Original Article



# Impact of prior cancer on outcomes in nasopharyngeal carcinoma

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**Background:** Prior cancer is a common exclusion criterion in nasopharyngeal carcinoma (NPC) trials. However, whether a prior cancer diagnosis affects trial outcomes is still unknown. We aimed to determine the impact of prior cancer on survival in NPC patients.

**Methods:** We identified patients diagnosed with NPC between 2004 and 2009 in the Surveillance, Epidemiology, and End Results (SEER) database. Variables were compared by chi-squared test and *t*-test as appropriate. Propensity score-adjusted Kaplan-Meier methods and Cox proportional hazard models were used to evaluate the impact of prior cancer on overall survival (OS).

**Results:** Among 3,131 eligible NPC patients, 349 (11.15%) patients had a history of prior cancer. The Kaplan-Meier curves did not show a statistically significantly different OS (P=0.19). Subgroup analyses stratified by timing of prior cancer and AJCC TNM stage of index cancer displayed the same tendency: prior cancer did not adversely affect OS compared to patients without prior cancer (P>0.05). Furthermore, in propensity score-adjusted COX models analysis, patients with prior cancer had the same/non-inferior OS [hazard ratio (HR) =1.12; 95% confidence interval, 0.88 to 1.42].

**Conclusions:** Among patients with NPC, prior cancer does not convey an adverse effect on clinical outcomes, regardless of the timing of prior cancer and AJCC TNM stage of index cancer. Broader inclusion trial criteria could be adopted in NPC patients with a history of prior cancer. However, further studies are still needed to confirm this conclusion.

**Keywords:** Prior cancer; nasopharyngeal carcinoma (NPC); survival; clinical trial; Surveillance, Epidemiology, and End Results (SEER)

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## Introduction

Nasopharyngeal carcinoma (NPC) is a head and neck cancer common in South China and Southeast Asia (1). With the primary treatment of radiotherapy or chemoradiotherapy, the 5-year overall survival (OS) of early stage NPC is greater than 90% (2). However, recurrent or primary metastatic NPC still represents a critical unmet medical need in oncology research. Despite the ability of intensity-modulated radiation therapy to significantly

improve the tumor local control rate, distant metastasis is still poorly controlled, which remains the major reason for treatment failure. Many large clinical trials have been conducted to find the optimum comprehensive therapy for these patients in order to improve survival, which includes the standard first-line treatment option, gemcitabine plus cisplatin, and induction chemotherapy plus concurrent chemoradiotherapy (3,4).

Clinical trials are essential for better management of these patients. Fewer than 5% of adults with cancer in the United States participate in clinical trials (5). Clinical trial eligibility criteria present a major barrier to the study's enrollment, especially in oncology clinical trials, where patients with a prior cancer diagnosis are frequently excluded (6). For instance, over 80% of lung cancer trials sponsored by the Eastern Cooperative Oncology Group (ECOG) exclude patients with prior cancer (7). This practice is mainly based on the long-held assumption that prior cancer diagnosis and treatment could interfere with study outcomes. However, our previous pan-cancer study suggested that not all prior cancers actually interfere with study outcomes (8). The number of cancer survivors has had a four-fold increase in the United States over the last three decades (9). Due to the improved survival of cancer patients, the prevalence of multiple primary cancer has also increased rapidly (10). Twenty-five percent of older adults and more than 10% of younger adults diagnosed with cancer have a history of prior cancer (11). Given the increased number of cancer survivors, the impact of this exclusion criteria will likely increase.

Until now, no study has specifically evaluated the impact of prior cancer on NPC outcomes, and little is known about the characteristics of NPC patients with prior cancer. There is also no available database report in South China and Southeast Asia yet. To address this absence in data, we identified the characteristics and determined the prognostic impact of prior cancer among patients with NPC using the Surveillance, Epidemiology, and End Results (SEER) database.

## Methods

### *Data source and population*

We extracted data from the SEER database by using the SEER*Stat software version 8.3.5, which covers approximately 30% of the population in the United States (https://seer.cancer.gov/, accession number: 13693-Nov2015) (12,13).

The study population included patients diagnosed with NPC from January 2004 to December 2009. Patients who met any of the following criteria were excluded from the study: (I) age at diagnosis younger than 18 years, (II) patients with only autopsy or death certificate records, and (III) patients with incomplete survival data and follow-up information.

We extracted demographic and clinicopathological data from the SEER database, including sex, age, race, marital status, pathology grade, TNM stage, surgery, and radiotherapy. We classified the race as white, black, and others. Patients were divided into married or unmarried. The TNM stage was based on the AJCC (6th edition) staging system. Considering that the survival data were available in the measurement unit of months, the survival time of 0 months was recorded as 0.5 months to include patients who died within 1 month of diagnosis.

### *Measures*

A history of prior cancer was determined from SEER sequence numbers, as described in our previous study (8). In brief, sequence numbers represent the order of all primary reportable neoplasms diagnosed in a lifetime. The timing of the prior cancer was calculated by using the SEER diagnosis dates of the index cancer and the most recent of any prior cancers. Cases with full timing records were used for further study. The primary outcome of this study was OS. We set December 31$^{st}$, 2014, as the follow-up cutoff date to ensure that all included cases were followed up for at least 5 years.

### *Statistical analysis*

We categorized patients into two groups based on prior cancer history. Differences in patients' characteristics were assessed by Pearson chi-squared analysis for categorical variables and *t*-test for continuous variables as appropriate. In this study, we employed a propensity score matching (PSM) method to minimize the effect of confounding from differences in baseline characteristics (14). Propensity scores were calculated based on race, sex, age, marital status, TNM stage, pathologic grade, and treatment. A one-to-one PSM with a caliper of 0.2 was performed. The characteristics were balanced after PSM. These PSM pairs were used in subsequent analyses.

OS was calculated with the Kaplan-Meier method, and differences were compared using log-rank tests. Finally, we built a multivariate Cox proportional hazards

 

model to identify whether prior cancer impacted the prognosis independently. The common demographic and clinicopathological data, including race, sex, age, marital status, TNM stage, pathologic grade, and treatment, were entered as covariates. Statistical significance was set as a two-sided P value of less than 0.05. Analyses were performed using R Statistical software (version 3.4.2, Institute for Statistics and Mathematics, Vienna, Austria; www.r-project.org).

## Results

In total, we identified 3,131 eligible NPC patients diagnosed between 2004 and 2009. Among these cases, 11.15% (n=349) had a history of prior cancer. Compared with cases without previous malignancies, patients with prior cancer were older (66.25 *vs.* 54.59 years, P<0.001), female (37.0% *vs.* 29.5%, P=0.005), white (70.5% *vs.* 48.5%, P<0.001), and unmarried (47.3% *vs.* 40.7%). The percentage of surgery was larger among patients with prior cancer (15.8% *vs.* 11.9%, P=0.047), and patients with prior cancer received less radiotherapy (67.9% *vs.* 80.1%, P<0.001). Additional baseline characteristics are displayed in *Table 1*. Characteristics were balanced between groups after adjustment for propensity score (*Table 1*, P>0.05). Among 349 NPC patients with a history of cancer, the

**Table 1** Baseline characteristics of patients with nasopharyngeal carcinoma in the original/matched data sets (N=3,131)

| Characteristics | Original data set | | | Matched data set | | |
|---|---|---|---|---|---|---|
| | No prior cancer, N=2,782 (%) | With prior cancer, N=349 (%) | P value | No prior cancer, N=349 (%) | With prior cancer, N=349 (%) | P value |
| Age [mean (SD)] | 54.59 (14.53) | 66.25 (12.15) | <0.001 | 66.83 (12.98) | 66.25 (12.15) | 0.543 |
| Gender | | | 0.005 | | | 0.585 |
| Male | 1,962 (70.5) | 220 (63.0) | | 212 (60.7) | 220 (63.0) | |
| Female | 820 (29.5) | 129 (37.0) | | 137 (39.3) | 129 (37.0) | |
| Race | | | <0.001 | | | 0.932 |
| White | 1,348 (48.5) | 246 (70.5) | | 243 (69.6) | 246 (70.5) | |
| Black | 313 (11.3) | 35 (10.0) | | 38 (10.9) | 35 (10.0) | |
| Others/unknown | 1121 (40.3) | 68 (19.5) | | 68 (19.5) | 68 (19.5) | |
| Marital status | | | 0.022 | | | 0.405 |
| Married | 1,649 (59.3) | 184 (52.7) | | 172 (49.3) | 184 (52.7) | |
| Unmarried | 1,133 (40.7) | 165 (47.3) | | 177 (50.7) | 165 (47.3) | |
| Site | | | 0.466 | | | 0.998 |
| Superior wall | 30 (1.1) | 3 (0.9) | | 4 (1.1) | 3 (0.9) | |
| Posterior wall | 268 (9.6) | 40 (11.5) | | 42 (12.0) | 40 (11.5) | |
| Lateral wall | 240 (8.6) | 28 (8.0) | | 26 (7.4) | 28 (8.0) | |
| Anterior wall | 31 (1.1) | 7 (2.0) | | 7 (2.0) | 7 (2.0) | |
| Overlapping lesion | 106 (3.8) | 17 (4.9) | | 17 (4.9) | 17 (4.9) | |
| NOS | 2,107 (75.7) | 254 (72.8) | | 253 (72.5) | 254 (72.8) | |
| Grade | | | <0.001 | | | 0.617 |
| Well differentiated | 57 (2.0) | 17 (4.9) | | 10 (2.9) | 17 (4.9) | |
| Moderately differentiated | 253 (9.1) | 56 (16.0) | | 53 (15.2) | 56 (16.0) | |

**Table 1** (*continued*)

 

**Table 1** (*continued*)

| Characteristics | Original data set | | | Matched data set | | |
|---|---|---|---|---|---|---|
| | No prior cancer, N=2,782 (%) | With prior cancer, N=349 (%) | P value | No prior cancer, N=349 (%) | With prior cancer, N=349 (%) | P value |
| Poorly differentiated | 884 (31.8) | 112 (32.1) | | 120 (34.4) | 112 (32.1) | |
| Undifferentiated | 773 (27.8) | 48 (13.8) | | 43 (12.3) | 48 (13.8) | |
| Unknown | 815 (29.3) | 116 (33.2) | | 123 (35.2) | 116 (33.2) | |
| AJCC TNM stage | | | 0.009 | | | 0.617 |
| I | 230 (8.3) | 47 (13.5) | | 42 (12.0) | 47 (13.5) | |
| II | 565 (20.3) | 70 (20.1) | | 67 (19.2) | 70 (20.1) | |
| III | 679 (24.4) | 70 (20.1) | | 73 (20.9) | 70 (20.1) | |
| IV | 865 (31.1) | 99 (28.4) | | 115 (33.0) | 99 (28.4) | |
| Unknown | 443 (15.9) | 63 (18.1) | | 52 (14.9) | 63 (18.1) | |
| Surgery | | | 0.047 | | | 0.917 |
| Yes | 331 (11.9) | 55 (15.8) | | 53 (15.2) | 55 (15.8) | |
| No/unknown | 2,451 (88.1) | 294 (84.2) | | 296 (84.8) | 294 (84.2) | |
| Radiotherapy | | | <0.001 | | | 0.460 |
| Yes | 2,227 (80.1) | 237 (67.9) | | 247 (70.8) | 237 (67.9) | |
| No/unknown | 555 (19.9) | 112 (32.1) | | 102 (29.2) | 112 (32.1) | |

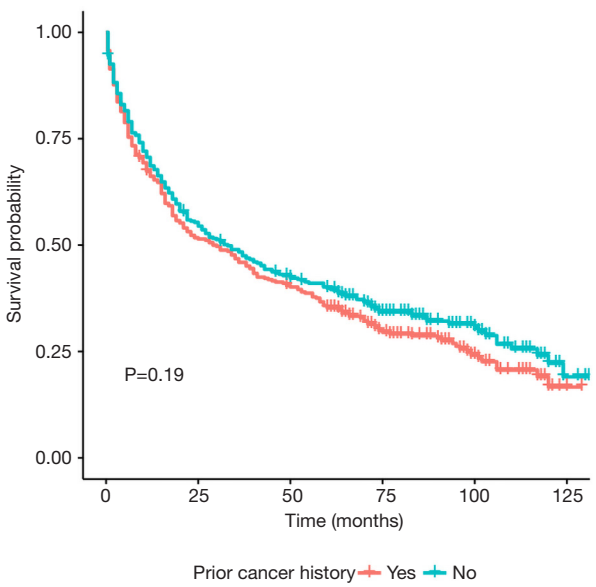


**Figure 1** The Kaplan-Meier survival curves of prior cancer impact on the overall survival in nasopharyngeal carcinoma. The overall survival of nasopharyngeal carcinoma was similar compared with that of patients without prior cancer (P>0.05).

types of prior cancer were clearly recorded for 225 patients in the SEER database. The most common prior cancers in our study cohort were head and neck (21.78%), prostate (21.33%), gastrointestinal (14.22%), other genitourinary and gynecologic types (13.34%), and breast cancer (9.78%). Localized and regional stages accounted for 77.46% of cases. Over 60.52% of the prior cancers were diagnosed within 5 years of the index NPC. The median time between the most recent prior cancer diagnosis and the index NPC was 3.5 years.

In unadjusted Kaplan-Meier analysis, NPC patients with prior cancer demonstrated similar OS compared to patients without prior cancer (log-rank tests P=0.19) (*Figure 1*). The overall 5-year survival rates for patients with or without prior cancer were 35.2% [95% confidence interval (CI), 30.5–40.6] and 39.8% (95% CI, 35.0–45.4), respectively. *Figure 2* depicts Kaplan-Meier survival curves stratified by the timing of prior cancer and index cancer TNM stage. Subgroup analyses stratified by timing of prior cancer and AJCC TNM stage of index cancer displayed the same tendency; prior cancer did not adversely

 

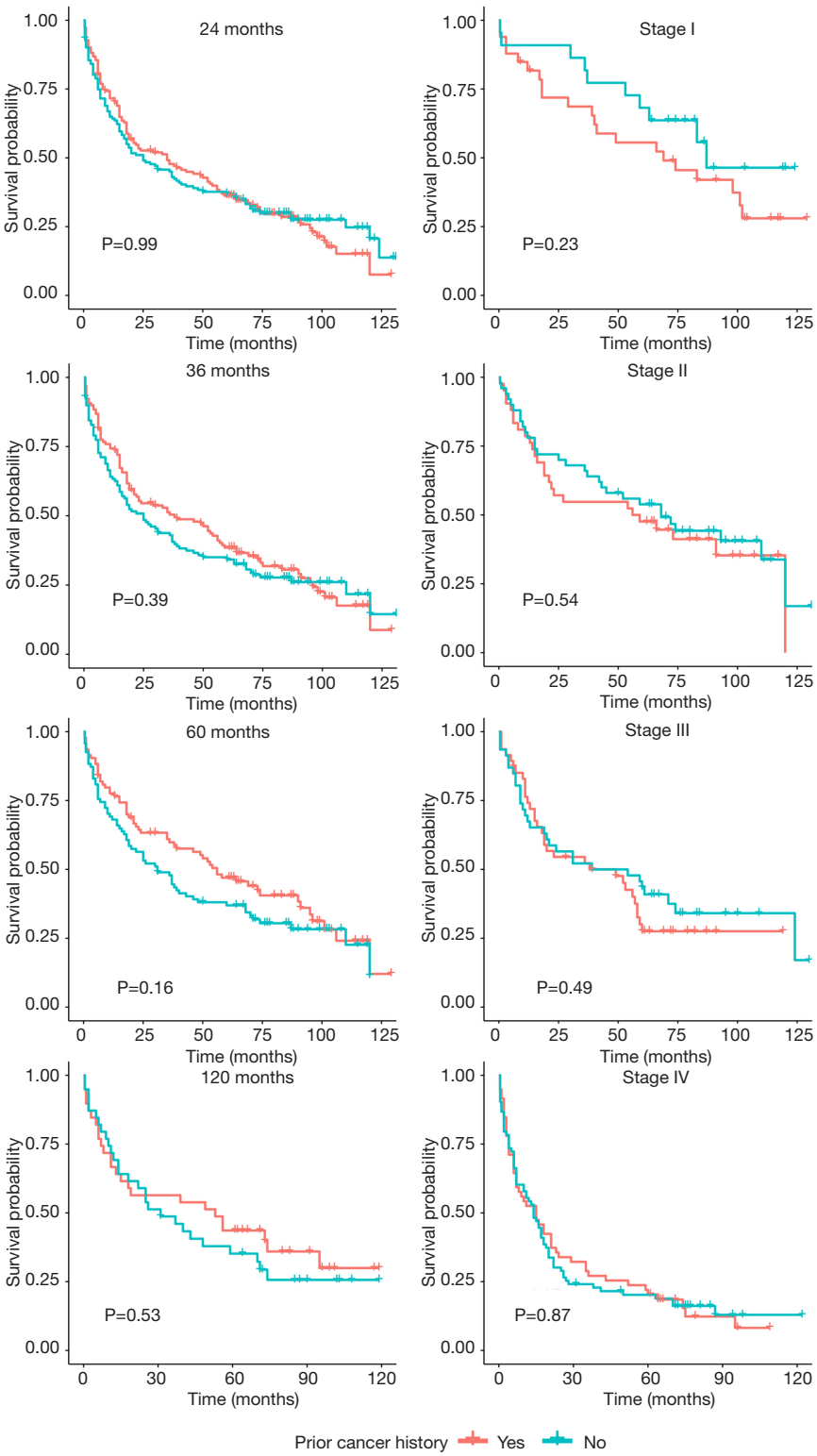


**Figure 2** Subgroup analysis of prior cancer impact on the overall survival stratified by the timing of prior cancer and AJCC stage in nasopharyngeal carcinoma. The nasopharyngeal carcinoma patients with prior cancer show a similar survival when compared with patients with no prior cancer, regardless of the timing of prior cancer and stage.

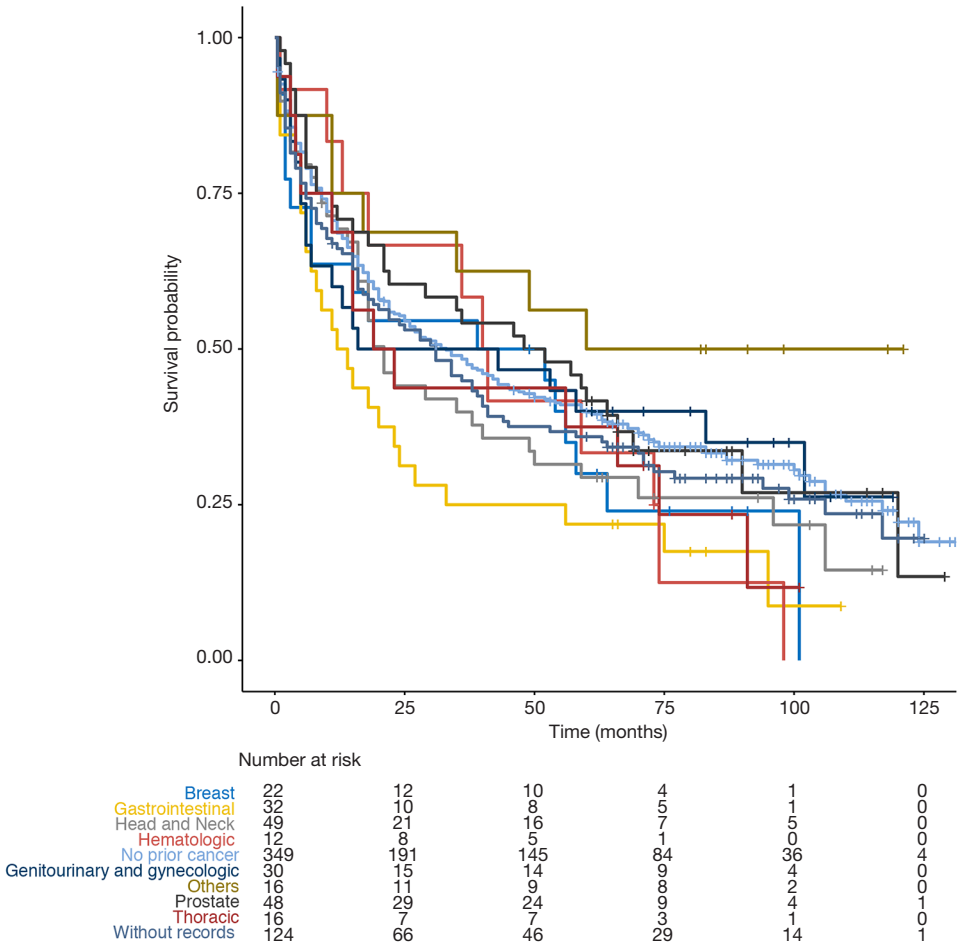


**Figure 3** Subgroup analysis of prior cancer impact on the overall survival stratified by the type of prior cancer in nasopharyngeal carcinoma. Patients with prior gastrointestinal cancer tend to have inferior survival compared with patients without prior cancer (P=0.008), while other cancer types demonstrate a similar OS. ("Without records": patients with prior cancer but without exact prior cancer type in the SEER database). OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.

affect OS compared with patients without prior cancer (P>0.05). *Figure 3* shows OS according to prior cancer type. Patients with prior gastrointestinal cancer tend to have inferior survival compared with patients without prior cancer (P=0.008), while other cancer types demonstrate a similar OS.

In propensity-score—adjusted Cox models, patients with prior cancer had the same/non-inferior OS [hazard ratio (HR) =1.12, 95% confidence interval, 0.88 to 1.42], compared to patients without a prior cancer (*Table 2*).

## Discussion

Stringent eligibility criteria for oncology clinical trials can minimize the risks to the participants, but they can also significantly affect the accrual and external validity of a clinical trial (15). In practice, patients with a prior cancer history are usually excluded in cancer clinical trials due to the potential interference of study outcomes. However, there is no authoritative data currently available to support this assumption. Given the sizeable number of cancer survivors, the impact of these criteria will increase, and it is critical to understand the impact of prior cancer. Until now, whether NPC patients with prior cancer faced a worse prognosis had remained unknown; our study was precisely aimed to elucidate this problem. We observed that cases of NPC patients with prior cancer did not result in inferior survival outcomes when compared with those without prior

 

**Table 2** Cox regression analysis of prior cancer history impact on patients with nasopharyngeal carcinoma

| Variables | Hazard ratio (95% CI) | P value |
|---|---|---|
| Age | 1.03 (1.02, 1.04) | <0.001 |
| Gender | | |
| Female | Reference | |
| Male | 0.97 (0.76, 1.24) | 0.809 |
| Race | | |
| Black | Reference | |
| White | 1.09 (0.74, 1.62) | 0.648 |
| Others/unknown | 0.63 (0.38, 1.02) | 0.061 |
| Marital status | | |
| Married | Reference | |
| Unmarried | 1.54 (1.20, 1.97) | <0.001 |
| Prior cancer | | |
| No | Reference | |
| Yes | 1.12 (0.88, 1.42) | 0.347 |
| Grade | | <0.001 |
| Well-differentiated | Reference | |
| Moderately differentiated | 0.88 (0.48, 1.61) | 0.672 |
| Poorly differentiated | 0.58 (0.33, 1.03) | 0.061 |
| Undifferentiated | 0.55 (0.29, 1.04) | 0.067 |
| Unknown | 0.66 (0.37, 1.16) | 0.152 |
| AJCC TNM stage | | |
| I | Reference | |
| II | 1.35 (0.80, 2.30) | 0.263 |
| III | 1.77 (1.06, 2.94) | 0.028 |
| IV | 3.40 (2.12, 5.46) | <0.001 |
| Unknown | 2.33 (1.41, 3.84) | <0.001 |
| Surgery | | |
| No/unknown | Reference | |
| Yes | 0.52 (0.35, 0.77) | 0.465 |
| Radiotherapy | | |
| No/unknown | Reference | |
| Yes | 0.84 (0.53, 1.33) | 0.001 |

cancer. To our knowledge, this is the first study to evaluate the characteristics and prognostic impact of prior cancer among NPC patients. Thus, we need to rethink the long-held assumptions which exclude patients with prior cancer from clinical trials.

Our previous study has mentioned the varying impact of prior cancer according to specific cancer types (8). The novelty in our approach was dividing these cancers into two categories, "prior cancer inferior" (PCI), in which patients had lower survival rates than those without prior cancer; and "prior cancer similar" (PCS), in which survival rates were similar. From this point of view, NPC is one kind of PCS cancer. Several studies also addressed the same questions for other cancer types. Although prior cancer might impact the OS in patients with prostate cancer (16), prior cancer does not contribute to poor survival outcome in many other cancer types, such as in lung, glioblastoma, esophageal, gastrointestinal tract, and pancreatic cancer (17-23). Notably, the impact of prior cancer on early-stage, locally advanced, and advanced lung cancer are consistent, showing a lack of adverse effect on clinical outcomes (17,18,20). Our results also confirmed similar phenomena in the different stages of first-time NPC, which suggests that our findings are applicable to clinical trials for different stages of NPC.

The timing of prior cancer also needs to be fully considered when determining the impact of prior cancer exclusion criteria on clinical trials (24). Generally, a 5-year exclusion window is commonly employed in most trials (7), and over 60% of prior cancers occurred within this window in our study. The median interval between prior cancer and the index NPC was 3.5 years. This information indicates that active surveillance and screening for NPC is necessary for cancer survivors. Subgroup analysis stratified by timing of prior cancer displayed the same tendency: prior cancer did not adversely affect OS. In other words, the impact of prior cancer is independent of timing. From this perspective, NPC patients with prior cancer can be considered for enrollment in trials regardless of timing, and improve accrual without affecting outcomes.

There are, however, several limitations in interpreting our study. Firstly, there is a paucity of detailed characteristics concerning prior cancers diagnosed outside of the registry state, which are recorded in sequence

 

number only. So, our study only focused on the timing of prior cancer. Additionally, the efficacy and tolerability of therapy on prior cancer, which may disrupt the management for the index cancer, cannot be considered due to the data restriction. Secondly, we could not obtain detailed data on treatments and comorbidities from the SEER database. Therefore, neither could comorbidities be matched in our PSM analyses, nor could they be included in the regression models. Thirdly, PSM analysis only accounts for observable covariates, and hidden bias resulted from unobserved confounders that remained after matching. Finally, the data obtained from the SEER database covers only approximately 34.6% of the total U.S. population, thus making it necessary to confirm the generality of our findings.

## Conclusions

Among patients with NPC, prior cancer does not convey an adverse effect on clinical outcomes, regardless of the timing of prior cancer and the stage of index cancer. Broader inclusion trial criteria could be adopted in NPC patients with a history of prior cancer. However, further studies are warranted to confirm the appropriateness of this exclusion criterion in NPC trials.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* Institutional review board approval was waived for this study because the SEER database is a public anonymized database. The author, HQ Zhou obtained access to the SEER database (accession number: 13693-Nov2015).

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