Influence of the second primary cancer on clinical outcomes of nasopharyngeal carcinoma following definitive chemoradiotherapy

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Abstract. Nasopharyngeal carcinoma (NPC) is a distinct type of head and neck cancer characterized by undifferentiated histopathological features and a notably high incidence in Taiwan and Southeastern China. Advances in NPC diagnosis and treatment have led to improved prognosis and long-term survival rates. Compared with other head and neck cancers, NPC tends to occur at a younger age, and is associated with a relatively higher rate of second primary cancers (SPCs) that may develop during follow-up. Therefore, investigating the risk of SPCs in a non-metastatic NPC cohort treated with concurrent chemoradiotherapy (CCRT) is essential for developing tailored follow-up strategies. Patients with pathologically confirmed NPC were retrospectively enrolled between January 2012 and December 2022. The primary outcome of this study was overall survival (OS). A total of 161 eligible patients were analyzed. During a median follow-up period of 4.5 years, seven patients developed SPCs, yielding a crude incidence rate of 4.3%. The lung was the most common SPC site (42%, n=3). The median interval from NPC diagnosis to the first SPC was 2.7 years. Kaplan-Meier analysis with the log-rank test indicated that SPC development significantly affected OS (P=0.049). Using Firth's logistic penalized Cox regression, univariate analysis showed that the absence of SPCs [hazard ratio (HR)=0.27, 95% confidence interval (CI): 0.09-0.86] was associated with favorable OS, whereas older age (≥65 years) (HR=3.66, 95% CI: 1.60-8.40) was associated with worse OS. In the multivariate analysis, only older age (≥65 years) (HR=3.34, 95% CI: 1.43-7.80) remained significantly associated with unfavorable OS. Post-CCRT follow-up for patients with NPC should include surveillance not only for recurrence but also for the potential development of SPCs.

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Abbreviations: CCRT, concurrent chemoradiotherapy; CI, confidence interval; EBV, Epstein-Barr virus; HR, hazard ratio; IMRT, intensity-modulated radiation therapy; NPC, nasopharyngeal carcinoma; OS, overall survival; SPC, second primary cancer

Key words: nasopharyngeal carcinoma, head and neck cancer, second primary cancer, survival outcomes, concurrent chemoradiotherapy

Introduction

Nasopharyngeal carcinoma (NPC) is a distinct subtype of head and neck cancer characterized by undifferentiated histopathological features and a high incidence in Taiwan and Southeast China. Its etiology is multifactorial, involving complex interactions among genetic, environmental and lifestyle factors. Notable contributing factors include Epstein-Barr virus (EBV) infection, genetic susceptibility, oncogenic mechanisms, ethnicity, specific dietary habits, environmental exposures and lifestyle behaviors (1-3). Histopathologically, NPC is typically an undifferentiated carcinoma with a prominent lymphoid stroma, which accounts for its distinct biological and clinical characteristics compared with those of other head and neck squamous cell carcinomas. Because NPC is sensitive to both radiotherapy and chemotherapy, concurrent chemoradiotherapy (CCRT) remains the standard treatment for locally advanced disease. Recent advances in diagnostic techniques and therapeutic strategies have substantially improved prognosis and long-term survival rates for patients with NPC (4,5).

A comprehensive approach is essential to address the complex challenges faced by patients with head and neck cancers, particularly the elevated incidence of second primary cancers (SPCs). Aerodigestive malignancies share several common risk factors, including tobacco use, alcohol consumption, dietary habits and environmental exposures. These SPCs contribute substantially to morbidity and mortality among these patients (6-8). Compared with other head and neck malignancies, NPC typically presents at a younger age, underscoring the importance of long-term follow-up to monitor for recurrence and to maintain overall health and quality of life.

Although SPCs following NPC are relatively uncommon, they can have a substantial impact on patient survival. Observational studies have demonstrated NPC survivors face an elevated risk of SPCs among NPC survivors (9-14). A population-based study from Taiwan reported this increased risk of SPCs in NPC survivors, which was associated with unfavorable overall survival (OS) (9).

Despite these findings, real-world clinical data on SPCs in patients with NPC treated in the era of CCRT remain limited. Such data are crucial for bridging the gap between population-based evidence and detailed clinical observations. Therefore, the present study aimed to determine the occurrence and characteristics of SPCs in a non-metastatic NPC cohort treated with CCRT. Comprehensive case descriptions may provide valuable insights for tailoring long-term surveillance strategies.

Patients and methods

Study population. Patients diagnosed with pathologically confirmed NPC were enrolled retrospectively at Chi Mei Medical Center (Liouying, Taiwan) between January 2012 and December 2022. The patients' data were accessed and extracted after obtaining institutional review board (IRB) approval in November 2025. The follow-up period ended on December 31, 2024. Patients were excluded if they had a history of cancer prior to NPC diagnosis, distant metastasis at initial presentation, unknown pathological type, missing clinical and therapeutic data, and were aged <18 years. Clinical evaluations to assess SPC findings included reviews of radiographic, positron emission tomography, endoscopic, surgical and pathological records, alongside follow-up imaging to assess SPC findings. The possibility that an SPC was a metastasis of the primary NPC was strictly ruled out. To distinguish SPCs from recurrences or metastases, the SPC diagnosis was validated using pathological findings from resected specimens or biopsy examinations to distinguish SPC from recurrence or metastasis. The definition of SPC followed the Warren and Gates criteria, as modified by Morris *et al* (6). Additional diagnostic workups were conducted in response to clinical complaints or abnormal imaging findings.

Treatments. The standard CCRT regimen included platinum-based chemotherapy agents and radiation, with doses exceeding 6,600 cGy delivered in daily fractions to the gross target volume and high-risk regional neck region delivered in daily fractions. Highly conformal external beam radiation techniques, such as intensity-modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT), were used. All patients with non-metastatic NPC underwent definitive CCRT as described in a previous study by our group (5), in accordance with National Comprehensive Cancer Network guidelines (15).

Measurements of covariates and outcome definition. Data on sex, age, histology, American Joint Committee on Cancer (AJCC) clinical stages, clinical tumor (cT) stages, clinical node (cN) stages, year of diagnosis, pre-treatment EBV DNA load (4) and the last follow-up date were extracted. Clinical staging was determined according to the AJCC 8th edition for NPC (15). The pre-treatment blood EBV DNA load was evaluated using an EBV PCR Kit (cat. no. 8N54.85) with fully automated DNA extraction and amplification on the m2000 system (Abbott Pharmaceutical Co. Ltd.), according to the manufacturer's recommendations. The primary outcome of this study was OS, defined as the time from NPC diagnosis until death from any cause. All patients were followed up until death; surviving patients were censored on the last day of the database record (December 31, 2024).

Statistical analysis. Descriptive statistics were used to summarize categorical variables as frequencies and percentages, and continuous variables as means or medians with standard deviations or medians as appropriate. Age was analyzed both as a continuous variable, and also categorized as a categorical variable (dichotomized at a cutoff of 65 years). Differences between the SPC and non-SPC groups were compared using chi-square test for categorical variables when all expected cell counts exceeded 5 or when no more than 20% of cells had expected counts of 5 or less; otherwise, Fisher's exact test was applied. Continuous variables were compared using Student's t-test, as appropriate. Kaplan-Meier survival curves were generated and differences between groups were compared using the log-rank test. Firth's penalized Cox regression was used to mitigate analytical biases caused by the small sample sizes. To identify independent prognostic factors, multivariate regression analyses were conducted, incorporating variables with $P<0.10$ from the univariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A two-tailed $P<0.05$ was considered to indicate statistical significance. All analyses were performed using SPSS version 25 for Windows (IBM Corp.).

Results

Demographic characteristics of patients with NPC and SPC development. Between January 2012 and December 2022, 223 patients with confirmed NPC or referred for NPC were identified from the hospital's cancer registry database. The final analysis focused on 161 eligible patients with histologically confirmed NPC with no metastasis and clinical stage I to IVA. Table I summarizes the patients' characteristics and clinical details. The study cohort was predominantly male, comprising 117 men and 44 women. The median age was 51 years, with ages ranging from 25-84 years, and 86% of the patients were <65 years old. Based on the 8th edition of the AJCC staging manual, most patients (81%) had stage III-IVA disease. All patients received platinum-based chemotherapy as part of the CCRT regimen. Radiation and chemotherapy doses were highly consistent across the cohort. Between 2012 and 2022, the pre-treatment EBVDNA load was not mandatory for routine stage work-up. Only 124 patients (77%) had records of pre-treatment EBV DNA load, and EBV levels in the blood was detectable in 93 patients (75% of those with available records; 58% of the total cohort). During a median follow-up period of 4.5 years, seven patients developed an SPC, resulting in a crude incidence rate of 4.3%. The most common SPC site for an SPC development was the lung (42%, n=3), followed by the colon (n=1), thyroid (n=1), breast (n=1) and liver (n=1). The SPC cohort comprised six male and one female patients. The median age was 63 years (range, 45-68 years). Six cases occurred outside

Table I. Clinical characteristics of patients with nasopharyngeal carcinoma with vs. without second primary cancer.

Characteristic	Patients (n=161)	Second primary cancer (n=7)	Without second primary cancer (n=154)	P-value[a]
Age, years [median (range)]	51 (25-84)	56	51	0.05
Age, years				0.05
<65	139 (86)	4 (57)	135 (88)	
≥65	22 (14)	3 (43)	19 (12)	
Sex				0.68
Male	117 (73)	6 (86)	111 (72)	
Female	44 (27)	1 (14)	43 (28)	
AJCC clinical stage[b]				0.29
I	11 (7)	0 (0)	11 (7)	
II	20 (12)	0 (0)	20 (13)	
III	58 (36)	1 (14)	57 (37)	
IVA	72 (45)	6 (86)	66 (43)	
Clinical T stage				0.26
T1-2	84 (52)	2 (29)	82 (53)	
T3-4	77 (48)	5 (71)	72 (47)	
Clinical N stage				>0.99
N0-1	57 (35)	2 (29)	55 (36)	
N2-3	104 (65)	5 (71)	99 (64)	
Pre-treatment EBV DNA load				>0.99
Not detected	31 (25)	1 (20)	30 (23)	
DNA detected	93 (75)	4 (80)	89 (77)	

[a]Comparisons between patients with vs. without a second primary cancer were performed using Fisher's exact test when expected cell counts were <5. [b]AJCC Staging Manual 8th edition. Values are expressed as n (%) unless otherwise specified. AJCC, American Joint Committee on Cancer; CCRT, concurrent chemo-radiotherapy; EBV, Epstein-Barr virus.

Table II. Summary of clinical findings, treatment and outcomes in patients with NPC with second primary cancer.

No	Sex/age, years	AJCC stage[a] of NPC	Latent period, years	Second primary cancer (pathology/stage)	Treatment of second primary cancer	Outcome (cause of death)
1	M/45	IVA (T4N2M0)	7.1	Lung (adenocarcinoma/ pT2aN0M0)	Lobectomy, CCRT	Alive
2	M/49	IVA (T3N3M0)	2.4	Lung (SCC/cT4N2M1a)	CCRT	Dead (lung cancer)
3	M/57	III (T3N0M0)	2.6	Lung (adenocarcinoma/ pT1bN0M0)	Lobectomy	Alive
4	M/68	IIIA (T2N3M0)	2.6	Colon (adenocarcinoma/ pT1bN0M0)	Sigmoidectomy	Dead (NPC)
5	M/63	IVA (T4N0M0)	1	Thyroid (papillary carcinoma/pT3N1bM0)	Thyroidectomy, neck dissection	Alive
6	F/67	IVA (T4N2M0)	2.6	Breast (T2N1M0)	Lumpectomy, CT and RT	Alive
7	M/68	IVA (T4N3M0)	0.3	HCC (T1bN0M0)	Radiofrequency ablation, TACE	Dead (COVID-19)

[a]AJCC Staging Manual 8th edition. M, male; F, female; AJCC, American Joint Committee on Cancer; ARDS, acute respiratory distress syndrome; CCRT, concurrent chemoradiotherapy; HCC, hepatocellular carcinoma; NPC, nasopharyngeal carcinoma; SCC, squamous cell carcinoma; TACE, trans-arterial chemoembolization.

Table III. Univariate and multivariate Cox regression analyses with Firth's correction were performed to identify potential factors associated with overall survival in patients with nasopharyngeal carcinoma.

	Univariate		Multivariate[a]	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Second primary cancer (no vs. yes)	0.27 (0.09-0.86)	0.03	0.43 (0.13-1.41)	0.16
Age at diagnosis (<65 vs. ≥65 years)	3.66 (1.60-8.40)	0.002	3.34 (1.43-7.80)	0.005
Sex (female vs. male)	0.47 (0.17-1.32)	0.15	-	-
AJCC clinical stage[b] (III-IV vs. I-II)	4.35 (0.81-23.30)	0.07	1.83 (0.22-15.12)	0.57
Clinical T stage (T3-4 vs. T1-2)	2.17 (0.97-4.86)	0.06	1.62 (0.70-3.78)	0.26
Clinical N stage (N2-3 vs. N0-1)	2.70 (0.96-7.58)	0.06	1.82 (0.57-5.89)	0.32
Pre-treatment EBV DNA load (detected vs. not detected)	0.59 (0.20-1.80)	0.33	-	-

[a]Variables with P<0.1 in the univariate analysis were included in multivariate modeling. [b]AJCC Staging Manual 8th edition. Statistical significance was set at P<0.05. AJCC, American Joint Committee on Cancer; CCRT, concurrent chemoradiotherapy; EBV, Epstein-Barr virus; CI, confidence interval; HR, hazard ratio.

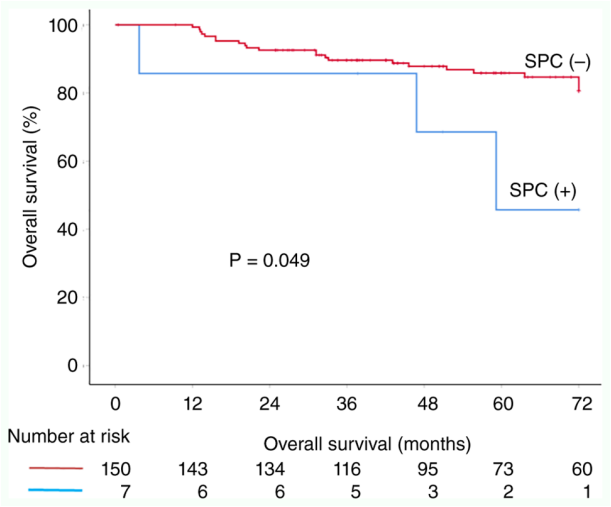

Figure 1. Kaplan-Meier survival curves comparing overall survival of patients with nasopharyngeal carcinoma with vs. those without SPC. SPC, second primary cancer. Surviving patients were censored on the last day of the database record (December 31, 2024).

the radiation field of the head and neck region, and only one case (14%) occurred within the field, a pathologically confirmed papillary thyroid carcinoma. The median interval from NPC diagnosis to the first SPC was 2.7 years. Table II details the characteristics of the patients who developed an SPC.

The cohort was categorized into two groups: Patients with the occurrence of an SPC and those without an SPC. Table I compares the demographic and clinical characteristics between these groups. The continuous age and the proportion of patients aged ≥65 years did not differ significantly between the two groups (all P=0.05). No significant differences were observed in sex (P=0.68), overall clinical stage (P=0.29), cT stage (P=0.26), cN stage, treatment (P>0.99) or pre-treatment EBV DNA viral load (all P>0.99).

Survival analyses between the SPC and non-SPC Groups. The mean follow-up time from diagnosis was similar between the two groups (SPC group: 4.6±3.1 years; non-SPC group: 5.5±3.3 years; P=0.48). The median OS for the entire cohort was 4.2 years. The median OS was 3.5 years for the SPC group and 4.0 years for the non-SPC group. At the end of the follow-up period, 26 patients (16.1%) in the overall cohort had died. In the SPC group there were three deaths: One attributable to the SPC (lung cancer), one to COVID-19 and one to relapsed NPC. Kaplan-Meier survival analysis indicated that SPC development significantly decreased OS (P=0.049; Fig. 1).

Univariate and multivariate regression analyses. Univariate analyses revealed that absence of an SPC was associated with better OS (HR=0.27, 95% CI: 0.09-0.86 P=0.03), whereas older age (≥65 years) was associated with worse OS (HR=3.66, 95% CI: 1.60-8.40, P=0.002). Overall clinical stage, cT stage and cN stage showed trends toward significance regarding OS. Sex and pre-treatment EBV DNA load were not significantly associated with OS. However, in the multivariate Firth's penalized Cox regression model, only the older age (≥65 years) (HR=3.34, 95% CI: 1.43-7.80, P=0.005) remained significantly associated with worse OS, while the presence of an SPC was no longer an independent predictor. Table III presents the results of the univariate and multivariate analyses.

Discussion

An SPC is defined as the development of a new malignancy in a patient who has previously been diagnosed with cancer. It is distinct from a recurrence or metastasis of the primary tumor, as it arises independently and often exhibits a different histological profile. SPCs may occur in the same or different organs and are diagnosed based on established criteria that distinguish them from the initial cancer. The core requirement for defining an SPC is histological confirmation of malignancy. The tumors must be anatomically distinct and separated by a clear margin of normal tissue from the previous tumor, and the possibility that the SPC is a metastasis of the primary tumor must be ruled out (6,16). With advances in early detection, supportive care and treatment, the number of

cancer survivors has increased substantially in recent decades. Consequently, greater clinical vigilance has led to the earlier identification of SPCs before they progress or metastasize. According to Travis, SPCs and multiple primary cancers account for ~16% of all incident cancers reported to the US National Cancer Institute Surveillance, Epidemiology and End Results Program (16). The diagnosis of an SPC represents one of the most serious events faced by cancer survivors. SPCs may reflect late treatment-associated sequelae, as well as the influence of lifestyle factors, environmental exposures, host susceptibility and complex gene-environment or gene-gene interactions.

A comprehensive approach is essential to address the complex challenges faced by patients with head and neck cancers, particularly the elevated incidence of SPCs within the aerodigestive tract. These malignancies share several common risk factors, including tobacco use, alcohol consumption, dietary habits and environmental exposures. Morris *et al* (6) reported that patients with head and neck cancer have a ~2.2-fold higher standardized incidence ratio for developing SPCs, most frequently involving the head and neck region, esophagus and lungs. These SPCs contribute substantially to morbidity and mortality among these patients (6-8). NPC typically presents at a younger age compared to other head and neck cancers (mean age, 49.9 vs. 53.4 years) (7), underscoring the importance of long-term follow-up to monitor for recurrence, manage late radiation-related complications, and maintain overall health and quality of life.

Observational studies have demonstrated an elevated risk of SPCs among patients with NPC, with reported crude incidences ranging from 2.0 to 5.6% across different follow-up periods (9-14). A population-based study by Lin *et al* (9), involving 10,299 patients with NPC in Taiwan, reported a 1.59-fold higher incidence of SPCs in NPC survivors compared with age- and sex-matched controls. The aforementioned study also found that the increased risk of SPCs in NPC survivors was associated with worse OS. Among patients with head and neck cancers, a nationwide cohort study in Taiwan identified 9,996 SPCs in 93,891 patients, corresponding to a crude incidence of 10.6% between 1986 and 2008. In a subgroup analysis, the crude incidence among patients with NPC was lower than that for other head and neck cancers, at 5.6% (1,545 SPCs among 27,834 patients) (7). Svärd *et al* (10) reviewed data from 21 studies encompassing 89,168 patients with NPC and found a mean SPC incidence of ~6.6%, ranging from 2.5 to 9.2% in endemic regions such as Taiwan, Hong Kong, Singapore and China. This systematic review also noted that the most frequent SPC sites include the oral cavity, pharynx, nasal cavity and paranasal sinuses, esophagus and lungs; furthermore, although the mean incidence rate of SPCs after NPC is lower than that observed in other head and neck cancers, the risk remains clinically significant (10). The elevated risk of SPCs among NPC survivors compared with the general population may be attributed to persistent behavioral risk factors, genetic predisposition, prolonged survival and the long-term effects of CCRT (10). In the present study, 7 SPCs were identified among 161 patients with NPC, corresponding to a crude incidence of 4.3%, which is consistent with previous reports (9-14). Therefore, long-term follow-up for NPC survivors is essential, not only for monitoring recurrence and managing late treatment effects but also for providing comprehensive and earlier identification of SPCs before they progress or metastasize.

The present retrospective study demonstrated that the development of an SPC was associated with worse OS in the unadjusted analysis, but this association was not independent after adjustment, likely because of limited statistical power. According to previous reports, the 5-year OS rates for patients with non-metastatic NPC treated with CCRT typically range from ~70 to 85% (4-5). Given the high curability of NPC and its relatively younger age of onset compared with that of other head and neck cancers, long-term follow-up is crucial. Notably, >60% of SPCs were detected within the first 3 years after the initial NPC diagnosis (10). Previous studies have reported poorer survival among patients with oral cancer who developed SPCs within 2 years, primarily due to the inability to administer curative radiotherapy or chemotherapy in this setting, as critical organ tolerances had already been reached (17-22). Therefore, the present study may offer valuable clinical insights into the early detection of SPCs within this time frame. However, SPCs may occur many years after treatment, particularly radiation-related malignancies; thus, the present study may underestimate the long-term cumulative incidence of SPCs. The proportion of deaths attributable to SPCs continued to increase over the long-term follow-up period, accounting for 4.3 and 9.0% of all deaths at the end of the 5- and 10-year follow-up durations, respectively (22). This upward trend in SPC-related mortality highlights the importance of early recognition of this serious complication, particularly during the later phases of survivorship and among patients with early-stage NPC who generally achieve excellent primary tumor control. During extended follow-up, SPCs may become a leading cause of mortality among survivors of head and neck cancers (8,16). Consistent with the present findings, two population-based studies from Taiwan reported that patients with NPC with NPC who developed SPCs had significantly lower survival rates (9,14). Furthermore, multiple studies have confirmed SPCs as an independent negative prognostic factor for survival in patients with NPC (9,11,14,17,18). Similarly, in other head and neck cancers, the diagnosis of an SPC has been associated with a markedly worse prognosis compared with that of patients who do not develop SPCs. Most population-based or hospital-based studies in the literature, including the present study, have used OS as the primary outcome (7,8,19-22). However, cancer-specific survival or competing-risk analysis may be optimal for evaluating the impact of SPCs. Because of the small number of SPC events observed in the present study, it was not possible to compare cancer-specific survival between the two groups.

In the current study, three cases of lung cancer, one case of thyroid cancer and one case of sigmoid colon cancer were identified, with a median latency period of 2.7 years. Consistent with the present findings, several previous studies have also reported lung cancer as the most common SPC among patients with NPC (11,21). Notably, 59% of respiratory SPCs occurred within the first 2 years of follow-up, while 53% of oral cavity SPCs developed during the 3-to-4-year and >5-year follow-up intervals (9). Tobacco smoking has been established as a risk factor for NPC, and previous studies that included smoking history have identified it as an independent risk factor for the

development of SPC (10,11,21). By contrast, alcohol consumption has not shown a statistically significant association with survival in patients with metachronous multiple primary cancers of NPC (22).

NPC is an EBV-related malignancy, and EBV DNA levels before and after treatment affect the prognosis of patients with NPC (4,23). The current study did not identify an association between pre-treatment EBV DNA load and SPCs. However, a previous review indicated that EBV status is significantly associated with SPC development. The mean incidence of SPCs among patients with NPC is ~6.6%, ranging from 4.9% in endemic regions to 8.7% in non-endemic regions (10). This variation suggests that the epidemiology of both NPC and SPCs may differ between areas of low and high endemicity. In the era of IMRT and VMAT, patients with NPC are exposed to broader radiation fields, resulting in greater irradiation of surrounding head and neck tissues. Wang *et al* (12) reported that, compared with conventional radiotherapy, treatment with IMRT is associated with a higher risk of SPCs, possibly reflecting the increased total volume of head and neck tissue exposed to radiation.

In the multivariate Cox regression analysis with Firth's correction of the present study, older age (≥65 years) was associated with unfavorable OS. However, there is consistency in the literature indicating that younger patients with NPC have a higher risk of developing SPCs. Studies have reported an increased risk of SPCs when NPC is diagnosed at a younger age (e.g., <40 or <50 years) (10). This finding is biologically plausible; although the baseline risk of sporadic cancers naturally increases with aging, younger patients have a longer survivorship period during which a radiation-induced or second malignancy may develop.

The present retrospective, hospital-based study included only 161 eligible cases; therefore, the development of an SPC was not an independent predictor in the adjusted analysis due to the limited statistical power caused by the small number of SPCs. Furthermore, the present study had lacked data regarding the role of smoking, alcohol consumption, betel nut use, family history and comorbidities, which may all influence the development of SPCs. Finally, as with all retrospective studies, it is impossible to eliminate all potential sources of bias. Nevertheless, the present real-world analysis of SPCs in patients with NPC treated during the CCRT era helps bridge the gap between population-based studies and clinical practice by providing detailed clinical insights. As earlier diagnosis and advances in treatment continue to improve the survival of patients with NPC, the incidence of SPCs may increase, underscoring the importance of careful long-term follow-up in this population.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Author's contributions

SCY and SYH conceived the study. SCY and SYH designed the study. LTS, SWL and CCC analyzed and interpreted data. SCY and SYH analyzed and interpreted the data and wrote the manuscript. SCY and CHH performed the statistical analysis. SCY edited the manuscript. SCY and SYH confirm the authenticity of all the raw data. All authors reviewed the manuscript. All authors and have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was conducted according to the Declaration of Helsinki and was approved by the Research Ethics Committee of Chi Mei Hospital (IRB permit no. 11406-L1). The Research Ethics Committee of Chi Mei Medical Center waived the requirement for informed consent. All data were fully anonymized before access. Written informed consent for participation was not required for the present retrospective study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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