

The clinical characteristics of secondary primary tumors in patients with nasopharyngeal carcinoma after intensity-modulated radiotherapy

A retrospective analysis

Wei Zhao, MD^a, Hao Lei, MD^{a,b}, Xiaodong Zhu, MD^{a,*}, Ling Li, MD^a, Song Qu, MD^a, Xia Liang, MD^a, Xiao Wang, PhD^c

Abstract

To investigate the clinical characteristics associated with the risk of developing secondary primary tumors (SPTs) in patients with nasopharyngeal carcinoma (NPC) who underwent intensity-modulated radiotherapy (IMRT).

Data from 527 patients with biopsy-proven nonmetastatic NPC who were treated with IMRT between January 2007 and December 2011 were analyzed retrospectively. The cumulative incidence of SPTs after IMRT completion was estimated using the Kaplan–Meier method. Intergroup differences in the cumulative incidence were determined using the log-rank test. The Cox proportional hazards regression model was used to confirm the risk factors associated with IMRT-induced SPTs.

The median follow-up duration was 45.5 months (range, 4–97 months). Of the 527 patients, 12 (2.3%) developed posttreatment SPTs (9 men, 3 women), 6 of which were located in the irradiation field. SPTs were mostly located in the upper aerodigestive tract ($n=7$), head and neck ($n=6$), lungs ($n=3$), and tongue ($n=2$). The 1-, 3-, and 5-year cumulative SPT risk rates were 0.4%, 1.4%, and 3.1%, respectively, and the mean annual growth in cumulative incidence was approximately 0.6%. The 1-, 3-, and 5-year cumulative in-field SPT risk rates were 0.4%, 0.8%, and 1.5%, respectively, and the mean annual growth in the in-field cumulative incidence was approximately 0.3%. Univariate and multivariate analysis revealed that sex, age, clinical stage, chemotherapy, and overall IMRT duration did not significantly affect SPT risk. However, the history of smoking was the independent risk factor associated with SPT.

The 5-year SPT incidence among patients with NPC after IMRT is concordant with or lower than that in previous 2-dimensional radiotherapy studies. Among patients with NPC who underwent IMRT, the upper aerodigestive tract was the most common SPT site, and lung cancer was the most common pathology. Smoking history, but not sex, age, clinical stage, chemotherapy, and overall IMRT duration is the independent risk factor associated with SPT. Additional large-scale studies with longer-term follow-ups are needed to determine risk factors associated with SPT development after IMRT.

Abbreviations: AC = adjuvant chemotherapy, CCT = concurrent chemotherapy, CT = computed tomography, EBV = Epstein–Barr virus, IMRT = intensity-modulated radiotherapy, MRI = magnetic resonance imaging, NACT = neoadjuvant chemotherapy, NPC = nasopharyngeal carcinoma, PTV = planned target volume, SPT = secondary primary tumor.

Keywords: intensity-modulated radiotherapy, nasopharyngeal carcinoma, retrospective, secondary primary tumors

1. Introduction

Advances in modern irradiation techniques have prolonged the survival durations of patients with malignant tumors who

undergo radiotherapy. Accordingly, the incidence of radiotherapy-induced secondary primary tumors (SPTs) has increased.^[1,2] SPTs can be life-threatening and have become the most serious complication in patients who have achieved long-term survival

Editor: Yuan Lin.

Funding: This work was supported by grants from the Natural Science Foundation of Guangxi Province (grant number: 2013GXNSFBA019199), the National Natural Science Foundation of China (grant number: 81260346), and the Guangxi Zhuang Region Health Department (CN) (grant number: Z2012346).

WZ and HL contributed equally to this work.

Authors' contributions: XZ and LL designed the study. WZ and HL performed the literature searches and data acquisition. SQ performed the statistical analysis described in this article, with assistance from XL. XW is responsible for the writing of the manuscript. All authors have read and approved the final manuscript.

The authors have no conflicts of interest to disclose.

^a Department of Radiation Oncology, Cancer Hospital of Guangxi Medical University, Nanning, ^b Department of Radiation Oncology, Hubei Cancer Hospital, Wuhan, China, ^c Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Rutgers Robert Wood Johnson Medical School, Rutgers The State University of New Jersey, New Brunswick, NJ.

* Correspondence: Xiaodong Zhu, Department of Radiation Oncology, Cancer Hospital of Guangxi Medical University, 71 Hedi Road, Nanning, China (e-mail: zhuxidongxmu@126.com).

Copyright © 2016 the Author(s). Published by Wolters Kluwer Health, Inc. All rights reserved.

This is an open access article distributed under the Creative Commons Attribution-NoDerivatives License 4.0, which allows for redistribution, commercial and non-commercial, as long as it is passed along unchanged and in whole, with credit to the author.

Medicine (2016) 95:45(e5364)

Received: 5 August 2016 / Received in final form: 14 October 2016 / Accepted: 14 October 2016

<http://dx.doi.org/10.1097/MD.0000000000005364>

after radiotherapy.^[3–6] In Asian countries, and particularly in Southern China, nasopharyngeal carcinoma (NPC) is the most common malignant tumor of the head and neck. Intensity-modulated radiotherapy (IMRT) has improved the clinical efficacy of radiotherapy in patients with NPC and has widely replaced conventional radiotherapy, leading to increased survival durations.^[7]

The SPT incidence among patients with NPC after conventional radiotherapy is approximately 2.0% to 5.6%^[5,6,8–13]; however, data concerning the incidence of SPT after IMRT are scarce. A previous study indicated that IMRT doubled the radiation-induced cancer risk when compared with conventional radiotherapy.^[14] To date, no reports have detailed the characteristics of IMRT-induced SPTs in patients with NPC. To evaluate the risk factors associated with IMRT-induced SPTs, in this study we retrospectively analyzed the clinical characteristics of SPTs in patients with biopsy-proven nonmetastatic NPC who underwent IMRT.

2. Materials and methods

2.1. Patients

The ethical committee of Ren Ji Hospital approved this study. A total of 527 patients with NPC who were treated with IMRT at the Cancer Hospital of Guangxi Medical University between January 2007 and December 2011 were enrolled. The inclusion criteria were as follows: histologically confirmed NPC by nasopharyngeal biopsy, no evidence of metastasis, no previous malignancy or concomitant malignant disease, no previous treatment for NPC, a Karnofsky performance status of ≥ 70 , and completion of a course of radical IMRT. Of the 527 patients, 394 were men and 133 were women (ratio, 2.9:1), the median age was 44 years (range, 15–79 years).

The initial work-up included a complete physical examination, computed tomography (CT) or magnetic resonance imaging (MRI) of the head and neck, histological confirmation of nasopharyngeal lesions, chest radiography or CT, abdominal ultrasound or CT, and single-photon emission CT (SPECT) whole-body bone scan to exclude distant metastases.

The baseline characteristics of the 527 included patients are listed in Table 1. Patients were staged according to the 2010 Union for International Cancer Control staging system. Pathology classification was based on the World Health Organization grading system, with Grade I representing squamous cell carcinoma, Grade II representing nonkeratinizing carcinoma, and Grade III representing undifferentiated carcinoma.

2.2. Radiotherapy and chemotherapy

All patients were immobilized in the supine position with individually manufactured precision mask positioned from the head to the shoulders. Contrast-enhanced CT images were obtained using a CT simulator. After completing target delineation, data were imported to a treatment planning system for treatment design. The prescribed radiation doses were 69.96 to 74.09 Gy to the planned target volume (PTV) within the primary nasopharyngeal gross tumor volume, including the cervical lymph nodes, 60 to 65.1 Gy to the PTV of high-risk regions, and 51.62 to 57.6 Gy to the PTV of low-risk and neck nodal regions. IMRT was delivered via 9 fixed-gantry angles using the step-and-shoot treatment technique. All patients were treated with 1 daily fraction on 5 days per week.

Table 1

Patient characteristics and treatment factors for the cohort (n = 527).

Characteristics	No. of patients	%
Sex		
Male	394	74.8
Female	133	25.2
Age, y		
>44	255	48.4
≤44	272	51.6
Histological type		
Nonkeratinizing carcinoma	523	99.2
Keratinizing squamous carcinoma	4	0.8
Tumor stage		
T1–2	218	41.4
T3–4	309	58.6
Node stage		
N0–1	244	46.3
N2–3	283	53.7
Clinical stage		
I–II	129	24.5
III–IVa–b	398	75.5
Overall IMRT time, d		
>44	203	38.5
≤44	324	61.5
Chemotherapy		
Yes	468	88.8
No	59	11.2
Concurrent chemotherapy		
Yes	450	85.4
No	77	14.6
Neoadjuvant chemotherapy		
Yes	94	17.8
No	433	82.2
Adjuvant chemotherapy		
Yes	310	58.8
No	217	41.2
Smoking		
Yes	141	26.8
No	386	73.2

IMRT = intensity-modulated radiotherapy.

During the study period, 468 of the 527 patients underwent chemotherapy. Of the 398 patients with stage II–IVa/b disease, 41 were treated with radiotherapy alone for economic or personal reasons. Concurrent chemotherapy (CCT) consisted of cisplatin (100 mg/m²) on day 1 of a 21-day cycle. Neoadjuvant plus adjuvant chemotherapy (NACT+AC) consisted of either cisplatin (80 mg/m²) on day 1 plus fluorouracil (750 mg/m²) on days 1 to 4 of a 21-day cycle (PF); docetaxel (60–75 mg/m²) plus cisplatin (60–80 mg/m²) on day 1 of a 21-day cycle (TP); or cisplatin (60 mg/m²) plus docetaxel (60 mg/m²) on day 1 plus fluorouracil (600 mg/m²) on days 1 to 5 of a 21-day cycle (TPF). Patients underwent 1 to 8 cycles of chemotherapy. CCT was administered to 112 patients, NACT+CCT to 40 patients, CCT+AC to 258 patients, NACT+CCT+AC to 40 patients, and NACT or AC to 18 patients.

2.3. Follow-up

After the initial treatment, patients were follow-up every 3 months during the first 3 years, every 6 months during the next 2 years, and annually thereafter. Chest radiography, abdominal ultrasonography, MRI of the nasopharynx and neck

Table 2
List of secondary primary tumors (SPTs) in patients who underwent intensity-modulated radiotherapy (IMRT).

Sex	Age	NPC				Smoking	MBD	SPT			Within RT field
		Histology	Treatment	Cycles of CT	Age			Location	Histology		
Male	55	Nonkeratinizing carcinoma	CCRT+AC	4	Yes	49	59	Lung	Adenocarcinoma	No	
Male	28	Nonkeratinizing carcinoma	CCRT	3	No	47	32	Neck	Lymphoepithelioma-like carcinoma	Yes	
Female	48	Nonkeratinizing carcinoma	CCRT	3	Yes	43	52	Tongue	Squamous cell carcinoma	Yes	
Male	41	Nonkeratinizing carcinoma	NACT+CCRT+AC	5	Yes	41	45	Kidney	Papillary renal cell carcinoma	No	
Male	57	Nonkeratinizing carcinoma	CCRT+AC	4	Yes	37	60	Lung	Non-small cell lung cancer	No	
Male	45	Nonkeratinizing carcinoma	CCRT+AC	5	No	35	48	Stomach	Adenocarcinoma	No	
Male	49	Nonkeratinizing carcinoma	CCRT+AC	4	No	30	52	Neck	Non-Hodgkin lymphoma	Yes	
Female	58	Nonkeratinizing carcinoma	CCRT	3	Yes	29	60	Brain	Glioma	Yes	
Male	35	Nonkeratinizing carcinoma	Only IMRT	0	Yes	26	37	Lung	Squamous cell carcinoma	No	
Female	13	Nonkeratinizing carcinoma	CCRT	2	No	21	15	Kidney	Neuroblastoma	No	
Male	46	Nonkeratinizing carcinoma	CCRT+AC	3	Yes	12	47	Tongue	Squamous cell carcinoma	Yes	
Male	78	Nonkeratinizing carcinoma	IMRT+AC	1	No	12	79	Oral	Squamous cell carcinoma	Yes	

AC=adjuvant chemotherapy, CCRT=concurrent chemoradiotherapy, CT=chemotherapy, IMRT=intensity-modulated radiotherapy, MBD=months between diagnosis, NACT=neoadjuvant chemotherapy, NPC=nasopharyngeal carcinoma, RT=radiotherapy.

region, and laboratory analyses were performed at each assessment. Chest and abdominal CT and bone scan SPECT were performed every 6 months.

SPTs were diagnosed according to the criteria of Warren and Gates^[15] as follows: occurrence of a new cancer of a different histology from the initial primary tumor, anatomical barrier or lack of continuity between the SPT and the initial cancer, and/or recurrence or metastasis of the initial primary tumor was ruled out.

2.4. Statistical analyses

All statistical analyses were performed using SPSS 22.0 software (SPSS, Chicago, IL). Data are presented as means±standard deviations. The Kaplan–Meier method and log-rank test were used to calculate cumulative incidences and intergroup differences in cumulative incidences, respectively. The Cox proportional hazards regression model was used to confirm the risk factors associated with IMRT-induced SPTs. All statistical tests were 2-tailed, and a P-value of <0.05 was considered statistically significant.

3. Results

3.1. Follow-up

At the end of the study, the follow-up rate was 98.3%, the median follow-up duration was 3.8 years (range, 0.3–8.1 years), and the mean follow-up duration was 4.1±1.5 years. Of the 527 patients, 12 (2.3%) developed SPTs (Table 2). Of these 12, 9 were men and 3 were women (ratio, 3:1). The mean age of patients with SPTs was 48.8±4.7 years, and the median age was 50 years (range, 15–79 years). The mean latency interval was 2.7±0.3 years, and the median latency interval was 2.7 years (range, 1.0–4.1 years). Six cases each occurred in-field and out-field. The most common pathological SPT was squamous cell carcinoma (4 cases, 33.3%).

3.2. SPT locations and cumulative incidence rate

The 1-, 3-, and 5-year cumulative SPT risk rates were 0.4%, 1.4%, and 3.1%, respectively, and the mean annual cumulative incidence growth rate was approximately 0.6% (Fig. 1). The 1-,

3-, and 5-year cumulative in-field SPT risk rates were 0.4%, 0.8%, and 1.5%, respectively, and the mean annual growth cumulative incidence growth rate was approximately 0.3% (Fig. 2).

Specific locations, incidence rates, and the cumulative 5-year risk rate are shown in Table 3.

3.3. Univariate analysis of factors associated with 5-year cumulative incidence of SPT development

None of the following factors was associated with the 5-year cumulative incidence of SPT development: sex, age, stage, chemotherapy, or duration of IMRT. Regarding sex, the 5-year cumulative incidences of SPT were 3.3% and 2.8% for men and women, respectively (P=0.89, Fig. 3). Patients were stratified according to the age at diagnosis. The 5-year cumulative incidence rates for those aged ≤40 and >40 years were 2.0% and 3.8%,

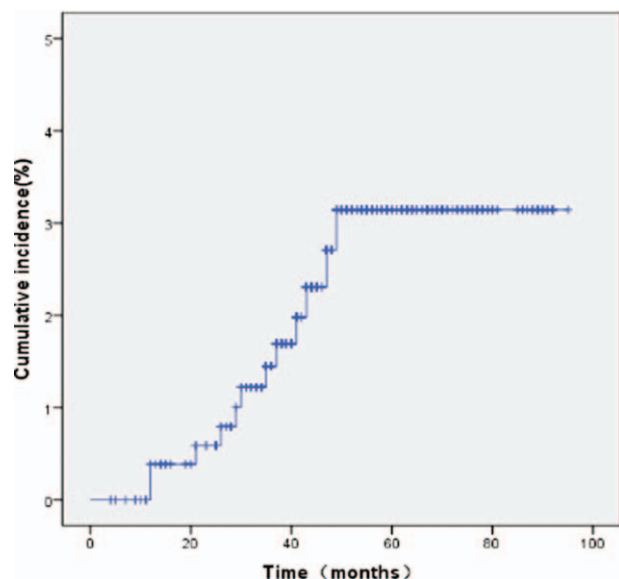


Figure 1. Cumulative incidence of secondary primary tumors (SPTs).

Table 3

Locations of secondary primary tumors (SPTs) in patients who underwent intensity-modulated radiotherapy (IMRT).

Site	No. of SPTs	Disease incidence, %	Cumulative incidence of 5 y, %
UADT	7	1.3% (7/527)	0.018
Head/neck	6	1.1% (6/527)	0.015
Lung	3	0.6% (3/527)	0.009
Tongue	2	0.4% (2/527)	0.005
Neck	2	0.4% (2/527)	0.006
Kidney	2	0.4% (2/527)	0.005
Brain	1	0.2% (1/527)	0.002
Oral	1	0.2% (1/527)	0.002
Stomach	1	0.2% (1/527)	0.002

No. = number, UADT = upper aerodigestive tract.

respectively ($P=0.31$). Furthermore, the 5-year cumulative incidence rates were 4.4% and 2.0% for those aged <44 and ≥ 44 years, respectively ($P=0.14$, Fig. 4), and 2.7% and 4.3% for those aged ≤ 50 and >50 years, respectively ($P=0.53$). Further age subgrouping revealed 5-year cumulative incidence rates of 2.0%, 3.5%, and 4.3% for those aged ≤ 40 , 41 to 50, and >50 years, respectively ($P=0.60$). Regarding stage, the 5-year cumulative incidence rates for stage I–II and stage III–IVa/b disease were 0.8% and 4.1%, respectively ($P=0.12$, Fig. 5). The 5-year cumulative incidence rates for tumor stage among T1–2 and T3–4 patients were 3.2% and 3.1%, respectively ($P=0.80$). The 5-year cumulative incidence rates for node stage among N0–1 and N2–3 patients were 1.9% and 4.2%, respectively ($P=0.10$).

The 5-year cumulative incidence rates of patients who did and did not undergo CCT were 3.3% and 1.8%, respectively ($P=0.66$, Fig. 6). The 5-year cumulative incidence rates for those who did and did not undergo NACT were 1.4% and 3.5%, respectively ($P=0.35$). The 5-year cumulative incidence rates for the CRT and non-CRT groups were 3.3% and 2.7%, respectively ($P=0.96$). The 5-year cumulative incidence rates for

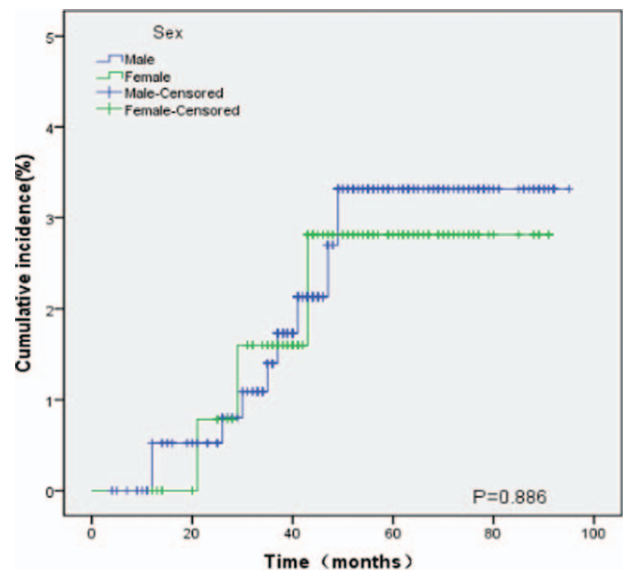


Figure 3. Cumulative incidence of secondary primary tumors (SPTs) according to sex.

the AC and non-AC groups were 3.2% and 3.0%, respectively ($P=0.89$). Finally, the 5-year cumulative incidence rates for patients with an IMRT duration of ≤ 44 and >44 days were 2.9% and 4.0%, respectively ($P=0.97$, Fig. 7).

3.4. Multivariate analysis of risk factor associated with SPT development in NPC patients treated with IMRT

We performed a multivariate logistic regression analysis, in which we initially introduced the following variables: sex, age, clinical stage, chemotherapy, duration of IMRT, and smoking.

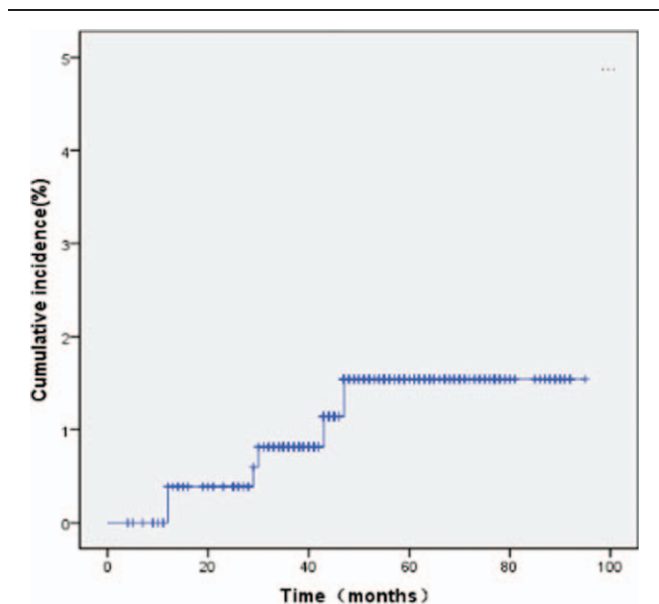


Figure 2. Cumulative incidence of secondary primary tumors (SPTs) within the intensity-modulated radiotherapy (IMRT) field.

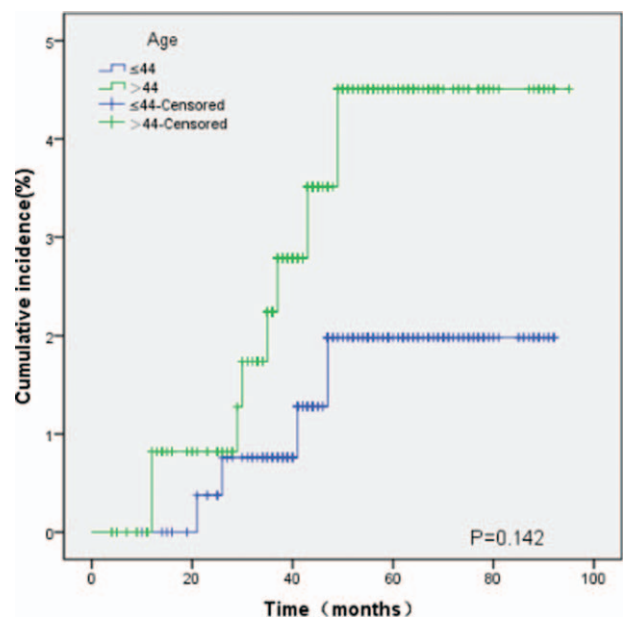


Figure 4. Cumulative incidence of secondary primary tumors (SPTs) according to age.

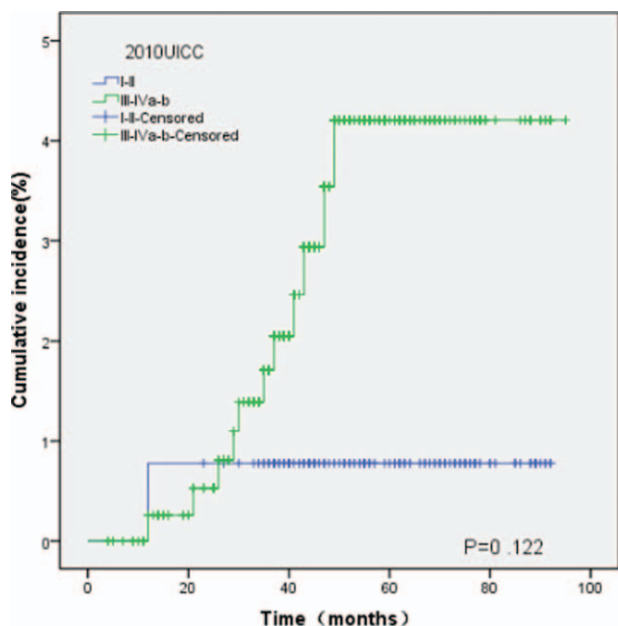


Figure 5. Cumulative incidence of secondary primary tumors (SPTs) according to clinical stage.

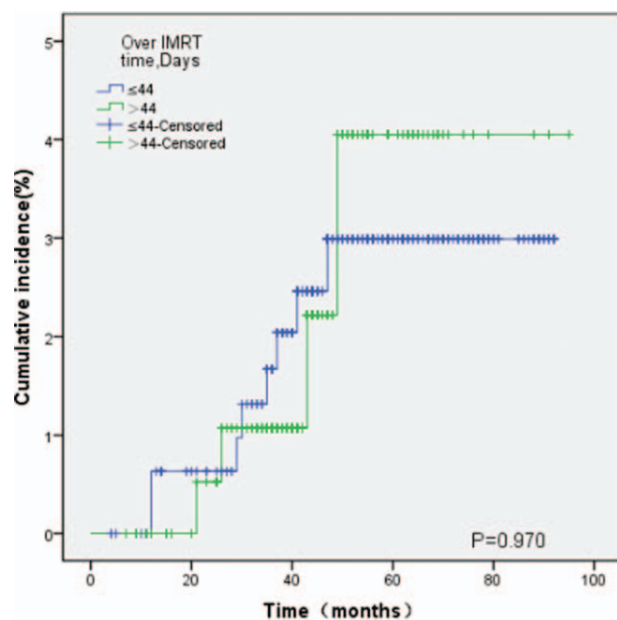


Figure 7. Cumulative incidence of secondary primary tumors (SPTs) according to the duration of intensity-modulated radiotherapy (IMRT).

These variables were selected as from the univariate analysis or because they were clinically relevant. We found that smoking history (HR=2.525, 95% CI=1.324–4.824, P=0.015) was the only independent prognostic factor associated with SPT. However, the other factors, including sex (HR=1.375, 95% CI=0.799–2.390, P=0.347), age (HR=1.844, 95% CI=0.803–3.363, P=0.174), clinical stage (HR=1.883, 95% CI=0.914–3.480, P=0.086), chemotherapy (HR=1.128, 95% CI=0.551–1.973, P=0.931), and duration of IMRT (HR=1.459,

95% CI=0.518–2.593, P=0.052) were not significantly associated with the development of SPT (Table 4).

4. Discussion

Compared with conventional radiotherapy, IMRT, with multi-field rotational radiation, can increase the exposure of normal tissue or surrounding organs-at-risk to doses of radiation.^[16] Radiation leakage from a multileaf collimator can increase the exposure of normal tissue because of the increased size of the radiation field, as well as the increased treatment duration, both of which can result in unplanned irradiation or a bystander effect.^[17,18] Furthermore, the IMRT dark current is approximately 7-fold higher than that of conventional radiotherapy, leading to further increases in the exposure of normal tissue to low-dose irradiation that might induce lethal damage.^[19–21]

Table 5 summarizes the results of the present study and those of recent studies. The 5-year SPT incidence in the present study was concordant with or lower than that of previous studies. Some studies have demonstrated an SPT incidence rate of 3% to 3.3%^[5,7] however, these data were obtained from a tumor

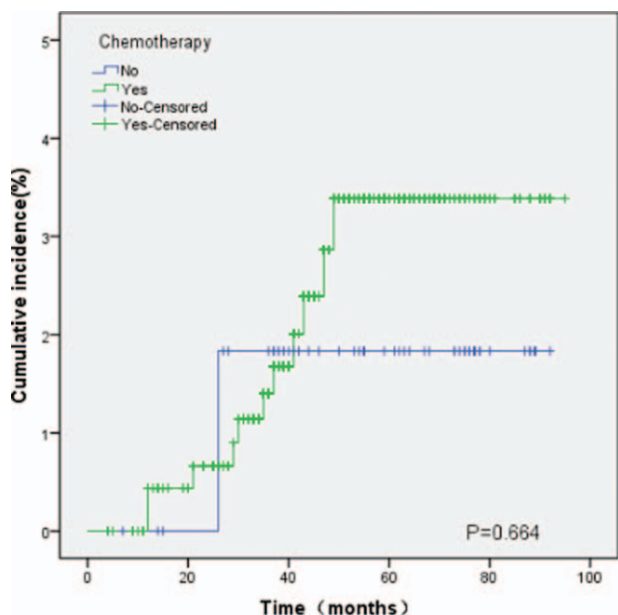


Figure 6. Cumulative incidence of secondary primary tumors (SPTs) according to the concurrent chemotherapy (CCT) status.

Table 4
Cox proportional hazards analyses of risk factors associated with SPT in NPC patients treated with IMRT.

Variables	P	HR	95% CI
Sex (female vs male)	0.347	1.375	0.799–2.390
Age (>44 vs ≤44 y)	0.174	1.844	0.803–3.363
Clinical stage (III–IVa–b vs I–II)	0.086	1.883	0.914–3.480
IMRT duration (yes vs no)	0.052	1.459	0.518–2.593
Chemotherapy (yes vs no)	0.931	1.128	0.551–1.973
Smoking (yes vs no)	0.015	2.525	1.324–4.824

95% CI=95% confidence interval, HR=hazards ratio, IMRT=intensity-modulated radiotherapy, NPC= nasopharyngeal carcinoma, SPT=secondary primary tumors.

Table 5**Comparison of secondary primary tumor (SPT) characteristics from the present and recent studies.**

Study	Year	Treatment period	Treatment technology	No. of patients	No. of SPTs	Disease incidence, %	Follow-up
Sham et al ^[8]	1990	1976–1983	2D-RT	759	15	2.00	5.3 y (median)
Cooper et al ^[9]	1991	—	2D-RT	—	121	4.10	5.5–15 y
Teshima et al ^[10]	1992	1977–1989	2D-RT	221	12	5.60	—
Teo et al ^[11]	1999	1984–1989	2D-RT	903	19	2.20	5.75 y (median)
Wang et al ^[12]	2000	1979–1993	2D-RT	1549	39	2.80	7.0 y (median)
Kong et al ^[13]	2006	1994–1994	2D-RT	326	17	5.20	5.6 y (median)
Tsou et al ^[6]	2007	1995–2005	2D-RT	584	17	2.90	3.3 y (average)
Scelo et al ^[7]	2007	1943–1978	2D-RT	8947	291	3.30	4.3 y (average) 2.3 y (median)
Chen et al ^[5]	2008	1979–2003	2D-RT	23,639	712	3.00	5.38 y (average)
Our series	2015	2007–2011	IMRT	527	12	2.30	4.1 y (average) 3.8 y (median)

2D-RT = 2-dimensional radiotherapy, IMRT = intensity-modulated radiotherapy.

registry in which the treatment characteristics were not clear. Other studies have suggested an SPT incidence rate of 2.0% to 5.6%, but these values were based on data obtained after conventional 2-dimensional radiotherapy (2D-RT).^[6,8–13] Discrepancies in the incidence rates might also arise because of differences in follow-up durations. In the present study, the follow-up duration was relatively short; however, the mean follow-up duration was higher than that reported by Tsou et al,^[6] and the median follow-up duration was higher than that of Scelo et al.^[7] Wang et al^[12] reported a 5-year incidence rate of 1.7%; however, this rate increased to 2.8% at the 7-year follow-up. This suggests that as the follow-up duration increased, an upward trend can be observed in the cumulative incidence of SPTs, congruent with the results of the present study. This finding was also concordant with the results of a study by Kong et al,^[13] who indicated an upward trend in the cumulative incidence rate with an increasing follow-up duration after 2D-RT; in that study, the mean annual growth rate was approximately 1%. Moreover, previous studies have indicated that the incidence of SPTs increased as the survival time increased.^[5] Given these data, we could speculate that at 5 years after IMRT, the incidence of SPTs among patients with NPC would probably continue to increase, given the findings of patients treated with conventional radiation therapy.

In the present study, the most common site of SPTs was the upper aerodigestive tract (UADT), in agreement with the results of previous 2D-RT studies.^[5,7,12,13] Some studies have suggested that this location might indicate a “mucosa syndrome”^[22] or “field cancerization.”^[23] In contrast, Kong et al^[13] contradicted this theory and stated that irradiation itself was the main factor underlying the development of SPTs in the UADT, given the differences in characteristics between primary tumors and SPTs. Patients with undifferentiated and Epstein–Barr virus (EBV) RNA-positive primary tumors usually develop EBV-negative, differentiated SPTs. In agreement with Kong et al,^[13] we suggest that radiotherapy is likely the main cause of SPTs in the UADT of patients with NPC because, in the present study, the pathologies of SPTs in the UADT differed from those of the primary NPC tumors.

The present study showed that lung cancer was the most common SPT among patients with NPC who underwent IMRT. These findings are similar to those of Tsou et al.^[6] However, Kong et al^[13] reported a much higher incidence of lung SPTs and proportion of these tumors among all SPTs; in addition, although the proportion of lung SPTs was higher in a study by Chen et al,^[5]

the incidence was similar to that of the present study. Lung SPTs can be attributed to be multiple causes, including radiotherapy and smoking.^[24] In the present study, smoking history, but not sex, age, clinical stage, chemotherapy, and overall IMRT duration is the independent risk factor associated with SPT, which result is consist with former study. Although it has been confirmed by many studies that cigarette smoking is a causative factor for developing SPTs in head and neck cancer (oral cavity, pharynx, and larynx).^[25] And, Teo et al^[11] defined the risk of tongue and other aerodigestive tract cancers developing after primary 2D-RT for NPC and observed smoking history of who subsequently developed tongue cancer were significantly different from the novo tongue cancer patient population. The study on the risk of SPTs following a primary NPC treated with IMRT is rare. The present study have further confirmed that a history of cigarette smoking increased the incidence of SPTs by 2.5-fold in NPC treated with IMRT. With regard to cigarette smoking is relatively prevalent in males of China, the positive tobacco control may be beneficial for reduction of SPTs following a primary NPC treated with IMRT.

The potential contributions of imaging modalities, especially during long-term follow-up, to the development of SPTs should also be considered. In UK patients aged >75 years, Gonzalez and Darby^[26] indicated that the cumulative incidence of SPTs caused by diagnostic radiography irradiation was approximately 0.6%, accounting for 700 patients per year. Furthermore, in 45-year-old patients, Brenner and Elliston^[27] demonstrated that a single full-body CT examination would lead to an estimated lifetime attributable cancer mortality risk increase of approximately 0.08%; in addition, if annual scans were conducted for a further 30 years, the accrued estimated lifetime attributable risk of cancer mortality would increase by approximately 1.9%.

Theoretically, IMRT has advantages over conventional radiotherapy with respect to reducing both the high-dose region of the tongue and the risk of oral mucositis. Teo et al^[11] indicated that 7 of 903 patients with NPC who underwent radical conventional radiotherapy developed tongue cancer, mostly at the tongue root or the junction between the tongue and tongue root, where the estimated radiation dose was significantly higher than that of the cancer-free tongue. Sun et al.^[28] indicated that 68 of 55,620 patients with NPC who underwent conventional radiotherapy developed tongue cancer, mostly at the edge and back of the tongue, and these tumors were considered to be related to radiotherapy-induced oral mucositis. However, in the present study, the incidence of tongue cancer was relatively high,

suggesting that IMRT might not yield the expected advantages. Whether this discrepancy is related to an increased irradiation volume of the tongue will require confirmation in further studies.

In patients with NPC who underwent 2D-RT, Kong et al^[13] identified age (≥ 50 years) as an independent risk factor for developing a SPT. Chen et al^[5] suggested that patients younger than 40 years had an increased incidence and risk of SPT development. Other studies have suggested that an increased duration of irradiation, low-dose irradiation, and large area of irradiation might accelerate cancer development.^[21] Further studies involving larger sample sizes and longer follow-up durations are needed to identify the factors associated with the SPT risk. In cancers other than NPC, chemotherapy has been shown to increase the SPT risk. Although there are no data that specifically delineate the role of chemotherapy in an increased SPT risk among patients with NPC, it is reasonable to suppose that chemotherapy could increase the SPT risk.^[25,29–31]

Our study had some limitations. Although 527 patients were included in this study, only 12 developed posttreatment SPTs in the irradiation field. The above-described time effect on irradiation-induced SPTs suggests that a longer-term follow-up of more is needed and would better support the study results.

5. Conclusions

In conclusion, studies have demonstrated a close relationship between SPTs and irradiation in patients with NPC, although data regarding the incidence of SPT after IMRT is less well studied. Our present study reveals that the 5-year SPT incidence among patients with NPC after IMRT was concordant with or lower than that reported in previous 2D-RT studies. Among patients with NPC who underwent IMRT, the UADT was the most common SPT site, and lung cancer was the most common pathology. Smoking history, but not sex, age, clinical stage, chemotherapy, and overall IMRT duration is the independent risk factor associated with SPT. Additional large-scale studies with longer-term follow-ups are needed to determine risk factors associated with SPT development after IMRT.

Acknowledgment

The authors are grateful to Ying Chen, the head of the Department of Administration and Office of Disease Process, for her assistance with the follow-up.

References

- Boice JD Jr, Day NE, Andersen A, et al. Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. *J Natl Cancer Inst* 1985;74:955–75.
- Brenner DJ, Curtis RE, Hall EJ, et al. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 2000;88:398–406.
- Travis LB, Rabkin CS, Brown LM, et al. Cancer survivorship—genetic susceptibility and second primary cancers: research strategies and recommendations. *J Natl Cancer Inst* 2006;98:15–25.
- Argiris A, Brockstein BE, Haraf DJ, et al. Competing causes of death and second primary tumors in patients with locoregionally advanced head and neck cancer treated with chemoradiotherapy. *Clin Cancer Res* 2004;10:1956–62.
- Chen MC, Feng JJ, Lu CH, et al. The incidence and risk of second primary cancers in patients with nasopharyngeal carcinoma: a population-based study in Taiwan over a 25-year period (1979–2003). *Ann Oncol* 2008;19:1180–6.
- Tsou YA, Hua CH, Tseng HC, et al. Survival study and treatment strategy for second primary malignancies in patients with head and neck squamous cell carcinoma and nasopharyngeal carcinoma. *Acta Otolaryngol* 2007;127:651–7.
- Scelo G, Boffetta P, Corbex M, et al. Second primary cancers in patients with nasopharyngeal carcinoma: a pooled analysis of 13 cancer registries. *Cancer Causes Control* 2007;18:269–78.
- Sham JS, Wei WI, Tai PT, et al. Multiple malignant neoplasms in patients with nasopharyngeal carcinoma. *Oncology* 1990;47:471–4.
- Cooper JS, Scott C, Marcial V, et al. The relationship of nasopharyngeal carcinomas and second independent malignancies based on the Radiation Therapy Oncology Group experience. *Cancer* 1991;67:1673–7.
- Teshima T, Inoue T, Chatani M, et al. Incidence of other primary cancers in 1,569 patients with pharyngolaryngeal cancer and treated with radiation therapy. *Strahlenther Onkol* 1992;168:213–8.
- Teo PM, Chan AT, Leung SF, et al. Increased incidence of tongue cancer after primary radiotherapy for nasopharyngeal carcinoma—the possibility of radiation carcinogenesis. *Eur J Cancer* 1999;35:219–25.
- Wang CC, Chen ML, Hsu KH, et al. Second malignant tumors in patients with nasopharyngeal carcinoma and their association with Epstein-Barr virus. *Int J Cancer* 2000;87:228–31.
- Kong L, Lu JJ, Hu C, et al. The risk of second primary tumors in patients with nasopharyngeal carcinoma after definitive radiotherapy. *Cancer* 2006;107:1287–93.
- Hall EJ, Wu CS. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. *Int J Radiat Oncol Biol Phys* 2003;56:83–8.
- Warren S, Gates O. Multiple malignant tumors: a survey of literature and statistical study. *Am J Cancer* 1932;51:1358–414.
- Verellen D, Vanhavere F. Risk assessment of radiation-induced malignancies based on whole-body equivalent dose estimates for IMRT treatment in the head and neck region. *Radiother Oncol* 1999;53:199–203.
- Cheng CW, Das IJ. Comparison of beam characteristics in intensity modulated radiation therapy (IMRT) and those under normal treatment condition. *Med Phys* 2002;29:226–30.
- Lillicrap SC, Morgan HM, Shakeshaft JT. X-ray leakage during radiotherapy. *Br J Radiol* 2000;73:793–4.
- Williams PO, Hounsell AR. X-ray leakage considerations for IMRT. *Br J Radiol* 2001;74:98–100.
- Mutic S, Low DA, Klein EE, et al. Room shielding for intensity-modulated radiation therapy treatment facilities. *Int J Radiat Oncol Biol Phys* 2001;50:239–46.
- Redpath JL. Radiation-induced neoplastic transformation in vitro: evidence for a protective effect at low doses of low LET radiation. *Cancer Metastasis Rev* 2004;23:333–9.
- Bedi GC, Westra WH, Gabrielson E, et al. Multiple head and neck tumors: evidence for a common clonal origin. *Cancer Res* 1996;56:2484–7.
- Slaughter DHW. Field cancerization in oral stratified squamous epithelium; clinical implications of multicentric origin. *Cancer* 1953;6:963–8.
- Swerdlow AJ, Schoemaker MJ, Allerton R, et al. Lung cancer after Hodgkin's disease: a nested case-control study of the relation to treatment. *J Clin Oncol* 2001;19:1610–8.
- Chuang SC, Scelo G, Tonita JM, et al. Risk of second primary cancer among patients with head and neck cancers: a pooled analysis of 13 cancer registries International. *J Cancer* 2008;123:2390–6.
- Gonzalez A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *Lancet* 2004;363:345–51.
- Brenner DJ, Elliston CD. Estimated radiation risks potentially associated with full-body CT screening. *Radiology* 2004;232:735–8.
- Sun C, Hu Z, Zhong Z, et al. Clinical and prognostic analysis of second primary squamous cell carcinoma of the tongue after radiotherapy for nasopharyngeal carcinoma. *Br J Oral Maxillofac Surg* 2014;52:715–20.
- Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst* 1993;85:25–31.
- Cheruku R, Hussain M, Tyrkus M, et al. Myelodysplastic syndrome after cisplatin therapy. *Cancer* 1993;72:213–8.
- Biti G, Cellai E, Magrini SM, et al. Second solid tumors and leukemia after treatment for Hodgkin's disease: an analysis of 1121 patients from a single institution. *Int J Radiat Oncol Biol Phys* 1994;29:25–31.