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Risk, pattern and survival impact of second primary tumors in patients with nasopharyngeal carcinoma following definitive intensity-modulated radiotherapy

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Abstract

Aim: Second primary tumor (SPT) is a serious late complication after definitive radiotherapy for nasopharyngeal carcinoma (NPC). We evaluated the incidence, pattern, risk factors and survival impact of SPT in NPC patients following definitive intensity-modulated radiotherapy (IMRT).

Methods: A retrospective review of 780 consecutive IMRT-treated NPC patients between February 2003 and September 2011 was conducted. Cumulative SPT incidence and overall survival after SPT diagnosis were estimated. Associations between clinical characteristics and SPT risk were analyzed. Standardized incidence ratios (SIR) were calculated using age, gender and calendar-year specific cancer incidences from the Hong Kong Cancer Registry.

Results: At a median follow-up of 7.5 years, 51 SPTs (6.7%) were identified, 22 (43.1%) of which occurred within previous radiotherapy fields. Tongue cancers (31.8%) and sarcomas of the head and neck (31.8%) were the most common in-field SPTs. Age [Hazard ratio (HR), 1.051; 95% confidence interval (CI), 1.025 – 1.078] and smoking status (HR, 1.755; 95% CI, 1.002 – 3.075) were independent risk factors associated with SPT development. Median overall survival after SPT diagnosis was 2.9 years. There was an 84% increase in cancer risk (SIR, 1.84; 95% CI, 1.37 – 2.42) compared with the general population. Significant excess risks were observed for sarcoma, tongue, oropharyngeal, prostate and liver cancer. Excess risks were higher beyond 5 years of follow-up.

Conclusion: Substantial risk of SPT, especially for in-field sarcoma and tongue cancers, exists after definitive IMRT for NPC. SPT severely negates longevity of NPC survivors. High awareness and careful surveillance is warranted for this late lethal complication.

Keywords: intensity-modulated radiotherapy, nasopharyngeal carcinoma, second primary neoplasms, incidence, registries

Background

Intensity-modulated radiotherapy (IMRT) has replaced conventional two-dimensional radiotherapy (2D RT) as the standard definitive treatment for non-metastatic nasopharyngeal carcinoma (NPC) for more than a decade. This technical advancement has improved disease control alongside with a reduction in radiotherapy late toxicities [1,2]. Although IMRT enables highly conformal tumor coverage thereby avoids excessive radiation to several critical structures, a large volume of normal tissue is exposed to a “low-dose radiation bath” due to its multiple-beam arrangement. The need for longer beam-on time also increases whole body integral dose from head leakage and collimator scatter [3]. These have led to concerns on an increased risk of radiation-induced second primary tumor (SPT) with this technique [4,5].

SPT is one of the most dreadful complications for survivors of head and neck cancers, accounting for 23% of deaths in patients with non-metastatic diseases who survived at least 3 years after diagnosis [6]. Incidences of SPT in NPC patients treated with definitive 2D RT have been reported in multiple series, quoting rates of 0.6-5.6% over variable follow-up periods [7-16]. However, data from cohorts treated with IMRT is scarce and of limited follow-up duration [17]. As radiation-associated tumors often develop after years or even decades of latency, the actual incidences and tumor patterns might be underrepresented if follow-up time is short. In addition, it is more informative when the observed incidences are quantified with reference to background population risk. This current study attempted to examine the risk of SPT in a large uniform cohort of IMRT-treated NPC patients, determine factors associated with SPT development, assess its impact on patients’

survival, and to check for excess cancer risks with comparisons made with registry-based incidence data of the general population.

Methods

Study population

This study was approved by a regional Research Ethics Committee of the Hong Kong Hospital Authority. All consecutive NPC patients who underwent definitive IMRT between February 2003 and September 2011 were identified from an institutional database. Demographic, clinical, pathologic and treatment data was reviewed retrospectively from patients' records. Due to the inconsistent quantitative report of smoking history in terms of pack-years, smoking status was categorized into never- or ever-smokers. All cases were staged using American Joint Committee on Cancer Staging Manual (7th edition) staging criteria.

Initial definitive treatments

All patients completed their planned course of definitive IMRT under thermoplastic head cast immobilization and computer tomography simulation. The gross tumor volume (GTV) for nasopharyngeal tumor (GTV-NP) and radiologically involved cervical lymph nodes (GTV-LN) were determined from individual clinical, imaging and endoscopic findings. The high-risk clinical target volume (HR-CTV) covers GTV with a 5-10mm margin, and the low-risk clinical target volume (LR-CTV) covers local structures at risk for microscopic involvement and bilateral level Ib to Vb nodal regions. The dose to GTV-NP and GTV-LN were 66-74Gy and 66-70Gy respectively.

Additional planned boost to the nasopharynx or lymph nodes beyond 70Gy were delivered at the discretion of individual oncologist. The HR-CTV and LR-CTV received 66-70Gy and 60-62Gy respectively. Radiotherapy was delivered in 33-35 fractions, 5 fractions per week, except for patients who had participated in a prospective clinical trial investigating the role of accelerated radiotherapy [18].

Selected stage II, and all stage III to IV patients with good performance status and renal function were treated with concurrent chemo-irradiation using cisplatin 100mg/m^2 every 3 weeks or 30mg/m^2 weekly. Neo-adjuvant or adjuvant chemotherapy regimens were used in advanced diseases, most commonly being cisplatin in combinations with either gemcitabine or 5-fluorouracil.

Follow-up

Follow-up duration was calculated from date of radiotherapy completion to last clinical visit. Patients were followed up every 3-6 months in first 3 years and then every 6-12 months thereafter. Diagnosis of SPT followed the criteria of Warren and Gates [19], modified by Morris et al [20]. Patients with history of prior malignancy, third primary tumors or SPTs diagnosed in less than 6-month interval from completion of radiotherapy were excluded. SPTs were considered as in-field if their epicenters lied within previous radiotherapy fields, which included hematological malignancies. All SPTs were pathologically confirmed, except for hepatocellular carcinomas which were diagnosed by raised alpha-fetoprotein levels and typical radiological features.

Statistical analysis

Descriptive statistics were used for patient demographics and clinico-pathologic characteristics. The Kaplan-Meier method was used to estimate cumulative incidence of SPT and overall survival after SPT diagnosis. Univariate analysis of the relationship between clinical characteristics and risk of SPT development was performed using the log-rank test. The Cox proportional hazards model was used in multivariate analyses, using a backward stepwise selection method including variables with p-value <0.1. Variables examined included age, sex, smoking status, stage of NPC, exposure to chemotherapy and history of re-irradiation.

In order to compare SPT incidences in our cohort with the general population, cancer incidence rates were obtained from the Hong Kong Cancer Registry, stratified by 5-year age, gender and calendar-year. The incidence rates were multiplied by person-years at risk to obtain the expected number of SPT for each cancer type. Standardized incidence ratios (SIR), defined by the ratios between expected and observed number, were then calculated. Ninety-five percent confidence intervals (CI) were determined using Byar's approximation, based on the assumption that the data followed a Poisson distribution.

All analyses were performed using SPSS Statistics, version 22.0 (SPSS Inc. Chicago, IL, USA). All tests were two-sided, statistical significance was set at the cut-off of $p<0.05$.

Results

Patient characteristics

There were 780 patients treated with definitive IMRT during study period, 21 of which had history of malignancy before diagnosis of NPC and were excluded from analysis. Table 1 summarizes the demographics, clinico-pathologic and treatment characteristics of the 759 eligible patients. Median age was 51 (range, 13-85), 70% were male and 43% were current or ex-smokers. Most cases were Epstein-Barr virus (EBV)-associated undifferentiated carcinoma. Majority of patients presented with stage III (60.0%) or IV (22.4%) diseases. Two-third of patients had chemotherapy as part of their definitive treatments with IMRT. Concurrent chemotherapy was used in 64.7% of patients. Neo-adjuvant and adjuvant chemotherapy were used at rates of 32.3% and 14.5% respectively. Fifteen patients (2.0%) received re-irradiation of curative intent for local or regional recurrences.

Incidence, pattern and survival impact of SPT

At a median follow-up of 7.5 years, 51 patients (6.7%) developed SPTs fitting the inclusion criteria (See Supplementary Materials). Three patients developed a third primary tumor and 4 patients developed SPTs within 6 months from completion of radiotherapy, they were excluded from analysis. The average annual rate of SPT development was 1.1%. The cumulative incidences of SPTs at 3 years, 5 years and 8 years were 1.0%, 3.7% and 7.7% respectively (Figure 1A). Median latency time of SPT development was 5.8 years. Of all the SPTs, 22 (43.1%) occurred within previously irradiated fields, among which 7 (31.8%) were head and neck sarcomas and another 7 (31.8%) were tongue cancers. The cumulative incidences of in-field SPTs at 3 years, 5

years and 8 years were 0.4%, 1.5% and 3.0% respectively. The median latency time of in-field and out-field SPT development were 6.3 and 5.1 years respectively (p=0.323) (Figure 1B). Nineteen SPTs (37.3%) occurred in lung and the upper aero-digestive tract. The median overall survival from diagnosis of SPT was 2.9 years, with a 1-year survival rate of 72.1%.

Factors associated with SPT development

Results of univariate and multivariate analyses are shown in Table 2. Both advanced age [Hazard ratio (HR), 1.051; 95% confidence interval (CI), 1.025 – 1.078] and smoking (HR, 1.755; 95% CI, 1.002 – 3.075) were independent predictive risk factors for SPT development. Similar associations were observed in the out-field SPT subgroup. For SPTs occurring within previous IMRT fields, no independent risk factor was identified. However, a history of re-irradiation showed a trend for higher risk of SPT development (HR, 4.000; 95% CI, 0.922 – 17.346).

Excess cancer risks

We compared the observed numbers of SPTs with those expected if our cohort came from the general Hong Kong population. SIRs derived from age, gender and calendar-year specific cancer incidences were shown in Table 3. The total number of SPTs observed (n=51) was significantly higher than the expected number of 27.73, giving an SIR of 1.84 (95% CI, 1.37 – 2.42). This result remained statistically significant after the exclusion of 2 patients who had undergone re-irradiation. Significant excess risks were observed for sarcoma (SIR, 38.10;

95% CI, 16.41 – 75.06), tongue cancer (SIR, 33.33; 95% CI, 13.36 – 68.67), oropharyngeal cancer (SIR, 25.00; 95% CI, 2.81 – 90.25), prostate cancer (SIR, 3.19; 95% CI, 1.17 – 6.95) and liver cancer (SIR, 2.80; 95% CI, 1.02 – 6.10). To evaluate latency of SPT development, cancer types with elevated SIRs at statistical significance were further stratified by follow-up intervals using 5 years as cut-off. Consistently higher excess risks were observed at follow-up beyond 5 years (Table 4).

Discussion

Nasopharyngeal carcinoma is a radiosensitive tumor, excellent disease control can be achieved after definitive chemo-irradiation using IMRT technique. With more long-term survivors, the detrimental impact of late complications such as second malignancies also correspondingly increases. Almost all of the current existing data on post-radiotherapy SPT incidence in NPC came from the 2D RT era, quoting estimates of 0.6-5.6% across variable follow-up durations [7-16]. Very few studies evaluated this risk in a uniform cohort of IMRT-treated patients.

In this study of 780 NPC patients who underwent definitive treatments using contemporary IMRT, we identified an overall SPT incidence of 6.7%. While this numerically higher incidence may have reflected our long follow-up duration, the point estimates of in-field SPT risks at 3 years (0.4%) and 5 years (1.5%) were similar to the 0.35% and 1.2% reported by Kong et al in the 2D RT era a decade ago [12]. More importantly, as patients' recurrence risk reduces with longer periods of disease remission, an upward trend of in-field SPT incidence

was observed, reaching an estimate of 3.0% at 8 years. This non-linear incidence pattern may be attributable to a combined effect of aging and the late carcinogenic property of radiation exposure.

Corroborated with findings from Tsou et al and Kong et al [12,14], we identified age as an independent risk factor for SPT development, estimating an 81% risk increment for every 10 years of age. This pattern follows those of most primary malignancies, of which incidences and age are often positively correlated. Another associating risk factor, tobacco smoking, is a strong established carcinogen for numerous cancer types, and was at the same time confirmed to promote EBV activation hence viral carcinogenesis in NPC [21]. This phenomenon of shared environmental risk factor potentially explains the large proportion of SPTs in lung andupper aero-digestive tract in the current NPC cohort, where such observation was previously reported in non-nasopharyngeal head and neck cancers as well[22]. Interestingly, neither age nor a history of smoking was predictive for the development of in-field SPTs. It is possible that in this subgroup, the carcinogenic effect of ionizing radiation was in dominant role, hence diluted the respective impact of these risk factors. Two-third of patients in this study received systemic chemotherapy, most commonly with platinum compounds and anti-metabolites such as gemcitabine and 5-fluorouracil. Without the use of alkylating agents which are classically carcinogenic, we did not observe an independent association between chemotherapy exposure and development of SPT.

The enhanced carcinogenic effect of additional radiation for NPC was previously demonstrated by Goggins et

al, showing a 3-fold risk of developing second cancers of the head and neck in NPC patients who received parapharyngeal radiation boost [11]. While this treatment technique has become obsolete in the era of IMRT, we observed a similar trend for an increased risk of in-field SPTs in patients who underwent re-irradiation for relapsed diseases. In this current cohort, 2 out of 22 patients with in-field SPTs had undergone a second course of radiotherapy for local recurrence, also with the use of IMRT technique. Despite the attempts of curative re-irradiation with IMRT, the long-term prognosis of relapsed NPC still remains guarded, with a 5-year overall survival rate of approximately 40% [23,24]. Therefore, the actual impact of re-irradiation on SPT risk was likely to be underestimated, as a significant proportion of patients would have died before the presentation of a second cancer. Still, given the further enhanced risk of developing a second cancer, careful surveillance is of particular relevance in this subset of patients.

In the current study, a very strong excess risk of second tongue cancers was observed, accounting for approximately one-third of all in-field SPTs. Our finding was consistent with that from Teo et al, who reported 7 (0.8%) cases of second tongue cancers in 903 NPC patients treated with 2D RT, most of which were found near the bases of tongue [25]. Interestingly, while a comparable second tongue cancer incidence of 0.9% was noted in our IMRT cohort, we observed a distinctly different pattern of tumor location. Among the 7 tongue cancers identified, 6 were found at lateral edges of mid-tongue, with only 1 situated at the base of tongue. Such a pattern change may be attributable to the difference in oral cavity dose distribution between the two radiotherapy techniques. In 2D RT, which traditionally employs a pair opposing facio-cervical fields, the tongue

base would typically fall into zones of high dose radiation. In contrast, with the use of multiple beam arrangements and the consistent inclusion of level Ib nodal group as treatment targets, IMRT produces plans with wider spread of low-dose volumes covering the anterior and lateral edges of tongue [26]. This change in locations of second tongue cancers along with the transition of radiotherapy techniques carries potential clinical implications, as oral tongue cancers tend to present early and are often more surgically treatable than primaries arising from base of tongue.

Another third of in-field SPTs in our series were post-irradiation head and neck sarcomas. In contrary to most other second cancers, post-irradiation sarcomas typically develop at heavily irradiated regions, and there were evidences supporting a dose-dependent incidence pattern [27]. By replacing 2D RT with IMRT, there is increased tissue exposure to low-dose radiation, in exchange for a reduction in high-dose volume from improved target conformity. Therefore, it was previously postulated that the risk of second sarcomas may drop with widespread use of IMRT [28]. In the 2D RT era, the crude incidence of in-field sarcomas was 0.14-0.35% across different series[29-31]. In the current study, the estimated crude incidence of in-field sarcomas was 0.9%. While direct comparisons with historical data is difficult due to great variations in follow-up durations and latency criteria, our finding does not support previous speculation for a risk reduction in second sarcomas with IMRT. Since post-irradiation sarcomas are known to develop at very long latency periods, together with current improvement of survival with IMRT, further observation with long term follow-up is required to fully reveal its actual risk.

The present series reported an 84% excess cancer risk in IMRT-treated NPC survivors compared with the general population. Our estimate agrees with a hospital-based study in the era of 2D RT, which reported an overall SIR of 1.93 and identified substantially elevated numbers of tongue, brain, nasal and middle ear cancers [11]. In concordance, we quantified a highly significant excess risk of tongue cancer (SIR, 33.33; 95% CI, 13.36 – 68.67), at a magnitude greater than the previously reported SIR of 25.7. However, in our cohort, no excess risk for second brain, nasal or middle ear cancers were observed. This discrepancy in SPT patterns potentially reflects the difference in radiotherapy field arrangements between 2D RT and IMRT. In conventional 2D RT for NPC, the middle ears typically lied within the parallel opposed fields, and a second-phase anterior facial field was often in place, which was at direct incidence to the whole nasal cavity. IMRT, on the other hand, could effectively spare auditory apparatuses from high dose radiation, and confine high doses mostly to posterior nasal spaces with the use of multi-directional incident beams. In a previous dosimetric study by Kam et al*,* IMRT was also superior in sparing temporal lobes in intermediate-stage NPC, and reduced the brain volume covered by high dose radiation in advanced tumors with intracranial extension [32]. Although radiation exposure from collimator scatter is higher in IMRT, this might be offset by its dosimetric properties, resulting in an overall lower incidence of second brain, nasal and middle ear cancers.

The reason for the small observed excess risks for liver and prostate cancer was however intriguing, as neither of them has known shared genetic predisposition or environmental risk factors with NPC. Of note, in our cohort,

2 out of 6 patients with second prostate cancers had asymptomatic, low-grade, early stage disease diagnosed by tumor marker testing in the setting of a tertiary oncology center. In the absence of population screening of prostate cancer in Hong Kong, this early detection could have led to a spuriously high SIR estimate in our cohort. These marginally positive results are best interpreted with caution, since these could have occurred due to chance association from small case numbers. Future population-based studies may help to clarify in this regard.

At a median latency interval of 5.8 years, we identified higher excess risks of SPTs after 5 years of follow-up. This finding was drastic for second sarcomas and tongue cancers, where the SIRs beyond 5 years were 6-fold and 3-fold higher respectively. This observation was in line with current knowledge on radiation carcinogenesis, that a long latency period after radiation exposure was required for mutations to accumulate along the process of malignant transformation [33]. Our result underpins the need for extended surveillance in NPC patients following radiotherapy, so as to allow early identification hence prompt management for latent development of second cancers.

This study also highlighted the devastating impact of SPT on NPC survivors. In a Taiwan population-based study, which evaluated survival outcomes of SPTs in NPC across 1979 - 2003, Chen et al reported a short median survival time of 1.7 years, where 48% of patients died within first year of SPT diagnosis [16]. In the present work which covered an immediate period of 2003 - 2011 after their study, we reported a longer overall

survival of 2.9 years, with a 1-year survival rate of 72.1%. This numerical improvement in survival could reflect improved prognosis of cancer patients along with advancements in medical care, including early cancer detection and effective oncological treatments. Nevertheless, considering that NPC incidence peaks at relatively young age at 40-50s and the high likelihood of long-term remissions after definitive treatments, the emergence of second malignancies still represent a major lethal complication which severely negates potential longevity of survivors.

To our knowledge, this current study was the largest published series to date in assessment of SPT risk in IMRT-treated NPC. This current study had the strengths of a long follow-up duration, and a high certainty on the diagnoses of SPTs as all data were verified with individual patient records. However, our work holds several limitations. First, in the absence of smoking-status specific cancer incidence data of the general population, our current estimates of excess cancer risks are likely a reflection of both the resultant effect of radiation exposure and differences in smoking pattern. The proportion of ever-smoker in our cohort was 43%, higher than the corresponding age- and sex-adjusted smoking prevalence of 22% in background Hong Kong population. Therefore, while the elevated sarcoma risk is chiefly attributable to radiation exposure, the excess risk noted for other cancers of the upper aerodigestive tract (including tongue cancer) is best interpreted as a mixed carcinogenic effect of smoking and radiation. Also, as limited by the retrospective nature of our study, other determinants of cancer such as details in smoking pack-years and alcohol consumption were not available. The dichotomization of smoking status may also have diluted its effect as an independent risk factor for SPT

development. Moreover, although the Hong Kong Cancer Registry reaches a high benchmark of data completeness with more than 85% of diagnoses being pathologically verified [34], comparisons made between hospital-based data with a population-based registry may still result in errors in SIR estimations due to their differences in case-capturing method. In addition, some of the observed SPTs were of small numbers, hence might have given rise to chance association in SIR calculations. Also, without direct comparison made between radiotherapy plans from 2D RT and IMRT, the observed differences in SPT patterns between our study and the published data remained hypothesis-generating. However, our findings can serve to provide foundation for future registry-based work to better illustrate the change in second cancer patterns along with this technical advancement.

Conclusions

In conclusion, our study confirmed SPT as a major health problem for NPC survivors after definitive IMRT. Very high excess risks of developing in-field sarcomas and second tongue cancers were identified, particularly after a latency period of more than 5 years. A change in SPT pattern was observed, potentially attributable to the dosimetric differences between radiotherapy techniques. Clinicians should maintain a high level of vigilance, and consider employing routine surveillance for this dreadful late complication in NPC survivors.

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Table 1

Patient demographics and treatment characteristics.

Characteristics	**Number of patients** (n=759)	**%**
Sex		
- Male	527	69.4
- Female	232	30.6
Age (years)		
- Median (range)	51 (13-85)	-
Smoking status		
- Non-smoker	417	54.9
- Current or ex-smoker	326	43.0
- Unknown	16	2.1
Histology		
- Squamous cell carcinoma	40	5.3
- Undifferentiated carcinoma	718	94.6
- Others	1	0.1
Tumor stage		
- T1	173	22.8
- T2	80	10.5
- T3	374	49.3
- T4	132	17.4
Nodal stage		
- N0	80	10.6
- N1	228	30.0
- N2	396	52.2
- N3	55	7.2
Group stage		
- I	39	5.1
- II	95	12.5
- III	455	60.0
- IVA	116	15.3
- IVB	54	7.1
Chemotherapy		
- Yes	514	67.7
- No	245	32.3
Neo-adjuvant chemotherapy		
- Yes	245	32.3
- No	514	67.7

Concurrent chemotherapy		
- Yes	491	64.7
- No	268	35.3
Adjuvant chemotherapy		
- Yes	110	14.5
- No	649	85.5
Re-irradiation		
- Yes	15	2.0
- No	744	98.0

Table 2

Univariate and multivariate analyses of factors associated with second primary tumor development.

	All SPTs (n=51)		***In-field SPTs (n=22)***		***Out-field SPTs (n=29)***	
Univariate analysis (Log-rank)						
	p-value		**p-value**		**p-value**	
Age†	0.008		0.631		0.002	
Gender	0.577		0.226		0.071	
Smoking	0.066		0.897		0.020	
Stage (I-II vs III-IV)	0.432		0.976		0.303	
Chemotherapy	0.913		0.342		0.480	
Re-irradiation	0.449		0.040		0.411	
Multivariate analysis (Cox proportional hazards model)						
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
Age	1.051	1.025 – 1.078	-	-	1.072	1.037 – 1.109
Smoking	1.755	1.002 – 3.075	-	-	2.510	1.187 – 5.310
Re-irradiation	-	-	4.000	0.922 – 17.346	-	-

†Cut-off of 50 years old used for log-rank test

Abbreviations: CI, confidence interval; HR, hazard ratio; SPT, second primary tumor

Table 3

Standardized incidence ratios of second primary tumors by sites.

SPT Type	Expected number	Observed number	SIR	95% CI
All SPTs	27.73	51	**1.84**	**1.37 - 2.42**
Lung	4.73	9	1.90	0.87 - 3.61
Sarcoma	0.21	8	**38.10**	**16.41** – **75.06**
Tongue	0.21	7	**33.33**	**13.36** - **68.67**
Liver	2.14	6	**2.80**	**1.02** - **6.10**
Prostate	1.88	6	**3.19**	**1.17** - **6.95**
Breast	2.14	4	1.87	0.50 - 4.78
Colon and rectum	4.53	3	0.66	0.13 - 1.93
Oropharynx (exclude tongue base)	0.08	2	**25.00**	**2.81** - **90.25**
Leukemia	0.27	2	7.41	0.83 - 26.74
Salivary gland	0.08	1	12.50	0.16 - 69.53
Thyroid	0.62	1	1.61	0.02 - 8.97
Oral cavity (exclude oral tongue)	0.14	1	7.14	0.09 - 39.73
Non-melanoma skin	0.70	1	1.43	0.02 - 7.95

CI, confidence interval; SIR, standardized incidence ratio; SPT, second primary tumor

Table 4

Standardized incidence ratios of second primary tumors by follow-up time.

SPT Type	Follow-up time	Expected number	Observed number	SIR	95% CI
All SPTs	0-5 years	18.84	22	1.17	0.73 – 1.77
	0-5 years†	18.84	26	1.38	0.90 – 2.02
	>5 year	8.89	29	**3.26**	**2.18 – 4.68**
Sarcoma	0-5 years	0.14	2	**14.29**	**1.61 – 51.57**
	>5 year	0.07	6	**85.71**	**31.31 – 186.55**
Tongue	0-5 years	0.15	3	**20.00**	**4.02 – 58.43**
	>5 year	0.06	4	**66.67**	**17.94 – 170.66**
Oropharynx	0-5 years	0.06	0	0.00	n/a
	>5 year	0.02	2	**100.00**	**11.24 – 360.99**
Prostate	0-5 years	1.25	3	2.40	0.48 – 7.01
	>5 year	0.63	3	4.76	0.96 – 13.91
Liver	0-5 years	1.26	2	1.59	0.18 – 5.73
	>5 years	0.88	4	**4.55**	**1.22 – 11.64**

†Included the 4 second cancers diagnosed within 6 months of IMRT completion

CI, confidence interval; n/a, not applicable; SIR, standardized incidence ratio; SPT, second primary tumor

Figure 1 Cumulative incidence of all SPTs (A) and SPTs within / outside IMRT field (B).