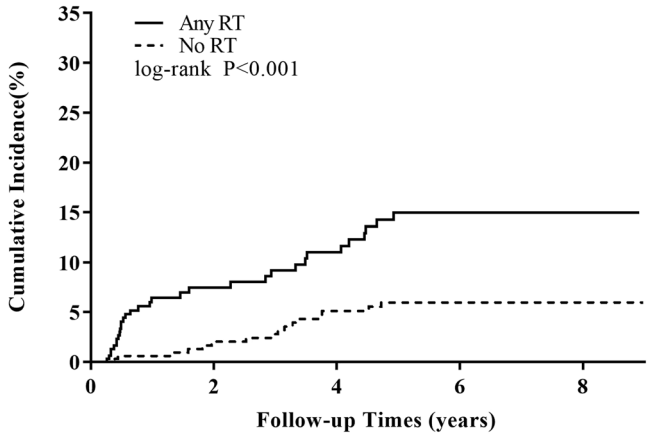

FIGURE 3. The cumulative incidence functions of chronic rhinosinusitis for any RT and no RT. RT = radiotherapy.

The any-RT and no-RT groups were compared with respect to the crude HR for CRS by using the Cox proportional hazards model, and the results are shown in Table 3. The HR for CRS in patients in the any-RT group was 2.91 times higher than that in patients in the no-RT group (HR 2.91; 95% CI, 1.60 to 5.31; $p = 0.001$). In addition, sex, oral cancer, NPC, and allergic rhinitis were identified as covariates for CRS in this model. Otherwise, 48% of patients with head and neck cancer underwent CT in this study. In order to eliminate the effects of the CT in CRS occurrence, we extracted the patients who had underwent CT and 361 patients were remained (74 in any-RT group and 287 in no-RT group). The remained patients in any-RT group also showed significant increased risk of developing CRS compared with patients in the no-RT group (HR 2.821; 95% CI, 1.098 to 7.249; $p = 0.031$). Figure 3 presents the cumulative incidence function curves for this relationship.

Because the patients with NPC (94.8%) and OPC (88.4%) more frequently underwent RT compared with the rest of the cohort, patients diagnosed as having NPC or OPC were selected and compared with patients that were not diagnosed as having NPC and OPC. Our further analyses of the RT-alone and no-RT groups revealed that the HR of the NPC or OPC patients was 6.54 times higher than that of the patients without NPC and OPC (HR 6.54; 95% CI, 2.56 to 12.7; $p < 0.001$), as presented in Table 2, suggesting that CRS risk correlated with RT, but not the specific types of cancer. Similarly, our comparison of the any-RT and no-RT groups revealed that the HR of the patients with NPC or OPC was higher than that of the patients without NPC and OPC (HR 4.69; 95% CI, 2.64 to 8.34; $p < 0.001$), as shown in Table 3.

Discussion

According to our review of the literature, this is the first study to investigate the association between RT and CRS risk in patients with head and neck cancer. Patients with NPC have a relatively high likelihood of experiencing CRS after RT treatment.[2] The 5-year incidence of postirradiation CRS reached 16.7% in a study conducted on 102 patients with NPC.[2] However, the applicability of this information is limited because these studies have mainly investigated patients with NPC and not with any other types of head and neck cancer. Methodology-wise, these previous studies have mostly collected their patients from a single medical institution that might not have been an accurate representation of the whole population landscape. Furthermore, potential confounders such as CT, allergic rhinitis, or asthma have not been properly considered or controlled. In this study, we used the NHIRD as the study database. Due to its nationwide population-based data size, which provides information of 99% of the 23.5 million residents in Taiwan,[5,6] we were able to trace nearly every patient with head and neck cancer within the designated period. In this study, we collected the data of 701 patients with various forms of head and neck cancer. The follow-up period of each patient spanned over 1532 days on average, providing us with an adequate time window to monitor the trends and observe any changes in CRS risks in the different subgroups. Because of the power of the large sample size and careful controls for confounding factors, we believe that our study provides a more accurate and reliable assessment than have previous studies.

The results obtained in this study reveal that the risk of CRS was significantly higher in the RT-alone and any-RT groups compared with the no-RT group. The 5-year cumulative incidence rates of CRS in the RT-alone, any-RT, and no-RT groups were estimated as 12%, 9.3%, and 4.5%, respectively. The HRs for CRS were 6.76 and 2.91 in the RT-alone and any-RT groups, respectively, compared with the no-RT group.

The origin of head and neck cancer is another factor associated with the risk of posttreatment CRS in Cox proportional hazards analysis. The patients with NPC had the highest incidence of CRS (HR 4.54; 95% CI, 2.56 to 8.03; $p < 0.001$), and patients with oral cancer had the lowest incidence rate of CRS (HR 0.29; 95% CI, 0.17 to 0.52; $p < 0.001$), as presented in Table 3. One of the major reasons for this finding could be the prevalence of RT in different cancer treatment policies (RT was most commonly prescribed in patients with NPC and least prescribed in patients with oral cancer). Furthermore, when we compared CRS risk in patients with NPC or OPC (who had mostly received RT) and patients without NPC and OPC (who had other types of head and neck cancer, such as oral cancer, laryngeal cancer, and hypopharyngeal cancer, in which RT was less commonly prescribed), we found that the patients with NPC or OPC had a significantly higher risk of developing CRS after initial treatment than did the patients without NPC and OPC. Our data strongly suggest that RT plays a direct role in enhancing the risk of CRS development.

The pathophysiologic mechanism of post-RT CRS could be attributed to radiation-induced damage to cilia and

mucus-secreting cell functions.[3,4] In a previous study on 32 patients with NPC, Kamel et al.[13] reported that RT resulted in a gradual but persistent delay in the saccharine response test; pre-RT saccharine test can, thus, be a predictor of post-RT rhinosinusitis. Accordingly, RT could promote ciliary motility, and the initial ciliary motility status would influence the occurrence of CRS. The dose of radiation provided to patients corresponds to the level of mucosal damage. A radiation dose of 40 Gy causes acute mucosal inflammation, whereas a radiation dose of 60 to 70 Gy causes ischemic necrosis and mucosal shedding.[4,14]

The histopathological features of CRS are different from those of post-RT CRS. Kuhar et al.[4] analyzed sinus tissues obtained from 15 patients with RT-induced CRS (CRSr), 43 patients with CRS without nasal polyps (CRSsNP), and 56 patients with CRS with nasal polyps (CRSwNP). They determined that the patients with CRSr exhibited greater squamous metaplasia and subepithelial edema compared with the patients with CRSsNP and that the patients with CRSr exhibited decreased eosinophilia and basement membrane thickening when compared with those with CRSwNP.[4]

An alternate explanation for postirradiation CRS involves the alterations in the tissue-resident microbiome. Studies have yet to be performed on the microbiota diversity within the sinus or nasopharynx to evaluate the effect of RT. Nevertheless, Xu et al.[15] examined 3 series of patients with NPC and revealed that patients with NPC who had received chemoradiotherapy exhibited changes in saliva microbiota. They also performed a principal coordinate analysis, which showed significant differences in saliva microbiota between a healthy population and patients with NPC ($p < 0.001$) as well as between pretherapy and posttherapy samples ($p < 0.001$).[15] The proportion of *Streptococcus* was lower in the NPC sample.[15] These observations suggest that microbiome diversity, in addition to RT, is a potential driver of CRS in patients with head and neck cancer.

This study has several limitations. First, the medical records and the diagnosis of CRS in the NHIRD may be not as precise as those pared and made in clinics. Second, individual patient computed tomography[14,16] or magnetic resonance[2] images, which would have served as an objective measurement for CRS diagnosis, were not available in the LHID2005 database. Third, detailed data on radiation dosage and cancer staging in each patient are not available in the database. Fourth, the study design applied a retrospective design instead of a prospective design. Accordingly, in the future, prospective clinical trials are necessary to evaluate the exact relation between RT and the risk of CRS in patients with head and neck cancer; furthermore, research is required to determine whether radiation dose or microbiome change influences CRS onset rates.

Conclusion

This is the first nationwide population-based cohort study to investigate the association between CRS and RT in patients with head and neck cancer. We revealed that the incidence of CRS was significantly higher in patients with head and neck cancer (regardless of the cancer type) who underwent RT compared with those who did not undergo RT. Thus, our study strongly demonstrates that RT is an important risk factor for CRS. According to these results, physicians should become aware of and consider this potential risk when prescribing treatments to patients with head and neck cancer.

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