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Effect of prior cancer on trial eligibility and treatment outcomes in nasopharyngeal carcinoma: Implications for clinical trial accrual

Ya-Qin Wang[a,1], Jia-Wei Lv[a], Ling-Long Tang[a,1], Xiao-Jing Du[a], Lei Chen[a], Wen-Fei Li[a], Xu Liu[a], Ying Guo[b], Ai-Hua Lin[c], Yan-Ping Mao[a,d], Ying Sun[a], Yu-Pei Chen[a,*], Jun Ma[a,*]

[a] Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, Guangzhou, Guangdong 510060, People's Republic of China
[b] Clinical Trials Centre, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, PR China
[c] Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-sen University, Guangzhou, PR China
[d] Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, United States

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ABSTRACT

Objective: In cancer trials, prior cancer is a common exclusion criterion. We evaluated the characteristics of prior cancer exclusion criteria in nasopharyngeal carcinoma (NPC) trials and determined its prognostic effect on patients with NPC.

Methods: We reviewed NPC trials for prior cancer exclusion criteria. Then we estimated the effect of prior cancer among NPC patients using the Surveillance, Epidemiology, and End Results database. Propensity score-matching was used to compensate for differences in baseline characteristics between patients with and without prior cancer.

Results: There were 109 clinical trials involving 10,437 patients; 49 trials (45%) excluded patients with prior cancer. Prior cancer exclusion was more common in recent or phase III trials. We identified 10,195 NPC patients; 6.2% had prior cancer. More than 70% of these cancers were in situ/localized/regional and diagnosed relatively close to the NPC diagnosis (median 3.3 years). Patients with certain prior cancer type (prostate, breast, gynecological, hematological), time of diagnosis (> 5 years ago), or stage (in situ/localized) did not have inferior survival compared with patients with no prior cancer. We tested one form of prior cancer exclusion criteria in an NPC cohort resembling a modern trial population: it did not adversely affect overall and NPC-specific survival.

Conclusions: Many NPC trials excluded patients with prior cancer, which impacts trial accrual and generalizability. Our findings suggest that broader inclusion in trials of patients with NPC with prior cancer might not affect trial outcomes. More research is needed to understand the appropriateness of this exclusion policy across cancer types and trials.

Introduction

Cancer is the leading and second leading cause of death in China and the United States, respectively [1,2]. Well-conducted cancer clinical trials are essential for confirming new treatments and improving outcomes. Enrolling sufficient participants to establish adequate statistical power is one key requirement for conducting these trials. Unfortunately, only 2–4% of US adults with newly diagnosed cancer participate in clinical trials annually [3,4]. Low patient accrual rates can prolong trial duration, limit generalizability, lead to premature trial termination, and leave important clinical questions unanswered [5,6]. Low clinical trial accrual rates have been attributed to patient, clinician, and system factors [7]. Clinical trial eligibility criteria are a major impediment to study accrual and represent one of the few factors directly controlled by investigators [8–10].

Despite proposals for simplification and providing relevant rationales, trial eligibility criteria have become numerous and stringent over time. In cancer trials, prior cancer diagnosis is a common exclusion

* Corresponding authors at: Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangdong Key Laboratory of Nasopharyngeal Carcinoma Diagnosis and Therapy, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China.
E-mail addresses: chenyup1@sysucc.org.cn (Y.-P. Chen), majun2@mail.sysu.edu.cn (J. Ma).
[1] Ya-Qin Wang, Jia-Wei Lv, and Ling-Long Tang contributed equally to this work.

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criterion. For example, > 80% of lung cancer trials exclude prior malignancy, excluding up to 18% of patients [11]. It is believed that prior cancer diagnosis could interfere with trial conduct or outcomes, though no sufficient data clearly support this. Laccetti et al. [12] found that, among patients with advanced lung cancer, prior cancer did not adversely affect treatment outcomes, regardless of prior cancer stage, type, or time of diagnosis. Relevant evidence for other malignancies is needed. Given the decreasing cancer death rate and the near four-fold increase in the number of US cancer survivors over the past 30 years [1,13], prior cancer exclusion criteria will more likely limit trial accrual.

Nasopharyngeal carcinoma (NPC) is a unique head and neck cancer endemic in Southeast Asia but relatively rare in the US [14,15]. Radiotherapy (RT) is the mainstay treatment modality for NPC. With a substantial reduction in mortality [16], NPC trials require more participants. Few NPC trials, especially phase III trials, have been reported, partially due to participant recruitment difficulties. Assessing eligibility criteria to increase NPC trial accrual rates is important. So far, no study has evaluated the prior cancer exclusion criteria characteristics in NPC trials, the frequency and time of prior cancer diagnoses in NPC populations, or the effect of prior cancer on NPC outcomes. To address these questions, we reviewed prior cancer eligibility criteria in all NPC clinical trials and used the Surveillance, Epidemiology, and End Results (SEER) database, a large, representative, population-based cancer registry, to determine the prevalence and prognostic effect of prior cancer among patients with NPC.

Methods

Trials selection and data sources

The Sun Yat-Sen University Cancer Center Institutional Review Board approved this study. We included all phase I, II, and III NPC trials published in English. Whether prior cancers were excluded and the corresponding exclusion timeframe were recorded.

Data were obtained from the SEER 18 database (1973–2012). The SEER database is a nationally representative collection of population-based cancer registries [17].

Detailed descriptions of trials selection and data sources are presented in the Supplementary Material.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.oraloncology.2019.01.023.

Measures

Overall (all-cause) and NPC-specific survival (NPC-cause) were measured as the primary and secondary outcome, respectively. Patients were considered to have had prior cancer if their SEER NPC variable sequence number was the second or any subsequent number. As the sequence number may have resulted in the inclusion of tumors unconfirmed by SEER registries (prior cancers occurring prior to registry formation, in locations outside SEER registries), we excluded patients (4.1%, n = 417) with a sequence number suggesting prior cancer but that was unconfirmed in the SEER 18 database to ensure accuracy. The number and characteristics of the prior cancer (type, stage, time of diagnosis in relation to index NPC) were recorded. The prior cancer time of diagnosis was determined using SEER diagnosis dates of the index NPC and the most recent of any prior cancer. We defined SEER diagnosis dates as the 15th of the month and the year of diagnosis (day of diagnosis is unavailable in SEER). In situ cervical cancer and nonmelanoma skin cancer are not reportable to SEER, therefore were not recorded as prior cancer.

Statistical analysis

We explored associations between trial characteristics and prior cancer exclusion criteria using chi-square or Fisher's exact tests where indicated. We used propensity score matching to adjust for baseline characteristics and account for potential treatment selection bias. Propensity scores across patients with and without prior cancer diagnosis were computed by logistic regression based on patient and tumor characteristics. Kaplan–Meier method was used [18]. Using the propensity score as a covariate, adjusted hazard ratios (HR) were calculated using the Cox regression model or the Cox regression model with time-dependent covariates if the proportional hazards assumption was not met using the Schoenfeld residuals test [19,20]. Detailed descriptions of statistical methods are presented in the Supplementary Material. Analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX) and SPSS (version 19.0; SPSS Inc., Chicago, IL). All statistical tests were two-sided; $P < 0.05$ was considered statistically significant.

Results

Characteristics of included trials and prior cancer exclusion criteria

We identified 109 NPC trials (Supplementary Fig. S1) enrolling a total 10,437 patients (median, 44; range, 7–803). Table 1 summarizes the trial characteristics and relevant prior cancer exclusion criteria. Forty-nine trials (45%) excluded patients with prior cancer: any prior diagnosis (33%), or diagnosed within 10 years (1%), within 5 years (9%), or within 3 years (2%). Supplementary Table S1 shows the association between trial characteristics and prior cancer exclusion criteria. Overall, relatively modern studies excluded prior cancer more often. Excluding the few phase I trials, prior cancer exclusion was more common in phase III trials (62%) than in phase II trials (39%). As phase III NPC trials mainly investigate combined chemoradiotherapy for locoregionally advanced disease with a relatively larger sample size, prior cancer exclusion criteria were unsurprisingly also more common among such trials (Supplementary Table S1).

Characteristics of prior cancer status in SEER cohort

There were 10,195 eligible patients with NPC (Supplementary Fig. S2); 633 (6.2%) had a documented prior cancer. Table 2 lists the baseline characteristics of the SEER cohort. Table 3 presents the baseline characteristics of patients with NPC by prior cancer status in the original sample and the propensity score–matched cohort; prior cancer differed across all measured covariables in the original sample. After propensity scores adjustment, all covariables were balanced among patients with and without prior cancer.

Fig. 1 depicts the most recent prior cancer type, stage, and time of diagnosis. Head and neck (21.6%), prostate (19.6%), gastrointestinal (14.5%), and breast cancer (9.5%) were the most common prior cancers. Among women, the most common prior cancers were breast (26.9%), head and neck (19.4%), gynecological (18.4%), and gastrointestinal cancer (10.3%); in men, they were prostate (30.2%), head and neck (22.7%), gastrointestinal (16.8%), and other genitourinary cancer (10.0%). Localized and regional stages together accounted for 67.0% of cases; only 10.0% of prior cancers were distant. The median time of diagnosis for the most recent and second most recent prior cancers was 3.3 and 5.9 years, respectively. Supplementary Fig. S3 depicts additional characteristics of the second most recent prior cancers.

Impact of prior cancer status on propensity score–matched cohort

After propensity score matching, Kaplan–Meier survival curves demonstrated statistically significant differences between patients with

Table 1
Characteristics of NPC clinical trials and their prior cancer exclusion criteria.

Characteristic	No. (%)
Total trials	109
Phase of study	
I	8 (7.3)
II	75 (68.8)
III	26 (23.9)
Histology*	
Keratinizing squamous cell carcinoma > 20%	5 (4.6)
Non-keratinizing carcinoma	91 (83.5)
Not available	13 (11.9)
Cancer stage	
Early	2 (1.8)
Early & Locoregionally advanced	10 (9.2)
Locoregionally advanced	46 (42.2)
Advanced	51 (46.8)
Types of primary endpoint	
Survival	31 (28.4)
Response & Toxicity	69 (63.3)
Other	9 (8.3)
Primary treatment modality	
Radiation	7 (6.4)
Radio-chemotherapy	41 (37.6)
Medical therapy	41 (37.6)
Target & Immunotherapy	18 (16.5)
Other	2 (1.8)
Region in which trials were conducted	
Asia other than China	52 (47.7)
China	33 (30.3)
Europe & North America	20 (18.3)
Other	4 (3.7)
Sample size	
Median (Range)	44 (7–803)
< 50	62 (56.9)
50–100	19 (17.4)
> 100	28 (25.7)
Year of study activation	
1973–1991	18 (16.5)
1992–1999	26 (23.9)
2000–2015	62 (56.9)
Not available	3 (2.8)
Prior cancer exclusion†	
Yes	49 (45.0)
No	60 (55.0)
Timeframe of prior cancer exclusion	
Any prior cancer	36 (33.0)
Within 3 years	2 (1.8)
Within 5 years	10 (9.2)
Within 10 years	1 (0.9)
Without prior cancer exclusion	60 (55.0)

* Non-keratinizing carcinoma includes differentiated and undifferentiated non-keratinizing carcinoma. The main histological type in all included trials was non-keratinizing carcinoma. Therefore, we separated trials in which > 20% of patients had keratinizing squamous cell carcinoma.

† Of the 49 trials with prior cancer exclusion, 24 (49%) did not exclude patients with non-melanoma cancers of the skin and/or in situ cervical carcinoma.

and without prior cancer in 10-year overall (15.0% vs. 24.1%; $P < 0.001$) and NPC-specific survival (48.1% vs. 39.6%; $P = 0.003$) (Fig. 2). In the propensity score–adjusted Cox models, prior cancer was associated with unfavorable overall (HR = 1.20, 95% confidence interval [CI] = 1.07–1.35, $P = 0.002$) and superior NPC-specific survival (HR = 0.77, 95% CI = 0.66–0.89, $P = 0.001$).

Fig. 3 shows overall survival according to prior cancer time of diagnosis, stage, and type. Generally, patients with NPC with prior cancer diagnosed > 5 years ago or with in situ/localized disease did not differ statistically significantly from patients without prior cancer. Patients with prior prostate, breast, gynecological, and hematological cancer did not have inferior survival compared with patients with no prior cancer, but patients with prior gastrointestinal and other genitourinary cancer tended to.

Table 2
Baseline characteristics of nasopharyngeal carcinoma SEER cohort.

Patient characteristic	Overall (N = 10,195)	Prior cancer (n = 633), %
Age, years		
≤45	2635	32 (1.2)
45–65	4677	219 (4.7)
≥65	2883	382 (13.3)
Sex		
Female	3103	223 (7.2)
Male	7092	410 (5.8)
Race		
White	5047	433 (8.6)
Black	854	68 (8.0)
Chinese	2002	48 (2.4)
Other	2292	84 (3.7)
Marital status		
Married	6354	362 (5.7)
Single	1687	68 (4.0)
Separated/Divorced/Widowed	1634	161 (9.9)
Unknown	520	42 (8.1)
Histology		
Keratinizing squamous cell carcinoma	3998	336 (8.4)
Differentiated non-keratinizing carcinoma	1454	74 (5.1)
Undifferentiated non-keratinizing carcinoma	1966	61 (3.1)
Others	2777	162 (5.8)
SEER stage		
Localized	1159	98 (8.5)
Regional	5700	321 (5.6)
Distant	2514	137 (5.4)
Unstaged	822	77 (9.4)
Year of diagnosis		
1973–1991	2440	123 (5.0)
1992–1999	2004	108 (5.4)
2000–2012	5751	402 (7.0)
Radiation treatment		
Yes	8393	432 (5.1)
No	1596	183 (11.5)
Unknown	206	18 (8.7)
Cause of death		
Alive	4067	174 (4.3)
Nasopharyngeal carcinoma specific	4328	216 (5.0)
All other causes	1800	243 (13.5)

Abbreviations: SEER, Surveillance, Epidemiology, and End Results.

Impact of prior cancer status on patients stratified by stage, age, and histology

Supplementary Tables S2–S4 present the baseline characteristics of patients with NPC stratified by SEER stage, age, and histology, respectively. All covariables were balanced among patients with and without prior cancer in these strata after matching. Supplementary Figs. S4–S6 show their respective corresponding survival outcomes by Kaplan–Meier analyses. The unfavorable overall survival effect of prior cancer diminished with stage advancing, and disappeared among patients with distant disease (Supplementary Fig. S4). Overall survival between patients aged ≥65 years with and without prior cancer did not differ significantly (Supplementary Fig. S5). NPC histological type did not alter the overall survival effect of prior cancer; the effect was

Table 3
Baseline characteristics of nasopharyngeal carcinoma patients by prior cancer status in original sample and propensity-score matched cohort.

Patient Characteristic	Original Sample			Propensity-Score Matched Cohort		
	No Prior Cancer (n = 9562), %	Prior Cancer '(n = 633), %	P^*	No Prior Cancer (n = 1266), %	Prior Cancer (n = 633), %	P^*
Age, years			< 0.001			0.989
≤45	2603 (27.2)	32 (5.1)		63 (5.0)	32 (5.1)	
45–65	4458 (46.6)	219 (34.6)		442 (34.9)	219 (34.6)	
≥65	2501 (26.2)	382 (60.3)		761 (60.1)	382 (60.3)	
Sex			0.007			0.865
Female	2880 (30.1)	223 (35.2)		441 (34.8)	223 (35.2)	
Male	6682 (69.9)	410 (64.8)		825 (65.2)	410 (64.8)	
Race			< 0.001			0.119
White	4614 (48.3)	433 (68.4)		890 (70.3)	433 (68.4)	
Black	786 (8.2)	68 (10.7)		97 (7.7)	68 (10.7)	
Chinese	1954 (20.4)	48 (7.6)		114 (9.0)	48 (7.6)	
Other	2208 (23.1)	84 (13.3)		165 (13.0)	84 (13.3)	
Marital status			< 0.001			0.167
Married	5992 (62.7)	362 (57.2)		778 (61.5)	362 (57.2)	
Single	1619 (16.9)	68 (10.7)		138 (10.9)	68 (10.7)	
Separated/Divorced/Widowed	1473 (15.4)	161 (25.4)		289 (22.8)	161 (25.4)	
Unknown	478 (5.0)	42 (6.6)		61 (4.8)	42 (6.6)	
Histology			< 0.001			0.726
Keratinizing squamous cell carcinoma	3662 (38.3)	336 (53.1)		691 (54.6)	336 (53.1)	
Differentiated non-keratinizing carcinoma	1380 (14.4)	74 (11.7)		155 (12.2)	74 (11.7)	
Undifferentiated non-keratinizing carcinoma	1905 (19.8)	61 (9.6)		126 (10.0)	61 (9.6)	
Others	2615 (27.3)	162 (25.6)		294 (23.2)	162 (25.6)	
SEER stage			< 0.001			0.114
Localized	1061 (11.1)	98 (15.5)		164 (13.0)	98 (15.5)	
Regional	5379 (56.3)	321 (50.7)		685 (54.1)	321 (50.7)	
Distant	2377 (24.9)	137 (21.6)		295 (23.3)	137 (21.6)	
Unstaged	745 (7.8)	77 (12.2)		122 (9.6)	77 (12.2)	
Year of diagnosis			0.001			0.928
1973–1991	2317 (24.2)	123 (19.4)		243 (19.2)	123 (19.4)	
1992–1999	1896 (19.8)	108 (17.1)		225 (17.8)	108 (17.1)	
2000–2012	5349 (55.9)	402 (63.5)		798 (63.0)	402 (63.5)	
Radiation treatment			< 0.001			0.105
Yes	7961 (83.3)	432 (68.2)		909 (71.8)	432 (68.2)	
No	1413 (14.8)	183 (28.9)		336 (26.5)	183 (28.9)	
Unknown	1188 (2.0)	18 (2.8)		21 (1.7)	18 (2.8)	

NOTE. The following variables were used for propensity-score matching process: age, sex, race, marital status, histology, SEER stage, year of diagnosis, and radiation treatment.
Abbreviations: SEER, Surveillance, Epidemiology, and End Results.
* Two-sided *P*-values were calculated using the chi-square test or Fisher's exact test if indicated.

marginally significant among patients with non-keratinizing carcinoma ($P = 0.049$) (Supplementary Fig. S6). In multivariate analyses, prior cancer did not have an unfavorable overall survival effect among patients with regional and distant disease, age ≥65 years, or with non-keratinizing carcinoma.

Impact of prior cancer on modern cohort

In the modern cohort (n = 2278), 152 patients (6.7%) had prior cancer. We tested one form of prior cancer inclusion criteria in this cohort: we included patients with in situ/localized prior prostate, breast, and gynecological cancer diagnosed > 3 years ago in this analysis; 39 patients with prior cancers remained. Supplementary Table S5 lists the baseline characteristics of the 117 patients after propensity score matching. Prior cancer did not adversely affect overall ($P = 0.756$) or NPC-specific survival ($P = 0.676$) in this population (Supplementary Fig. S7).

Discussion

To our knowledge, this is the first study to comprehensively evaluate the prior cancer exclusion criteria in NPC clinical trials and their prevalence and prognostic effect in a large population-based NPC cohort, where 45% of trials excluded patients with prior cancer, and this practice extended to > 60% of phase III trials. The present study found that 6.2% of patients with NPC had a prior malignancy, of which > 70% were in situ/localized/regional. Prior cancers were diagnosed relatively close to the NPC diagnosis (median 3.3 years). Patients with certain prior cancer type (prostate, breast, gynecological, hematological), time of diagnosis (> 5 years ago), or stage (in situ/localized) did not have inferior survival compared with patients with no prior cancer. Furthermore, the adverse impact of prior cancers diminished or disappeared among patients with NPC with regional and distant disease, age ≥65 years, or with non-keratinizing carcinoma.

Numerous and stringent eligibility criteria, especially prior cancer exclusion, could result in reflexive exclusion of patients with prior cancer diagnoses from cancer clinical trials and likely hinders efforts to increase participation. In a recent NPC trial that excluded patients with

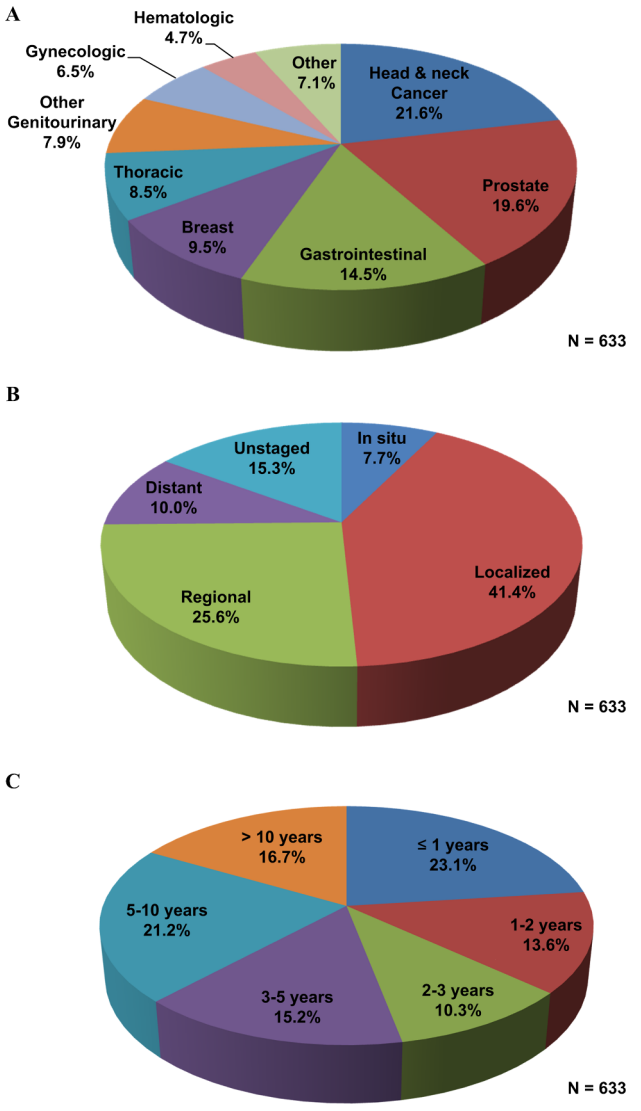

Fig. 1. Most recent prior cancer type (A), stage (B), and time of diagnosis (C).

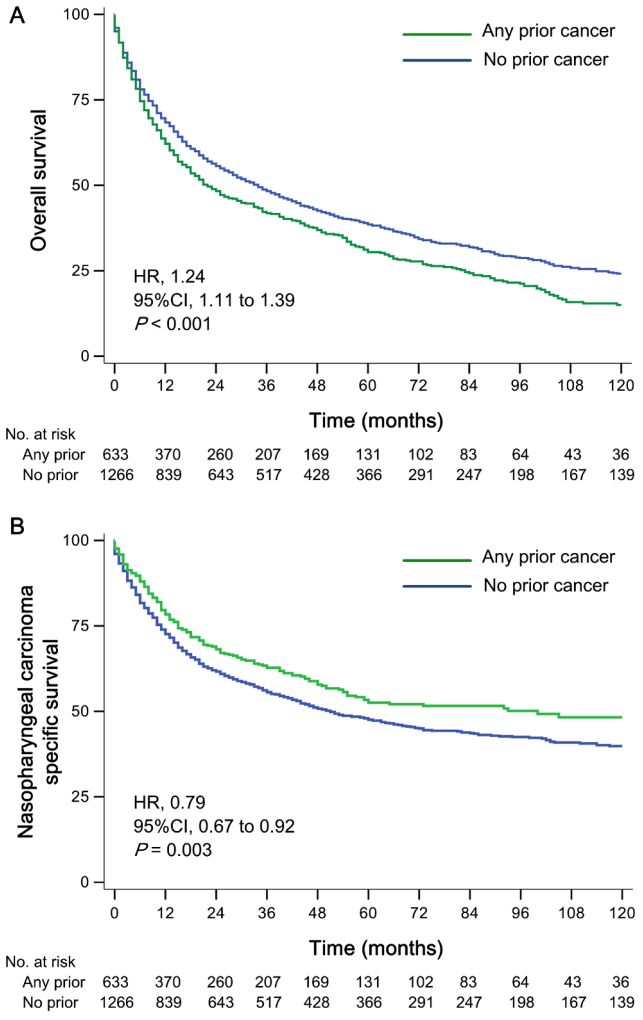

Fig. 2. Overall (A) and NPC-specific survival (B) of patients with and without prior cancer in propensity score–matched cohort. HRs were calculated using the unadjusted Cox proportional hazards model. *P*-values were calculated using the unadjusted log-rank test.

prior malignancy, 180 patients were randomized while 101 (56%) did not meet the eligibility criteria and were consequently excluded before randomization [21]. Compared with other common exclusion criteria, prior cancer may have a greater impact on participant enrollment; recently in a lung cancer case series, the proportion of patients with prior cancer was at least three times of that with other medical comorbidities [22]. As we had extracted published report data, the number of trials with prior cancer exclusion criteria was conservative, as some studies may not report their eligibility criteria clearly. Moreover, our data suggest that prior cancer exclusion is more common in more recent trials, suggesting that the exclusion of more cancer survivors will continue, hindering efforts to increase trial participation.

Potential reasons for excluding prior cancer include the possibility that such patients are less likely to tolerate treatment, be less responsive to investigational therapies, and are more prone to developing disease progression that cannot be clearly attributed to the investigated disease [11]. Sponsor or regulatory directives may also force investigators to exclude such patients, though Gerber et al. [11] found no mention of prior cancer diagnosis related to trial design in US Food and Drug Administration guidance documents. The most important concern may be that such patients may inherently have different prognoses from their counterparts without prior cancer. Little is known about the prognostic effect of prior cancer diagnosis and the appropriateness of this commonplace exclusion criterion in NPC.

We found that 6.2% of patients with NPC had documented prior cancer diagnosis. As 4.1% of patients with NPC with a sequence number suggesting prior cancer were unconfirmed in the SEER database and consequently excluded, the estimated number of patients with NPC with prior cancer was conservative, and approximately 10% of patients with NPC may have prior cancer diagnosis. In the propensity score–matched cohort, patients with prior cancer had inferior overall survival but superior NPC-specific survival compared with those without prior cancer, indicating that prior cancer may result in more non-NPC deaths. The most common prior cancers in our cohort were head and neck, prostate, gastrointestinal, and breast cancer. Originating from similar cell or tissue lineages, head and neck cancer is commonly a prior cancer of NPC. The high prevalence of prostate (in men) and breast cancer (in women) in the cohort reflects their overall prevalence in the general population [1]. Given their tendency for early diagnosis, indolent course, and good response to local treatments, it appears that antecedent prostate or breast cancer would not substantially affect outcomes in NPC. Survival analyses confirmed this hypothesis, where prior prostate, breast, gynecological, or hematological cancer did not worsen NPC outcomes. Furthermore, > 70% of prior cancers in our cohort were in situ/localized/regional; our results suggest that earlier diagnoses (in situ/localized) do not adversely affect NPC outcomes. We also found that patients with prior cancer diagnosed > 5 years ago, a

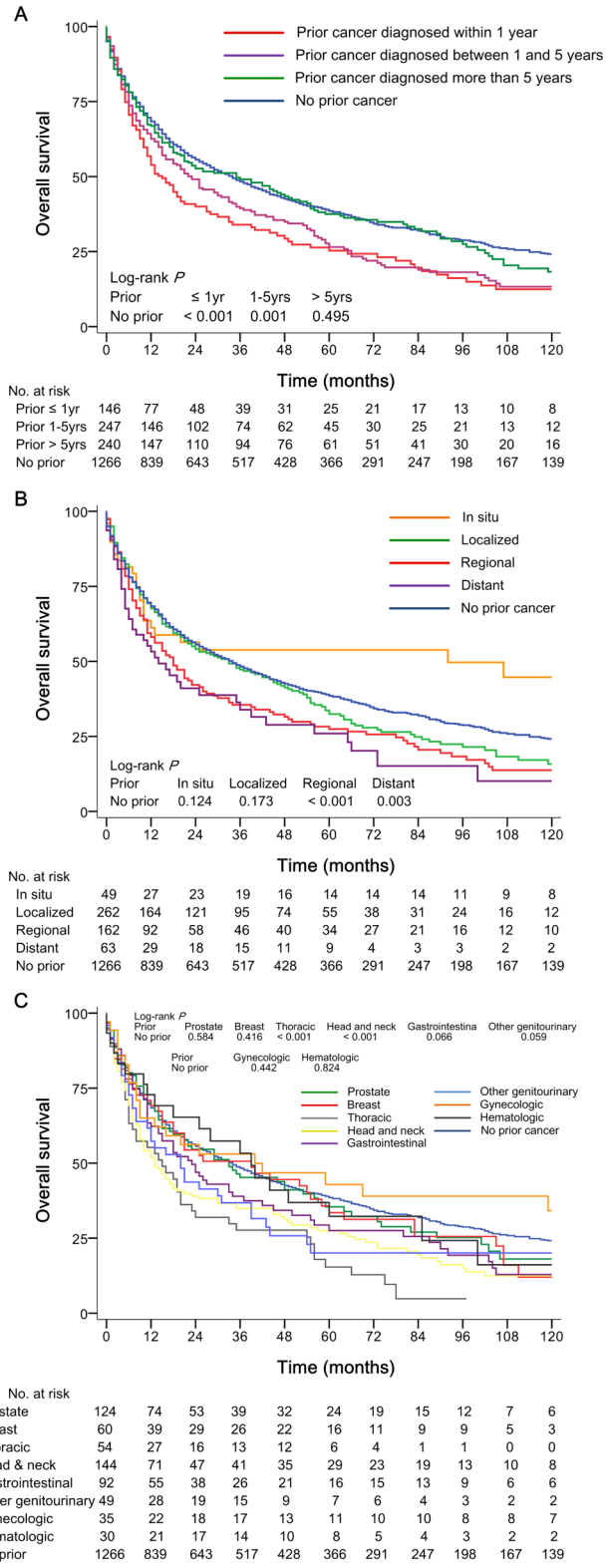

Fig. 3. Overall survival according to type (A), stage (B), and time (C) of prior cancer diagnosis. *P*-values were calculated using the unadjusted log-rank test.

commonly used timeframe for prior cancer in NPC trials, did not have inferior prognosis compared with those without prior cancer. Stratified analyses did not associate prior cancer (regardless of type, stage, time of diagnosis) with inferior overall survival among patients with distant disease and in patients aged ≥65 years. Its unfavorable effect was also weakened among patients with regional disease. A potential explanation for these trends is that early-stage NPC or young patients with NPC tend to have good treatment outcomes and are more vulnerable to the effect of prior cancer.

So far, information regarding the appropriate prior cancer exclusion criteria in cancer trials is insufficient. Laccetti et al. [12] reported that prior cancer did not adversely affect clinical outcomes among patients with advanced lung cancer, regardless of prior cancer stage, type, or time of diagnosis; broader inclusion in advanced lung cancer trials of patients with a history of prior cancer should be considered. The National Cancer Institute Cancer Therapy Evaluation Program stated that "An individual who has undergone potentially curative therapy for a prior malignancy, who has had no evidence of that disease for five years, and who is deemed at low risk for recurrence by his/her treating physician, should be presumed to be eligible for a cancer treatment trial for a second malignancy" [23]. Our findings support this five-year restriction. Furthermore, to test the appropriate prior cancer exclusion criteria, we included a subsection of the modern cohort in the analysis; prior cancer did not adversely affect their survival. Given the lack of eligible patients with prior cancer, we only tested these exclusion criteria, and the optimal form for NPC trials needs further research. Our study provides a reference for investigators from other fields, and we suggest that the broad inclusion of prior cancer that is presumably cured, or at least not life-limiting or is well-controlled for a long time (e.g., 5 years), is suitable. For investigating patients with advanced disease or older age, the exclusion criteria might be less strict.

Prior cancer treatment may render patients less likely to tolerate investigational treatments, though our analysis could not determine treatment toxicities. Nevertheless, this concern could be addressed in other ways. For example, other eligibility criteria regarding blood tests/organ function/functional status may adequately screen for treatment intolerance. Furthermore, prior cancer treatment (distinct from prior cancer diagnosis) can be employed as an exclusion criterion and would likely exclude much fewer patients [12]. To manage patients with prior cancer in study analyses, one could consider using stratified analyses (according to prior cancer diagnosis) or the Cox model (including prior cancer diagnosis as one covariate).

Several limitations should be addressed in interpreting our findings. First, the analyses of the exclusion criteria were limited to information published in the reports. The studies may have adopted unreported eligibility criteria, therefore more trials may have prior cancer exclusion criteria. The exact number of excluded patients with prior cancer was unavailable in most studies. Second, important patient characteristics such as chemotherapy and comorbidity information were not evaluated because these data were unavailable in the SEER database. Obtaining this information requires linking with the Medicare database. However, the vast majority of patients with NPC are diagnosed at a much earlier age to qualify for the SEER–Medicare database (age > 65 years) and are consequently excluded. Future large-scale studies with detailed NPC survival data are needed. Third, the rarity of NPC may limit our findings' generalizability to other cancer populations. The SEER cohort was from a non-endemic area, which may be of a different nature and treatment outcome. Nevertheless, it is more difficult to enroll patients with NPC from such non-endemic areas, and broader eligibility criteria can be an important means of increasing accrual rates and enhancing the conducting of trials.

In summary, many NPC trials exclude patients with prior cancer, which affects accrual, generalizability, and fair access to advanced treatments. The prevalence of multiple cancers will increase among cancer survivors as cancer outcomes continue to improve. We confirmed that certain prior cancer types, stages, and times of diagnosis do not adversely affect NPC survival, especially in patients with advanced disease and older age. Together, these findings suggest that broader inclusion in trials of patients with NPC with prior cancer could be considered without affecting outcomes. More research is needed to understand the appropriateness of this exclusion policy across cancer types and trials. Modifying this policy could lead to faster accrual,

higher completion rates, and more generalizable results, ultimately bringing better treatments to more patients sooner.

Conflicts of interest

The authors have no actual or potential conflicts of interest to declare.

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