Radiation-induced cancer after treatment for nasopharyngeal carcinoma: a study from a high prevalence area*

Xun Cao[1,4,#], Chao Wang[2,#], Zhuo-Chen Lin[3], Xiang Guo[1], Xing Lyu[1]

[1] Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou 510060, Guangdong, China

[2] Department of Surgical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong, China

[3] Department of Medical Records, The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, Guangdong, China

[4] Department of Critical Care Medicine, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou 510060, Guangdong, China

Rhinology 61: 1, 77 - 84, 2023

https://doi.org/10.4193/Rhin22.281

***Received for publication:**

July 15, 2022

Accepted: December 8, 2022

[#] These authors contributed equally

Abstract

Background: Radiation-induced cancer (RIC) is a late complication in patients who have been treated for nasopharyngeal carcinoma (NPC). The comparison of index anatomic location, index histological type, and survival of RIC in patients with NPC after different radiotherapy modalities (intensity-modulated radiotherapy [IMRT], 3-dimensional conformal radiotherapy [3D-CRT], and conventional 2D radiotherapy) is currently unavailable.

Methodology: A total of 38,565 patients with NPC who received curative-intent radiotherapy at Sun Yat-sen University Cancer Center between January 1986 and December 2017 were reviewed. A total of 141 patients who developed RIC and fulfilled the study criteria were included. Categorical variables were compared by the χ^2 test or Fisher's exact test. Kaplan-Meier curves were used to evaluate overall survival. Cox proportional hazards models were used to examine the independent significance of RIC treatment.

Results: Among IMRT, 3D-CRT, and conventional 2D radiotherapy, the incidence of mandible RIC was higher in patients who received 3D-CRT (0.07%) than in those who received IMRT (0%). The proportion of mandible RICs was higher in patients who received 3D-CRT (16.667%) than in those who received IMRT (0%) and conventional 2D radiotherapy (3.529%). Regarding the histological type, the incidence of squamous cell carcinoma (SCC) was higher in patients who received conventional 2D radiotherapy (0.266%) than in those who received 3D-CRT (0.175%); patients who received IMRT had a higher proportion of SCC than those who received 3D-CRT/conventional 2D radiotherapy (86.4% vs. 41.7% vs. 74.2%); the incidence of sarcoma was higher in patients who received 3D-CRT (0.175%) than in those who received IMRT (0.025%); and the proportion of sarcoma was higher in patients who received 3D-CRT (41.667%) than in those who received IMRT (6.818%) and conventional 2D radiotherapy (17.647%). Patients who received surgery for RICs had better survival than those who received no surgery (64.49 vs. 12.42 months). In the univariate and multivariate analyses, surgery was an independent prognostic factor for overall survival.

Conclusions: Our results have implications for long-term follow-up of RIC, multidisciplinary management, and patient counseling of RIC after nasopharyngeal carcinoma treatment by treating clinicians.

Key words: index anatomic location, index histological type, nasopharyngeal carcinoma, radiation-induced cancer, survival

Introduction

Long-term sequelae of nasopharyngeal carcinoma (NPC) treatment are increasingly being focused upon because of marked improvement in outcomes [1,2]. Radiation-induced cancer (RIC)

is a known late complication in patients who have been treated for NPC by radiation therapy [2,3]. Although the incidence of RIC is rare (range, 0.08%–0.3%), poor outcomes for patients with RIC have been reported in several studies [3-5]. Prevention, early detection, and treatment of RICs in patients with NPC is crucial and challenging.

As of yet, most published studies about RICs have included a mixed cohort of patients with a heterogeneity of primary cancers or with RICs occurring at a variety of locations [2,6]. Among them, the results detailing RICs in patients with NPC treated with definitive radiotherapy are limited [3]. These studies included relatively low numbers of NPC cases, inadequate numbers of anatomic locations, and limited histological types. Furthermore, the data regarding the effect of different radiotherapy modalities on the aforementioned factors are limited [3,7-9].

Here, we present a study involving a relatively large group of patients with NPC who developed RICs after curative-intent radiotherapy. We aimed to analyze and compare the index anatomic location, index histological type, and survival of patients with RICs after NPC treatment with intensity-modulated radiotherapy (IMRT), 3-dimensional conformal radiotherapy (3D-CRT), or conventional 2-dimensional (2D) radiotherapy.

Methods

Study population

From January 1986 to December 2017, 38,565 patients with NPC received curative-intent radiotherapy at Sun Yat-sen University Cancer Center. Based on the studies by Cahan et al. [10] and Arlen et al. [11], the following inclusion criteria were considered: 1) prior history of radiotherapy for NPC; 2) occurrence of cancer within the previously irradiated field; 3) histological confirmation of malignancies of the postirradiation lesion; and 4) latency period between radiotherapy for NPC and a second primary cancer of at least 3 years. Finally, the data of 141 patients with NPC who developed RIC were included in this study.

Patients were restaged based on the TNM staging system of the American Joint Committee on Cancer (7th edition, 2009).

Statistical analysis

Statistical analyses were performed using R (version 4.0.3) and SPSS (version 22.0). The data cutoff date for this analysis was December 31, 2019. Categorical variables were compared by means of the χ^2 test, adjusted χ^2 test, or Fisher's exact test. Kaplan-Meier curves were used to evaluate overall survival (OS, time period between the date of RIC diagnosis and the date of either death or last follow-up, whichever occurred first), and the group differences were compared by log-rank tests. Univariable and multivariable Cox proportional hazards models were used to examine the independent significance of RIC treatment, adjusting for other factors. P values <0.05 were considered statistically significant. The authenticity of this study has been validated by uploading the key raw data onto the Research Data Deposit public platform (www.researchdata.org.cn), with the approval RDD number RDDA2021583427.

Results

From January 1986 to December 2017, 38,565 patients with NPC received curative-intent radiotherapy, and 141 patients developed RICs. We estimated that the incidence of RICs in patients with NPC after receiving curative-intent radiotherapy was approximately 0.365%. Table 1 displays the clinical characteristics and treatment modalities of the cohort.

Compared with patients who received conventional 2D radiotherapy, those who received 3D-CRT were more likely to have RICs in the maxillary sinus (0.059% vs. 0.07%), hard palate (0.034% vs. 0.035%), mandible (0.013% vs. 0.07%), oropharynx (0.008% vs. 0.035%), maxilla (0.017% vs. 0.035%), and zygoma (0% vs. 0.035%); those who underwent 3D-CRT had a higher incidence of sarcoma (0.175% vs. 0.063%), carcinoma in situ (0.035% vs. 0.008%), and mucoepidermoid carcinoma (0.035% vs. 0.004%) than those who underwent conventional 2D radiotherapy; however, the patients who underwent conventional 2D radiotherapy had a higher incidence of squamous cell carcinoma (0.266% vs. 0.175%; P=0.041). Patients who received IMRT had a higher incidence of RICs in the tongue (0.208% vs. 0.105%), oral cavity (0.017% vs. 0%), soft palate (0.008% vs. 0%), and parotid gland (0.017% vs. 0%) than those who received 3D-CRT; the patients who underwent 3D-CRT had a higher incidence of RICs in the mandible (0.07% vs. 0%; P=0.037). The incidence of RICs, including squamous cell carcinoma (SCC) (0.175% vs. 0.315%), lymphoepithelioma-like carcinoma (LELC) (0% vs. 0.008%), and adenoid cystic carcinoma (ACC) (0% vs. 0.008%), was also higher in patients who received IMRT; the patients who underwent conventional 3D-CRT had a higher incidence of sarcoma (0.175% vs. 0.025%; P=0.002) (Table 2; Figures S1-S2).

Among the three subgroups, the most common anatomic location of RICs was the tongue. Notably, the proportion of RICs of the tongue was markedly higher in patients who received IMRT (56.8%) than in those who received conventional 2D radiotherapy (40%) and 3D-CRT (25%); the proportion of mandible RICs was higher in patients who received 3D-CRT (16.67%) than in those who received conventional 2D radiotherapy (3.529%) and received IMRT (0%) (P=0.04). Regarding the histological type, SCC was the most common RIC, followed by sarcoma. Patients who received IMRT had a higher proportion of SCC (86.364% vs. 41.667% vs. 74.118%; P=0.007) but a lower proportion of sarcoma than those who received 3D-CRT/conventional 2D radiotherapy (6.8% vs. 41.667% vs. 17.647%; P=0.017) (Table 2; Figure S3-S4). Further analyses to determine the differences between the three subgroups showed that SCC was predominant in almost all locations among patients who received conventional 2D radiotherapy and IMRT, especially for IMRT; however, SCC

Table 1. Patient characteristics of the study cohort.

Characteristic	No. of patients (n=141)	(%)
Sex		
Male	108	(76.6%)
Female	33	(23.4%)
Age at diagnosis of nasopharyngeal carcinoma, median (IQR), years		
	43 (37-50)	
Histologic type of nasopharyngeal carcinoma		
WHO type II	5	(3.5%)
WHO type III	136	(96.5%)
Stage of nasopharyngeal carcinoma		
I/II	43	(30.5%)
III/IV	98	(69.5%)
Radiation technique		
Conventional 2D radiotherapy	85	(60.3%)
3D-CRT	12	(8.5%)
IMRT	44	(31.2%)
Treatment of nasopharyngeal carcinoma		
Radiation alone	90	(63.8%)
Radiation plus chemotherapy	51	(36.2%)
Location of radiation-induced cancer		
Tongue	62	(44%)
Maxillary sinus	21	(14.9%)
Gingiva	17	(12.1%)
Hard palate	12	(8.5%)
Oropharynx	6	(4.3%)
Mandible	5	(3.5%)
Oral cavity	5	(3.5%)
Maxilla	5	(3.5%)
Parotid gland	4	(2.8%)
Soft palate	3	(2.1%)
Zygoma	1	(0.7%)
Histologic type of radiation-induced cancer		
Squamous cell carcinoma	106	(75.2%)
Sarcoma	23	(16.3)
Osteosarcoma	10	(7.1%)
Fibrosarcoma	7	(5%)
Undifferentiated pleomorphic sarcoma	3	(2.1%)
Chondrosarcoma	2	(1.4%)
Osteosarcoma/fibrosarcoma	1	(0.7%)
Carcinoma in situ	4	(2.8%)
Adenocarcinoma	2	(1.4%)
Mucoepidermoid carcinoma	2	(1.4%)
Myofibroblastoma	2	(1.4%)
Lymphoepithelioma-like carcinoma	1	(0.7%)
Adenoid cystic carcinoma	1	(0.7%)
Treatment of radiation-induced cancer		
Surgery alone	80	(56.7%)
Surgery and chemotherapy	21	(14.9%)
Chemotherapy alone	16	(11.3%)
Radiotherapy and chemotherapy	11	(7.8%)
Surgery and radiotherapy	8	(5.7%)
Surgery, chemotherapy and radiotherapy	3	(2.1%)
Radiotherapy alone	1	(0.7%)
Supportive care *	1	(0.7%)

* The patient rejected treatment.

Abbreviations: IQR = interquartile range; WHO = World Health Organization; Conventional 2D radiotherapy = conventional 2-dimensional radiotherapy; 3D-CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy.

and sarcoma were almost balanced in patients who underwent 3D-CRT and IMRT (Table 3; Figures S5-S7).

The median latency between radiotherapy initiation for NPC and diagnosis of RICs was 97.9 months (interquartile range [IQR], 48.0–142.3). The median RIC latency period was 122.2 months (IQR, 66.0–163.0) in patients who received conventional 2D radiotherapy versus 95.8 months (IQR, 60.6–144.6) in patients who received 3D-CRT versus 48.8 months (IQR, 41.8–92.8) in patients who received IMRT (P<0.0001). The RIC latency was shorter for patients who received radiation plus chemotherapy than for those who received radiotherapy alone (54.4 months [IQR, 42.3–106.8] vs. 118.0 months [IQR, 58.3–159.7], P<0.0001). The median follow-up time after diagnosis of RICs was 22.5 months (IQR, 9.3–56.6). Of the 141 patients who received curative-intent treatment for RICs, 87 (61.7%) developed locoregional recurrence and/or distant metastasis. The 5-year OS rate for the whole cohort was 33.0%, and the median OS was 33.5 months (95% CI, 21.2–46.8) (Figure 1A). Those who received surgery-based treatments had better survival outcomes than patients who received no surgery (64.49 months [95% CI, 23.84–105.15] vs. 12.42 months [95% CI, 4.26–20.58]) (P<0.0001); 5-year OS was 43% in the surgery-based group and 4% in the no surgery group (Figure 1B). In the univariate analyses, surgery and chemotherapy were prognostic factors for overall survival. In multivariate analyses by prognostic factor, surgery was the only independent prognostic factor for overall survival (P<0.0001) (Table 4).

Table 2. Comparison for incidence, proportion of radiation-induced cancers among patients who received conventional 2D radiotherapy, 3D-CRT, and IMRT according to index anatomic location, and index histological type.

	Conventional 2D radio therapy (n=23656)			3D-CRT (n=2864)			IMRT (n=12045)					
	No.	Incidence	Pro-portion	No.	Incidence	Pro-portion	No.	Incidence	Pro-portion	P-value*	P-value†	P-value‡
Anatomic location												
All types	85	(0.359%)		12	(0.419%)		44	(0.365%)		0.617[a]	0.673[a]	-
Tongue	34	(0.144%)	(40%)	3	(0.105%)	(25%)	25	(0.208%)	(56.818%)	0.598[a]	0.253[a]	0.073[a]
Maxillary sinus	14	(0.059%)	(16.471%)	2	(0.07%)	(16.667%)	5	(0.0415%)	(11.364%)	0.826[a]	0.529[a]	0.730[a]
Gingiva	13	(0.055%)	(15.294%)	1	(0.035%)	(8.333%)	3	(0.0249%)	(6.818%)	0.659[a]	0.574[b]	0.344[a]
Hard palate	8	(0.034%)	(9.412%)	1	(0.035%)	(8.333%)	3	(0.0249%)	(6.818%)	1.000[b]	0.574[b]	0.899[b]
Mandible	3	(0.013%)	(3.529%)	2	(0.07%)	(16.667%)	0	(0%)	(0%)	0.093[b]	**0.037[b]**	**0.040[b]**
Oral cavity	3	(0.013%)	(3.529%)	0	(0%)	(0%)	2	(0.0166%)	(4.545%)	1.000[b]	1.000[b]	1.000[b]
Oropharynx	2	(0.008%)	(2.353%)	1	(0.035%)	(8.333%)	3	(0.0249%)	(6.818%)	0.290[b]	0.574[b]	0.300[b]
Soft palate	2	(0.008%)	(2.353%)	0	(0%)	(0%)	1	(0.008%)	(2.273%)	1.000[b]	1.000[b]	1.000[b]
Parotid gland	2	(0.008%)	(2.353%)	0	(0%)	(0%)	2	(0.017%)	(4.545%)	1.000[b]	1.000[b]	0.725[b]
Maxilla	4	(0.017%)	(4.706%)	1	(0.035%)	(8.333%)	0	(0%)	(0%)	0.435[b]	0.192[b]	0.178[b]
Zygoma	0	(0%)	(0%)	1	(0.035%)	(8.333%)	0	(0%)	(0%)	0.108[b]	0.192[b]	0.085[b]
Histological type												
All types	85	(0.359%)		12	(0.419%)		44	(0.365%)		0.359[a]	0.673[a]	-
Squamous cell carcinoma	63	(0.266%)	(74.118%)	5	(0.175%)	(41.667%)	38	(0.315%)	(86.364%)	**0.041[a]**	0.206[a]	**0.007[b]**
Sarcoma	15	(0.063%)	(17.647%)	5	(0.175%)	(41.667%)	3	(0.025%)	(6.818%)	0.290[b]	**0.002[a]**	**0.017[b]**
Carcinoma in situ	2	(0.008%)	(2.354%)	1	(0.035%)	(8.333%)	1	(0.008%)	(2.273%)	1.000[b]	0.347[b]	0.382[b]
Adenocarcinoma	2	(0.008%)	(2.354%)	0	(0%)	(0%)	0	(0%)	(0%)	0.204[b]	1.000[b]	0.621[b]
Mucoepidermoid carcinoma	1	(0.004%)	(1.176%)	1	(0.035%)	(8.333%)	0	(0%)	(0%)	1.000[b]	0.192[b]	0.259[b]
Myofibroblastoma	2	(0.008%)	(2.354%)	0	(0%)	(0%)	0	(0%)	(0%)	1.000[b]	1.000[b]	0.621[b]
Lymphoepithelio-ma-like carcinoma	0	(0%)	(0%)	0	(0%)	(0%)	1	(0.008%)	(2.273%)	1.000[b]	1.000[b]	0.397[b]
Adenoid cystic carcinoma	0	(0%)	(0%)	0	(0%)	(0%)	1	(0.008%)	(2.273%)	0.359[b]	1.000[b]	0.397[b]

* Comparison for incidence of radiation-induced cancer between patients received conventional 2D radiotherapy and those received 3D-CRT. † Comparison for incidence of radiation-induced cancer between patients received 3D-CRT and those received IMRT. ‡ Comparison for proportion of radiation-induced cancer among patients received conventional 2D radiotherapy, those received 3D-CRT, and those received IMRT. [a] P-values were calculated with χ^2 test. [b] P-values were calculated with Fisher's exact test.

Abbreviations: Conventional 2D radiotherapy = conventional 2-dimensional radiotherapy; 3D-CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy.

Discussion

There are advantages to administering 3D-CRT/IMRT for the treatment of NPC; nevertheless, for reasons referred to in the study by Hall and colleagues [12], an increase in the incidence of RICs has been observed [2]. In this investigation, we first analyzed the incidence and proportion of RICs, including rare histological type (e.g., LELC and ACC) and rare anatomic location (e.g., zygoma and salivary gland). More importantly, our study highlighted the differences in index anatomic location and index histological type of RICs in patients after they received IMRT, 3D-CRT, or conventional 2D radiotherapy for NPC.

Over time, radiation techniques have progressed from conventional 2D radiotherapy to 3D-CRT and then to IMRT. Currently, IMRT is the most widely used technique. Locoregional control and survival have improved, and toxicity has been reduced [1,13-16]. In a meta-analysis reviewing 3,570 participants, IMRT was significantly associated with better 5-year locoregional control (odds ratio [OR], 1.94 [95% CI, 1.53–2.46]) and overall survival

Table 3. The distribution of index histological type of radiation-induced cancer in patients who received conventional 2D radiotherapy, 3D-CRT, and IMRT according to index anatomic location.

		Conventional 2D radiotherapy		3D-CRT		IMRT	
Anatomic location	**Histological type**	**No.**	**Distribution**	**No.**	**Distribution**	**No.**	**Distribution**
Tongue	All (n=62)	n=34		n=3		n=25	
	Squamous cell carcinoma	32	(94.1%)	2	(66.7%)	24	(96%)
	Carcinoma in situ	1	(2.9%)	1	(33.3%)	1	(4%)
	Adenocarcinoma	1	(2.9%)	-	-	-	-
Maxillary sinus	All (n=21)	n=14		n=2		n=5	
	Squamous cell carcinoma	7	(50%)	1	(50%)	3	(60%)
	Sarcoma	5	(35.7%)	1	(50%)	2	(40%)
	Myofibroblastoma	2	(14.3%)	-	-	-	-
Gingiva	All (n=17)	n=13		n=1		n=3	
	Squamous cell carcinoma	12	(92.3%)	1	(100%)	2	(66.7%)
	Sarcoma	1	(7.7%)	-	-	1	(33.3%)
	Carcinoma in situ	-	-	-	-	-	-
Hard palate	All (n=12)	n=8		n=1		n=3	
	Squamous cell carcinoma	6	(75%)	-	-	3	(100%)
	Sarcoma	1	(12.5%)	1	(100%)	-	-
	Carcinoma in situ	1	(12.5%)	-	-	-	-
Mandible	All (n=5)	n=3		n=2		-	
	Sarcoma	3	(100%)	2	(100%)	-	-
Oral cavity	All (n=5)	n=3		-		n=2	
	Squamous cell carcinoma	2	(66.7%)	-	-	2	(100%)
	Sarcoma	1	(33.3%)	-	-	-	-
Oropharynx	All (n=6)	n=2		n=1		n=3	
	Squamous cell carcinoma	2	(100%)	-	-	3	(100%)
	Mucoepidermoid carcinoma	-	-	1	(100%)	-	-
Soft palate	All (n=3)	n=2		-		n=1	
	Squamous cell carcinoma	1	(50%)	-	-	1	(100%)
	Sarcoma	1	(50%)	-	-	-	-
Parotid gland	All (n=4)	n=2		-		n=2	
	Mucoepidermoid carcinoma	1	(50%)	-	-	-	-
	Adenocarcinoma	1	(50%)	-	-	-	-
	Lymphoepithelioma-like carcinoma	-	-	-	-	1	(50%)
	Adenoid cystic carcinoma	-	-	-	-	1	(50%)
Maxilla	All (n=5)	n=4		n=1		-	
	Squamous cell carcinoma	1	(25%)	-	-	-	-
	Sarcoma	3	(75%)	1	(100%)	-	-
Zygoma	All (n=1)	-		n=1		-	
	Squamous cell carcinoma	-	-	1	(100%)	-	-

Abbreviation: 3D-CRT = 3-dimensional conformal radiotherapy; IMRT = intensity-modulated radiotherapy.

(OR, 1.51 [95% CI, 1.23–1.87]) than conventional 2D radiotherapy or 3D-CRT (13). In contrast, this transition has led to an increased incidence of RIC because of the exposure of a larger volume of normal tissue to low doses of radiation and a rise in the number

Table 4. Summary of univariable and multivariable analyses of prognostic factors.

	Univariable analyses		Multivariable analyses	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Overall survival				
Sex *	1.328 (0.766-2.304)	0.312	-	-
Age at diagnosis of RIC †	1.009 (0.985-1.034)	0.460	-	-
Smoking status ‡	1.324 (0.826-2.120)	0.243	-	-
Alcohol intake §	1.016 (0.967-1.068)	0.518	-	-
Medical history ¦	0.652 (0.159-2.668)	0.552	-	-
Surgery ¶	0.266 (0.163-0.463)	**<0.0001**	0.228 (0.111-0.470)	**<0.0001**
Chemotherapy **	1.887 (1.189-2.997)	**0.007**	0.817 (0.411-1.625)	0.565
Radiotherapy ††	1.360 (0.756-2.444)	0.304	-	-

P-values were calculated with an adjusted Cox proportional-hazards model. All hazard ratios are adjusted for other covariates. * Male vs female. † Age per year increase. ‡ Yes vs no. § Yes vs no. ¦ Yes vs no. ¶ Surgery vs no surgery. ** Chemotherapy vs no chemotherapy. †† Radiotherapy vs no radiotherapy. Abbreviations: RIC = radiation-induced cancer; HR = hazard ratio; 95% CI = 95% confidence interval.

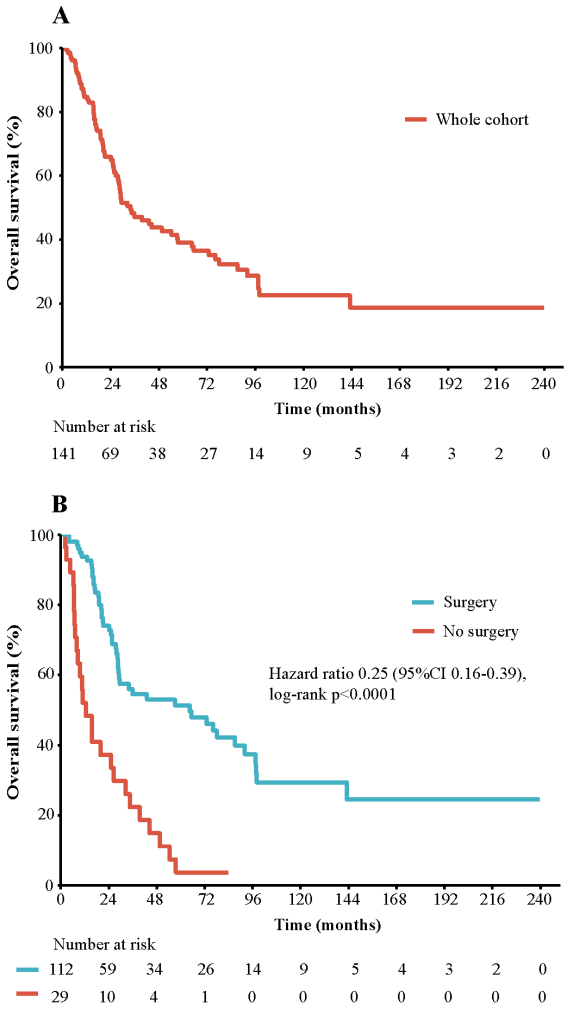

Figure 1. Kaplan- Meier analysis for (A) overall survival in the whole cohort and (B) in the patients with different treatments (surgery vs. no surgery) .

of monitor units by a factor of 2 to 3 [12]. Our results are inconsistent with those of previous studies [4]. There is likely one reason that can explain the lower incidence of RICs in patients treated with IMRT and/or 3D-CRT. The median latency period of RICs ranges from 7.6 to 22 years [3,17-19]. The shorter follow-up time for many patients who received 3D-CRT/IMRT, relative to conventional 2D radiotherapy, might have led to an underestimation of the incidence of RICs. In addition, our estimated incidence may be lower than the actual incidence because some patients did not return for follow-up, or some may have died before the presentation of RICs.

Our results are in line with previous studies suggesting that the radiation technique may be associated with the histologic type of RIC [5,6,12,20]. 3D-CRT is correlated with the development of sarcoma [3,12], while IMRT is believed to be associated with nonsarcoma malignancies (e.g., SCC) [5,20]. RICs after treatment for nasopharyngeal carcinoma are uncommon. In this study, we analyzed a series of rare histological types, including LELC and ACC, which were first reported as RICs. In addition, our estimated incidence of RIC was comparable to that reported by Liu et al. [5]. SCC is the most frequent histologic type of RIC [21]. For example, Liu et al. reported that the incidence rate of radiation-induced squamous cell carcinoma was 0.21% [5], and this finding was substantiated by our study (0.27%). Further studies will be needed to definitely determine whether radiation is related to this histological type.

In a study by Xi et al., latency did differ between the patients who received different radiation techniques [3]. Liu et al. found that the latency was significantly shorter for patients who underwent IMRT than for patients who underwent conventional 2D radiotherapy [5]. In our study, there was a shorter latency

interval in patients who received IMRT than in those who received conventional 2D radiotherapy and 3D-CRT, supporting a correlation between radiotherapy modality and latency [22]. In addition, our study suggested that the administration of chemotherapy shortens the interval between radiotherapy for NPC and the subsequent presentation of RICs. Previous studies have produced evidence that chemotherapy has an impact on the timing of RICs [23-25].

Regarding the prognoses of RIC, a study performed by Liu et al. found that the 5-year OS rate for patients with radiation-induced squamous cell carcinoma was 35.2% [5], which was consistent with that of 33% in the present study. The survival of patients with RICs is related to histological type, anatomic tumor location, and treatment modality. Surgery is the widely accepted modality for most RICs [3]. Liu et al. reported a 5-year OS rate of 47.1% for patients who received surgery [5]. We also found a relatively good 5-year OS rate of 44% for patients who underwent surgical resection. The higher 5-year OS rate in both studies indicated that the prognoses of patients with RIC after surgical resection were better. Anatomic location can limit a surgeon's ability to achieve complete resection of RICs with negative margins. However, complete resection with negative margins seems to offer the best chance for long-term survival [3]. In our study, the multivariate analysis revealed that surgery-based multidisciplinary treatment was the only independent predictive factor for better survival, a finding that is consistent with Liu et al.'s report.

Limitations of the study: 1) the differences in several incidences and proportions of RICs among the three subgroups appeared not to be statistically significant. This negative finding may be related to small absolute numbers of RICs; this is a common finding in studies of rare disease; 2) compared with patients receiving conventional 2D radiotherapy, those receiving 3D-CRT and IMRT had a shorter follow-up time, which might have resulted in an underestimation of the occurrence of RICs; 3) compared with previous studies, the increased number of anatomic sites and histological types of patients with RICs in our study may introduce the possibility of bias (e.g., the eligible patients were included until December 2017 with a median latency of RIC of approximately 9 years, and the inclusion/comparison with modern radiation techniques may be prone to bias); 4) the data used in this retrospective analysis, which were obtained from a single institution in Guangdong, southern China, where NPC is endemic, are limited when considering the applicability of these results outside of east and southeast Asia, where NPC is relatively rare. Hence, future research involving multicenter data and longer follow-up times is needed.

Conclusions

To the best of our knowledge, this is the first investigation demonstrating and comparing the incidence, proportion, and distribution of RICs in patients with NPC after IMRT, 3D-CRT, and conventional 2D radiotherapy. Our study results have implications for careful and long-term follow-up for the detection of RICs as well as multidisciplinary counseling and management of patients with RICs after NPC treatments.

Acknowledgements

The paper has been edited by American Journal Experts (verification code E584-664B-E7D8-37B7-B7D5).

Authorship contribution

All authors contributed to the conception of the study and interpretation of the data. XC, CW, ZCL contributed to the clinical data acquired and statistical analyses. The paper was drafted by XC, XG and XL. All authors have read and revised the paper and approved the final version. All authors had full access to all the data in the study, and the corresponding author had final responsibility for the decision to submit for publication.

Conflicts of interest

The authors declare that they have no competing interests.

Funding

This study was supported by grants from the National Natural Science Foundation of China (No. 81872375, No. 82172863), the Natural Science Foundation of Guangdong Province (No. 2021A1515010118), and the Science and Technology Planning Project Foundation of Guangdong Province (No. 2019B110233004).

References

1. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y, Ma J. Nasopharyngeal carcinoma. Lancet 2019; 394: 64-80.
2. Giannini L, Incandela F, Fiore M, et al. Radiation-Induced Sarcoma of the Head and Neck: A Review of the Literature. Front Oncol 2018; 8: 449.
3. Xi M, Liu MZ, Wang HX, et al. Radiation-induced sarcoma in patients with nasopharyngeal carcinoma: a single-institution study. Cancer 2010; 116: 5479-5486.
4. Taghian A, de Vathaire F, Terrier P, et al. Long-term risk of sarcoma following radiation treatment for breast cancer. Int J Radiat Oncol Biol Phys 1991; 21: 361-367.
5. Liu C, Liao L, Wu G, et al. Radiation-induced second primary squamous cell carcinoma of the oral cavity after radiotherapy for nasopharyngeal carcinoma. Oral Oncol 2020; 109: 104863.
6. Ng SP, Pollard C, 3rd, Kamal M, et al. Risk of second primary malignancies in head and neck cancer patients treated with definitive radiotherapy. NPJ Precis Oncol 2019; 3: 22.
7. Zhang LL, Li GH, Li YY, Qi ZY, Lin AH, Sun Y. Risk Assessment of Secondary Primary Malignancies in Nasopharyngeal Carcinoma: A Big-Data Intelligence Platform-Based Analysis of 6,377 Long-term Survivors from an Endemic Area Treated with Intensity-Modulated Radiation Therapy during 2003-2013. Cancer Res Treat 2019; 51: 982-991.
8. Goggins WB, Yu IT, Tse LA, Leung SF, Tung SY, Yu KS. Risk of second primary malignan-

cies following nasopharyngeal carcinoma in Hong Kong. Cancer Causes Control 2010; 21: 1461-1466.
9. Lin C, Lin SW, Weng SF, Lin YS. Risk of second primary malignancies after nasopharyngeal carcinoma: a population-based cohort study in Taiwan. Head Neck 2014; 36: 209-214.
10. Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL. Sarcoma arising in irradiated bone: report of eleven cases. 1948. Cancer 1998; 82: 8-34.
11. Arlen M, Higinbotham NL, Huvos AG, Marcove RC, Miller T, Shah IC. Radiation-induced sarcoma of bone. Cancer 1971; 28: 1087-1099.
12. Hall EJ, Wuu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys 2003; 56: 83-88.
13. Zhang B, Mo Z, Du W, Wang Y, Liu L, Wei Y. Intensity-modulated radiation therapy versus 2D-RT or 3D-CRT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. Oral Oncol 2015; 51: 1041-1046.
14. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys 2006; 66: 981-991.
15. Peng G, Wang T, Yang KY, et al. 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 2012; 104: 286-293.
16. Co J, Mejia MB, Dizon JM. Evidence on effectiveness of intensity-modulated radiotherapy versus 2-dimensional radiotherapy in the treatment of nasopharyngeal carcinoma: Meta-analysis and a systematic review of the literature. Head Neck 2016; 38 Suppl 1: E2130-2142.
17. Cha C, Antonescu CR, Quan ML, Maru S, Brennan MF. Long-term results with resection of radiation-induced soft tissue sarcomas. Ann Surg 2004; 239: 903-909; discussion 909-910.
18. Beaty O, 3rd, Hudson MM, Greenwald C, et al. Subsequent malignancies in children and adolescents after treatment for Hodgkin's disease. J Clin Oncol 1995; 13: 603-609.
19. Sale KA, Wallace DI, Girod DA, Tsue TT. Radiation-induced malignancy of the head and neck. Otolaryngol Head Neck Surg 2004; 131: 643-645.
20. Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys 2006; 65: 1-7.
21. Patel SG, See AC, Williamson PA, Archer DJ, Evans PH. Radiation induced sarcoma of the head and neck. Head Neck 1999; 21: 346-354.
22. Wiklund TA, Blomqvist CP, Raty J, Elomaa I, Rissanen P, Miettinen M. Postirradiation sarcoma. Analysis of a nationwide cancer registry material. Cancer 1991; 68: 524-531.
23. Cancer: Principles and practice of oncology. Philadelphia: Pennsylvania: Lippincott-Raven. 1997.
24. van Halteren HK, Taal BG, van Tinteren H, van Leeuwen FE. Risk factors for the development of oesophageal cancer as a second primary tumour. Eur J Cancer 1995; 31A: 1836-1839.
25. Tobias JS, Monson K, Gupta N, et al. Chemoradiotherapy for locally advanced head and neck cancer: 10-year follow-up of the UK Head and Neck (UKHAN1) trial. Lancet Oncol 2010; 11: 66-74.

Dr. Xing Lyu
Department of Nasopharyngeal Carcinoma
Sun Yat-sen University Cancer Center
State Key Laboratory of Oncology in South China
Collaborative Innovation Centre for Cancer Medicine
Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy
No. 651 Dongfeng Road East
Guangzhou 510060
Guangdong
China

Tel: +86-20-87343359
E-mail: lvxing@sysucc.org.cn

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

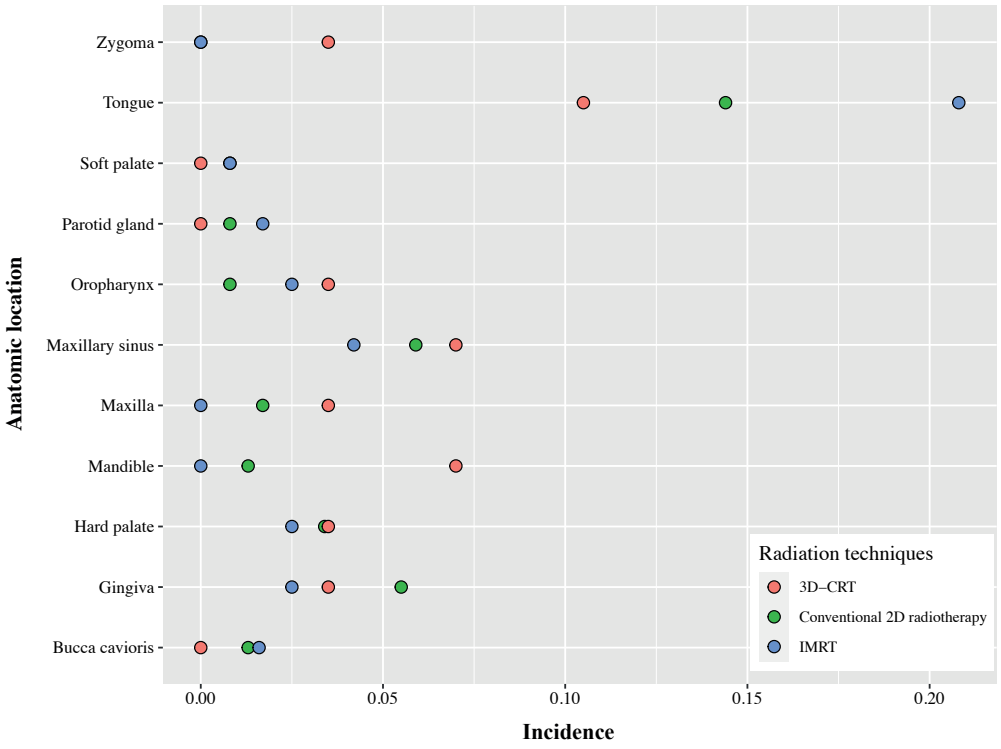

Figure S1. The incidence of radiation-induced cancers among patients who received IMRT, 3D-CRT, and conventional 2D radiotherapy according to index anatomic location. Abbreviations: IMRT = intensity-modulated radiotherapy; 3D-CRT = 3-dimensional conformal radiotherapy; Conventional 2D radiotherapy = conventional 2-dimensional radiotherapy.

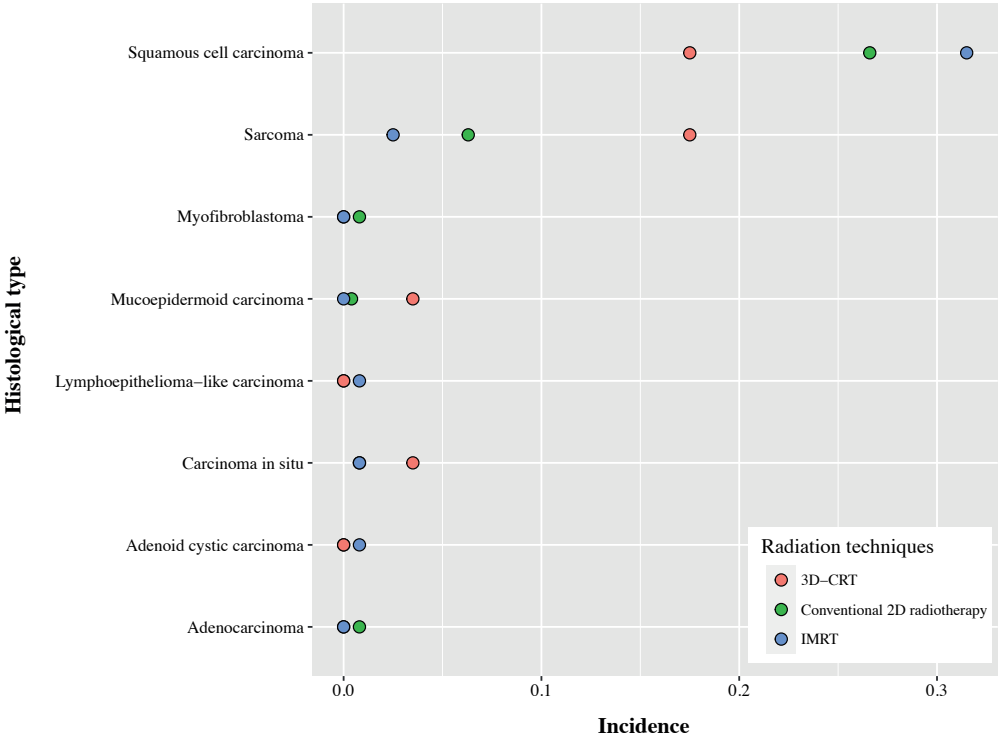

Figure S2. The incidence of radiation-induced cancers among patients who received IMRT, 3D-CRT, and conventional 2D radiotherapy according to index histological type. Abbreviations: IMRT = intensity-modulated radiotherapy; 3D-CRT = 3-dimensional conformal radiotherapy; Conventional 2D radiotherapy = conventional 2-dimensional radiotherapy.

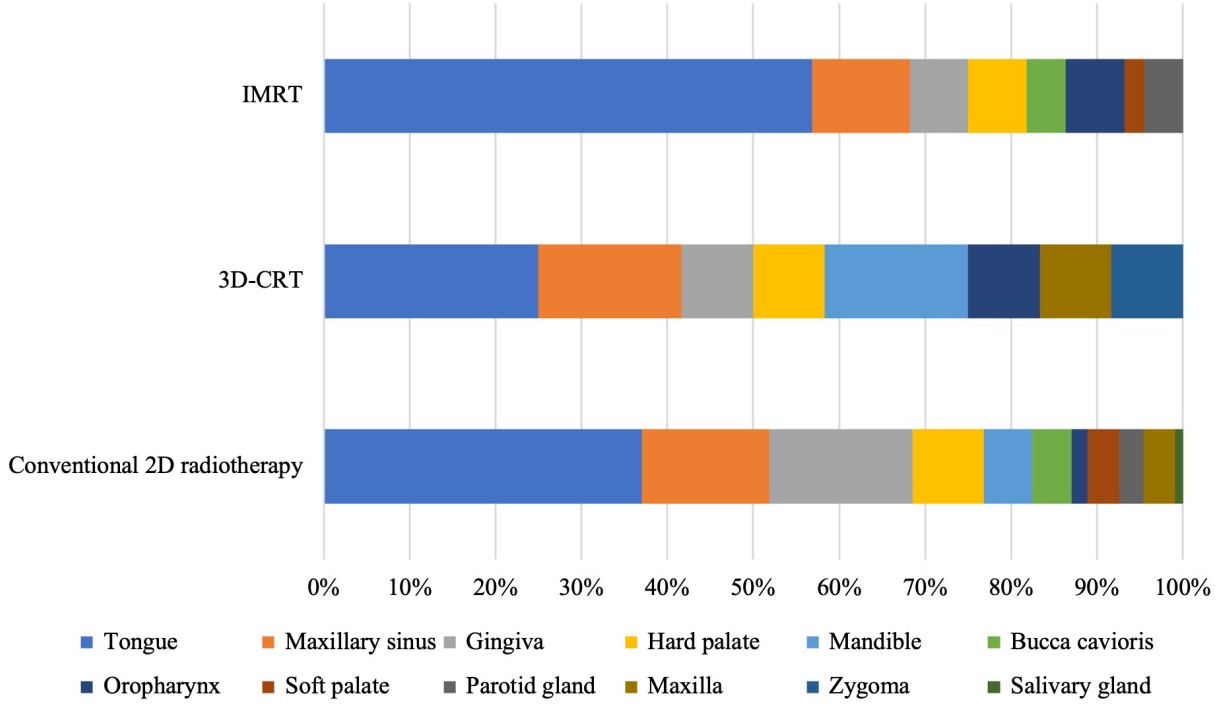

Figure S3. The proportion of index anatomic location of radiation-induced cancers according to patients who received IMRT, 3D-CRT, and conventional 2D radiotherapy. Abbreviations: IMRT = intensity-modulated radiotherapy; 3D-CRT = 3-dimensional conformal radiotherapy; Conventional 2D radiotherapy = conventional 2-dimensional radiotherapy.

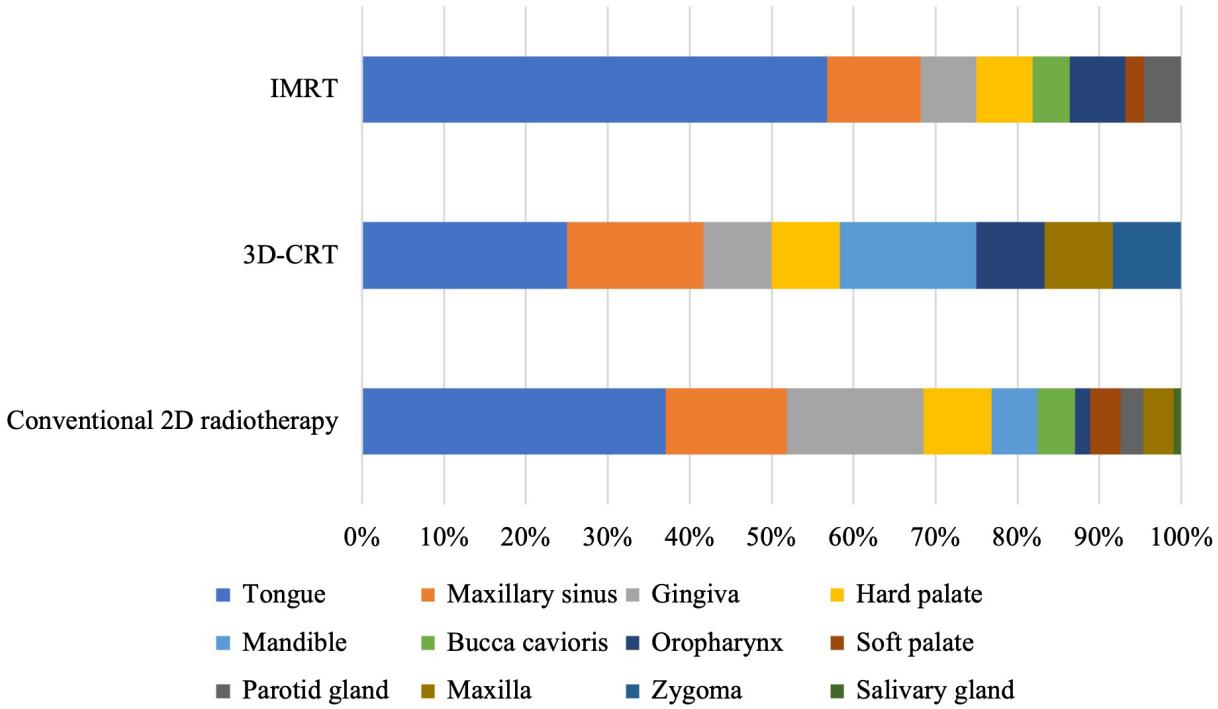

Figure S4. The proportion of index histological type of radiation-induced cancers according to patients who received IMRT, 3D-CRT, and conventional 2D radiotherapy Abbreviations: IMRT = intensity-modulated radiotherapy; 3D-CRT = 3-dimensional conformal radiotherapy; Conventional 2D radiotherapy = conventional 2-dimensional radiotherapy.

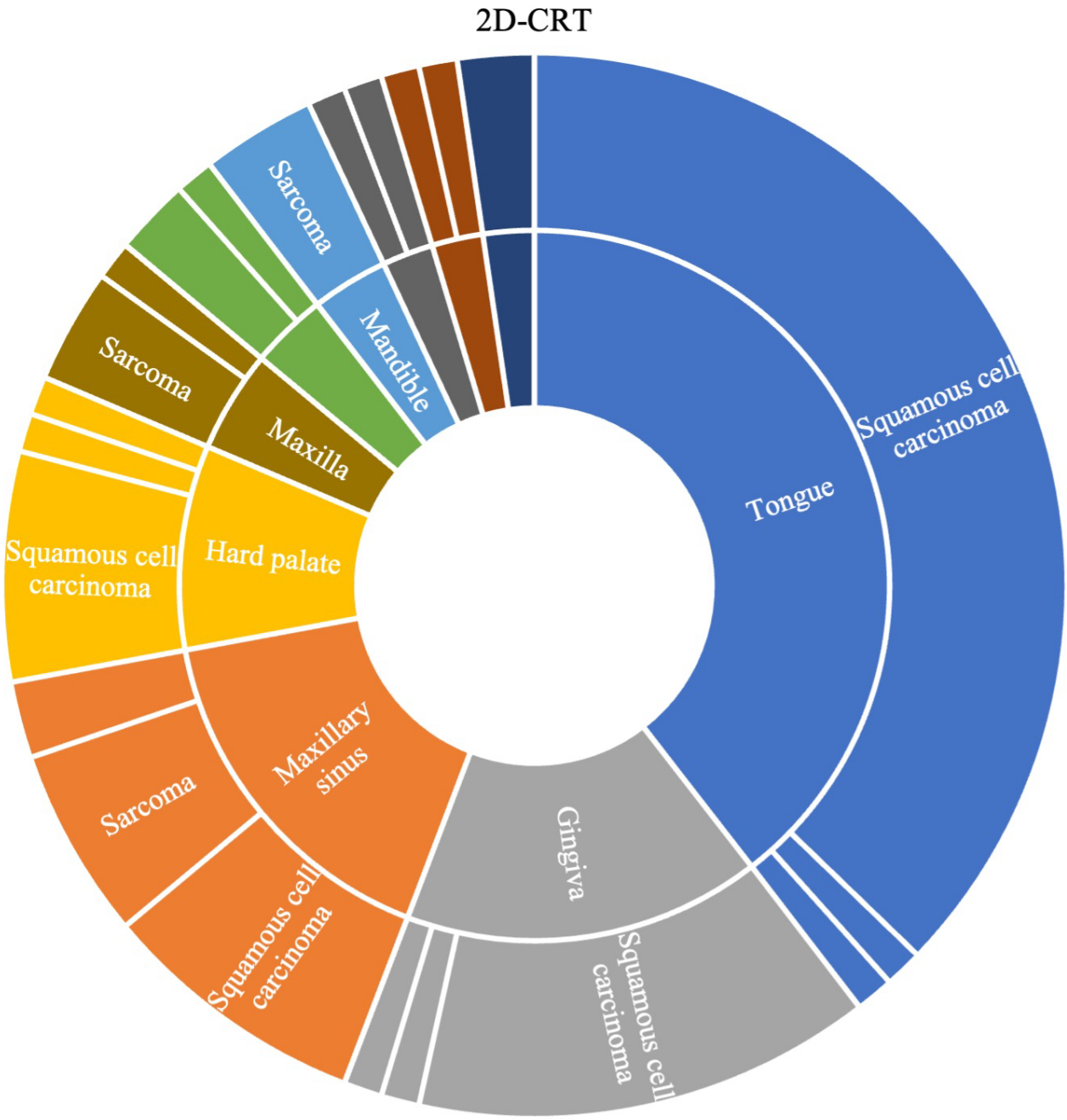

Figure S5. The distribution of index anatomic location and index histological type of radiation-induced cancers in patients who received conventional 2-dimensional radiotherapy.

Figure S6. The distribution of index anatomic location and index histological type of radiation-induced cancers in patients who received 3-dimensional conformal radiotherapy.

Figure S7. The distribution of index anatomic location and index histological type of radiation-induced cancers in patients who received intensity-modulated radiotherapy.