Benefit of chemotherapy differs in node-negative and node-positive stage III nasopharyngeal carcinoma: analysis of the SEER database

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Research Article

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Abstract

Objectives: Chemoradiotherapy is the standard treatment for locoregionally advanced nasopharyngeal carcinoma (NPC). We aimed to reveal factors associated with chemotherapy use and evaluate chemotherapy's benefit in patients with stage III NPC stratified by lymph node status.

Patients and Methods: Overall, 1,452 patients with stage III NPC who underwent radiotherapy with (n=1361) or without (n=91) chemotherapy were identified in the SEER database. We identified predictors for chemotherapy use using logistic regression analysis. We compared all-cause mortality (ACM) and cancer-specific mortality (CSM) using Kaplan-Meier method. Cox regression and competing risk analyses were used to evaluate chemotherapy benefit. The inverse probability of treatment weighting (IPTW) approach was applied to reduce selection bias and adjust for competing risks. Subgroup analyses and interaction effects were explored.

Results: Factors including age, sex, insured status, tumor grade, and N category were associated with chemotherapy use. Chemotherapy was associated with decreased 5-year ACM (31.4% vs. 48.4%, $p<0.001$) and CSM (25.5% vs. 35.8%; $p=0.017$) in stage III NPC patients. The IPTW-adjusted hazard ratio for 5-year ACM was 0.57 (95% CI: 0.38–0.86, $p=0.008$), whereas IPTW-adjusted sub-hazard ratio for 5-year CSM was 0.62 (95% CI: 0.42–0.93, $p=0.003$). A significant interaction effect existed between lymph node status and treatment modality. Chemotherapy offered a significant survival benefit in node-positive stage III NPC. However, no chemotherapy benefit for the node-negative disease was observed.

Conclusion: Chemotherapy adds survival benefit in stage III NPC, especially in patients with node-positive disease. The magnitude of chemotherapy benefit in node-negative stage III NPC warrants further investigation.

Highlights

Overall, 1452 patients with stage III NPC with or without chemotherapy were analyzed.

A significant interaction existed between lymph node status and treatment modality.

Patients with node-positive stage III NPC benefited from chemotherapy.

No chemotherapy benefit for the node-negative stage III NPC was observed.

Introduction

Nasopharyngeal carcinoma (NPC) is an uncommon head and neck cancer characterized by a unique geographical distribution. It is particularly prevalent in South China, Southeastern Asia, and North Africa, accounting for more than 70% of new cases. More than 130,000 new NPC cases are diagnosed worldwide annually, with approximately 70% of patients diagnosed with the locoregionally advanced disease at initial diagnosis [1]. Early-stage NPC is almost curable; however, patients with locoregionally

advanced NPC are associated with unfavorable prognosis, suffering from locoregionally recurrences and distant metastases. With significant progress achieved in modern radiotherapy techniques, locoregional relapse is uncommon, affecting less than 10% of patients. Of note, distant metastasis is the predominant pattern of treatment failure of NPC, accounting for approximately 70% of cancer-specific mortalities [2].

NPC is sensitive to chemoradiotherapy. In the past two decades, the integration of chemotherapy to radiotherapy has been considered a breakthrough for treating locoregionally advanced NPC. Notably, the rationale of chemotherapy use is mainly dependent on two clinical hypotheses: (1) chemotherapy potentially enhances radiotherapy (RT) sensitivity and kill primary tumor synergistically; (2) chemotherapy can eliminate systemic micrometastases and reduce the risk of distant metastases. Numerous randomized trials have shown relatively consistent results that chemotherapy combined with RT is associated with superior survival compared to when RT is used alone, for example, induction chemotherapy (IC), concurrent chemotherapy (CC), and adjuvant chemotherapy (AC) [3–14]. The contemporary National Comprehensive Cancer Network (NCCN) Guidelines recommend CCRT+AC and IC+CCRT as level 2A evidence and CCRT as level 2B for stage II-IVa NPC [15].

To our knowledge, there are no published randomized trials explicitly designed for stage III NPC in evaluating the efficacy of chemotherapy. Furthermore, whether chemotherapy is associated with a survival benefit in these patients remains mostly undefined. The current treatment strategy for locoregionally advanced NPC recommended by NCCN guidelines continues to be a “catch-all” one, covering stage II to stage IVa with heterogeneous prognoses that do not allow clinicians to make individualized treatments. The current study purposely examined chemotherapy’s effect on patients with moderate-risk locoregionally advanced disease (stage III NPC). It was hypothesized that chemotherapy combined with RT is associated with a substantial survival benefit in these patients. However, the magnitude of survival benefit might not equally apply to all the patients. To verify this hypothesis, we had to control the selection bias in treatment assignment and consider other competing causes of death and possible interaction effects. Therefore, we undertook a propensity score-weighted analysis with competing risks to evaluate chemotherapy’s survival benefit in stage III NPC patients.

Materials And Methods

Data Source

We obtained data from the Surveillance, Epidemiology, and End Results (SEER) database using SEER*Stat 8.3.8 software (<http://seer.cancer.gov/seerstat>). We were granted permission to access the custom databases with the radiation and chemotherapy recode fields in SEER*Stat’s client-server model from the SEER Program (register number 13013-Nov2019). The SEER registry records information on cancer diagnoses and outcomes in 18 regional registries covering approximately 27.8% of the U.S. population.

Study Cohort

We included data for NPC patients registered from 2004 through 2016 when the modern American Joint Committee on Cancer (AJCC) staging system (6th and 7th edition) was available in SEER. The inclusion criteria included: (1) pathologically confirmed NPC; (2) diagnosis of stage III disease according to the 6th and 7th edition of the AJCC Staging System; (3) patients without previous or other synchronous malignancies; (4) receipt of RT (patients who received external-beam RT and/or brachytherapy); (5) record of chemotherapy information (we coded chemotherapy types as yes/no/unknown).

Study Variables and Outcomes

Demographic and clinical variables were extracted from the SEER database directly, including age at diagnosis, sex, race recode, insurance status, marital status, histology types, the grade of tumor differentiation, derived AJCC T and N categories, radiation recode, chemotherapy recode, year of diagnosis, vital status, cause of death to site recode, SEER cause-specific death classification, SEER other cause of death classification, and survival months. Patients were categorized into two treatment groups using the SEER chemotherapy record: (i) chemotherapy group—patients had chemotherapy; (ii) no chemotherapy group—no chemotherapy evidence was found in the medical records examined. Cancer-specific mortality (CSM, death attributable to NPC) was the primary outcome of this study, determined by the SEER cause-specific death classification and the SEER cause of death to the site recode field. Secondary outcomes were all-cause mortality (ACM). We chose cancer-specific mortality as the primary outcome because healthier patients were thought to be more tolerable and were more likely to receive chemotherapy, which would confound all-cause mortality.

Statistical Analysis

Distributional differences in patient characteristics between groups were compared using Pearson's Chi-square test. Logistic regression analysis was used to determine predictors for receiving chemotherapy. We used Dominance analysis to evaluate the relative importance of independent predictors in the multivariable logistic regression model [16]. All-cause mortality was calculated via the Kaplan-Meier approach and compared using the log-rank test. An estimate of CSM against noncancer mortality (NCM) was taken revealed a cumulative incidence function and compared using Gray's test. The chemotherapy effect on stage III NPC survival was examined using univariable unweighted and inverse probability of treatment weighted (IPTW)-Cox proportional hazards models and Fine and Gray proportional subdistribution hazards models [17]. We applied the IPTW method to control selection bias to reduce observed differences in baseline characteristics between the two treatment groups [18]. Notably, we defined IPTW as the inverse of the probability of receiving the treatment and was calculated based on propensity scores estimated from a logistic regression model using a broad set of baseline variables.

Here, the IPTWs was calculated using the formula: $W_{ATE} = \frac{Z}{e} + \frac{1-Z}{1-e} \cdot Z$ is an indicator denoting treatment status ($Z = 0$ for no chemotherapy vs. $Z = 1$ for chemotherapy), while e represents the propensity score. Using IPTWs, we evaluated the average treatment effect (ATE), which yields a synthetic sample where the observed baseline covariates could not be confounded with treatment assignment. We evaluated covariate balances before and after IPTW, using absolute standardized differences (ASD). A difference of 0.1 or less represented a good balance. Besides, we explored subgroup analyses and potential interaction effects.

All statistical analyses were performed using R version 4.0.2. All statistical tests were 2-sided, and P values < 0.05 were considered statistically significant.

Results

Patient Characteristics

In total, 1,452 stage III NPC patients who had undergone chemotherapy combined with radiotherapy ($n = 1361$) or radiotherapy alone ($n = 91$) in the SEER database were included in this study (Fig. 1). The study population included 434 (29.9%) females and 207 (14.3%) node-negative stage NPC (T3N0M0), with a median age of 53 years (interquartile range, 43–63 years). After the 70-month median follow-up time (95% CI, 60.8–72.2 months), the 5-year and 10-year overall mortality rates for the patients were 32.3% (95% CI, 29.8–35.4%) and 45.5% (95% CI, 41.7–49.1%), respectively.

Chemotherapy-associated characteristics

A comparison of patient baseline characteristics stratified by no chemotherapy versus chemotherapy is highlighted in Table 1. Patients treated without chemotherapy tended to be older, females, white race, and were more likely to develop Grade I-II and node-negative disease. In multivariable logistic regression, age, sex, tumor grade, T category, and N category were identified to be independent predictors for chemotherapy management (Table 1). Dominance analysis demonstrated that the N category was the most crucial predictor for chemotherapy (average contribution, 0.041), followed by age (0.034), tumor grade (0.018), sex (0.01), and T category (0.003) (Fig. 2).

Chemotherapy Benefit for Patients with Stage III NPC

Through Crude Kaplan-Meier analysis, we revealed that ACM was more significantly reduced in patients treated with chemotherapy versus those without chemotherapy (5-year ACM rate: 31.6% vs. 48.4%, $P < 0.001$, Fig. 3A; crude HR: 0.51, 95% CI [0.38–0.70], Table 2). IPTW procedures conducted in the primary cohort resulted in a well-balanced weighted sample (Table 1 and Fig. 4). IPTW-adjusted Kaplan-Meier analysis revealed similar findings favoring treatment with chemotherapy (5-year ACM rate: 32.1% vs.

48.9%, $P = 0.008$, Fig. 3B; IPTW-adjusted HR: 0.57, 95% CI [0.38–0.86]). The crude cumulative incidence of CSM without competing risks was significantly lower for patients treated with chemotherapy versus those without chemotherapy (5-year CSM rate: 26.4% vs. 37.8%, $P = 0.005$, Fig. 3C; crude HR: 0.58, 95% CI [0.39–0.85], Table 2). IPTW-adjusted cumulative incidence function with noncancer death as the competing event yielded similar results favoring treatment with chemotherapy (5-year CSM rate: 32.7% vs. 35.7%, $P = 0.017$, Fig. 3D; IPTW-adjusted SHR: 0.62, 95% CI [0.42–0.92], Table 2).

Subgroup Analysis and Interaction Effect

According to NCCN guidelines, all patients with stage III NPC are recommended for chemotherapy. However, in this study, 34 (17.4%) patients with node-negative stage III NPC and 57 (4.6%) patients with node-positive stage III NPC received chemotherapy. The relatively large proportion of patients with node-negative stage III NPC who did not receive chemotherapy allowed us to hypothesize that the chemotherapeutic effect may be modified by lymph node status. Results for the subgroup analyses for ACM are summarized in a forest plot (Fig. 5). Moreover, we reported a significant interaction between chemotherapy and lymph node status for ACM (P for interaction: 0.048).

Chemotherapy Benefit for Patients with Node-negative Stage III NPC

The survival benefit of chemotherapy was insignificant for patients with node-negative stage III (T3N0M0) NPC. In crude Kaplan-Meier analysis, there was no difference in ACM for patients treated with chemotherapy versus those without (5-year ACM rate: 41.5% vs. 41.6%, $P = 0.618$, Fig. 3E; crude HR: 0.87, 95% CI [0.51–1.50], Table 2). IPTW procedures conducted in node-negative cohort generated a well-balanced weighted population (Table S1 and Fig. S1). IPTW-adjusted Kaplan-Meier analysis yielded similar results (5-year ACM rate: 41.9% vs. 42.5%, $P = 0.746$, Fig. 3F; IPTW-adjusted HR: 0.89, 95% CI [0.45–1.76], Table 2). The crude cumulative incidence of CSM without competing risks was comparable for patients treated with chemotherapy versus without (5-year CSM rate: 35.3% vs. 32.2%, $P = 0.960$, Fig. 3G; crude HR: 0.98, 95% CI [0.51–1.88], Table 2). IPTW-adjusted cumulative incidence function with noncancer death as the competing event yielded similar results (5-year CSM rate: 33.7% vs. 31.2%, $P = 0.982$, Fig. 3H; IPTW-adjusted SHR: 1.01, 95% CI [0.52–1.96], Table 2).

Chemotherapy Benefit for Patients with Node-positive Stage III NPC

We observed significant survival benefit associated with chemotherapy in patients with node-positive stage III (T3N1M0/T1–3N2M0) NPC. In crude Kaplan-Meier analysis, ACM was significantly lower for patients treated with chemotherapy versus those without (5-year ACM rate: 30.2% vs. 53.5%, $P < 0.001$,

Fig. 3I; crude HR: 0.44, 95% CI [0.30–0.65], Table 2). IPTW procedures conducted in the node-positive cohort generated a well-balanced weighted sample (Table S2 and Fig. S2). IPTW-adjusted Kaplan-Meier analysis revealed similar findings (5-year ACM rate: 30.4% vs. 42.8%, $P = 0.048$, Fig. 3J; IPTW-adjusted HR: 0.63, 95% CI [0.39–0.99], Table 2). The crude cumulative incidence of CSM was significantly lower for patients treated with chemotherapy versus those without (5-year CSM rate: 25.1% vs. 42.0%, $P = 0.005$, Fig. 3K; crude HR: 0.50, 95% CI [0.31–0.80], Table 2). IPTW-adjusted cumulative incidence function with noncancer death as the competing event showed similar findings (5-year CSM rate: 24.3% vs. 39.0%, $P = 0.012$, Fig. 3L; IPTW-adjusted SHR: 0.54, 95% CI [0.33–0.87], Table 2).

Discussion

The landmark study Intergroup 0099 trial first demonstrated prolonged survival benefit using CCRT+AC compared with RT alone in a nonendemic area [3]. Besides, confirmatory trials conducted in endemic regions supported that the Intergroup 0099 regimen could significantly improve disease control and survival outcomes [4–7, 12]. Apart from adjuvant sequencing, IC may offer a promising treatment strategy for advanced locoregionally disease in the intensity-modulated radiation therapy (IMRT) era [8–11, 14]. Compared with AC, IC is more tolerable and eliminates potential micrometastases earlier. Pooled analysis of four randomized trials confirmed the superiority of additional induction chemotherapy over concurrent Chemoradiotherapy alone in distant control and subsequent survival for patients with locoregionally advanced NPC [19]. We obtained consistent findings with those of randomized studies comprising stage IV disease. Furthermore, chemotherapy administration was associated with lower ACM and CSM in patients with stage III NPC, despite recipients having more advanced and/or node-positive disease. This finding persisted in the IPTW-adjusted analyses taking into account baseline confounders and competing risks.

On the other hand, results from meta-analyses, including two individual patient data meta-analyses, showed inconsistent results concerning the magnitude of chemotherapy benefit and the best chemotherapy sequence [20–22]. The indeterminate conclusions may have resulted from the heterogeneous participants recruited in these randomized trials. Although most trials focused on stage III–IVb diseases and seldomly included stage II disease patients, several trials excluded the low-risk stage III disease (T3N0M0 and/or T3N1M0) [9–13]. Numerous studies have demonstrated that the chemotherapy benefit's actual magnitude could be modified, owing to patients' tumor burden, toxicities of chemotherapy, follow-up duration, increased noncancer mortality, and RT technique [6, 7, 23–27]. Therefore, there have been concerns about the exact magnitude of the chemotherapy benefit in different subgroups in the IMRT era, especially for patients with low-risk or moderate-risk locoregionally advanced disease.

Given that patients with stage III NPC are disproportionately underrepresented in major clinical trials, the current study attempted to address the crucial clinical question of whether additional chemotherapy adds survival benefit to this subgroup. An accurate estimation of chemotherapy benefit in patients with stage III NPC is critically vital to optimize case selection for chemotherapy management and avoid futile

chemotherapy. To our knowledge, this is the first study to demonstrate the efficacy of chemotherapy in patients with stage III NPC according to lymph node status using a large sample obtained from the SEER database. Notably, our results are particularly noteworthy because chemotherapy might not benefit all subgroups of stage III NPC. We found a significant interaction between the chemotherapeutic effect and lymph node status. For instance, among patients with node-positive stage III NPC, additional chemotherapy could reduce ACM and CSM and be associated with a significant survival benefit. However, for patients with node-negative stage III disease, chemotherapy combined with RT did not prolong survival time and reduce cancer-related death compared with RT alone. Thus, stratified treatment based on lymph node status in stage III disease seems reasonable, which can spare more lower-risk patients from unbeneficial chemotherapy and unnecessary chemotherapy-induced toxicities. However, further prospective randomized trials are needed to validate these findings before this treatment strategy's application.

Our findings are in one way or the other agreeing with several previous reports. The efficacy of chemotherapy in survival of low-risk NPC warrants reevaluation. Pan and colleagues revealed that chemoradiotherapy showed similar survival outcomes to stage II NPC patients compared with radiotherapy only [28]. Chen and colleagues found that the N category is the dominant factor influencing chemotherapy effect and prognosis for patients with locoregionally advanced NPC treated by RT alone [25]. The subgroup analysis based on combined analyses of NPC-9901 and NPC-9902 trials showed that among NPC patients with T1-4N2-3M0 disease, the survival benefit of CCRT+AC was most remarkable for patients with moderate risk (stage III disease [T1-3N2M0] or lactate dehydrogenase <200 IU/L) [5, 23]. Similarly, Skye et al. indicated that CCRT+AC mainly benefited moderate-risk patients (T2b-3N0-2M0) [28]. The recent improvement achieved in managing NPC is partly attributable to IMRT. In recent days, locoregional relapse is uncommon, whereas distant metastasis predominates the pattern of treatment failure. Lymph node metastasis is the dominant risk factor for distant metastasis. Previous studies revealed that lymph node metastasis in NPC follows a predictable and orderly pattern [29]. Notably, the rarity of "skip" metastasis suggests that patients with node-negative NPC are at low risk of distant metastasis and supports that reduced treatment is feasible for these patients. However, there was no published information regarding the relapse of NPC in the SEER database. As a result, we did not explore the effect of chemotherapy on recurrence and distant metastasis in the present study.

The current study has some inevitable limitations. First, selection bias and competing risks may arise due to the nature of retrospective design and the treatment assignment. However, we attempted to minimize these confounds through the statistical methodology and recruitment of consecutive patients. Second, the SEER database lacks detailed information on treatment (for example, chemotherapy regimen, radiation dose, etc.), Epstein-Barr virus DNA information, and relapse data. The unavailability of these critical data limits further exploration of the underlying mechanisms. Finally, there are still some concerns about the completeness and underlying bias of chemotherapy data provided by the SEER database [30]. However, there is no available comparative analysis of SEER treatment data with Medicare claims concerning the NPC. As radiation therapy and chemotherapy are both primary treatment for stage III NPC,

we are highly confident that the SEER database would accurately capture individual radiation and chemotherapy data. The data would support our current analyses.

Conclusion

In conclusion, this work demonstrated that chemotherapy significantly improves overall survival and lower NPC-related mortality in stage III NPC, especially in patients with node-positive disease. Node-negative stage III disease might not benefit from additional chemotherapy. Nevertheless, our findings should be regarded as hypothesis-generating ones. Prospective clinical trials are needed to validate these findings.

Declarations

Ethics approval and informed consent

Not required.

Consent for publication

Not required.

Data availability statement

All data generated or analyzed during this study are derived from the Surveillance, Epidemiology, and End Results (SEER, <http://seer.cancer.gov/seerstat>) database. Everyone can obtain the related data given that they were granted permission to access the SEER Program database.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Tables

Table 1. Patient characteristics stratified by treatment modality, covariate balance, and predictors for receiving chemotherapy.

Variable	Baseline Characteristics			Covariate Balance		Multivariable Logistic Regression	
	No Chemotherapy		P-value	Standardized Difference			
	N=91	N=1361		Before IPTW	After IPTW	Adjusted OR (95% CI)	P-value
Age			0.003				
<50	23 (25.3%)	567 (41.7%)		-0.164	-0.064	Reference	
≥50	68 (74.7%)	794 (58.3%)				0.58 (0.34-0.95)	0.035
Sex			0.008	0.138	0.017		
Female	39 (42.9%)	395 (29.0%)				Reference	
Male	52 (57.1%)	966 (71.0%)				1.72 (1.08-2.70)	0.020
Race			0.029				
Black	12 (13.2%)	169 (12.4%)		-0.008	-0.003	Reference	
White	52 (57.1%)	600 (44.1%)		-0.130	-0.026	1.11 (0.54-2.15)	0.760
Others	27 (29.7%)	592 (43.5%)		0.138	0.029	1.57 (0.72-3.26)	0.234
Insurance status			0.115	0.079	-0.014		
Uninsured/Unknown	29 (31.9%)	326 (24.0%)				Reference	
Insured	62 (68.1%)	1035 (76.0%)				1.57 (0.96-2.52)	0.064
Marital status			0.561	0.037	-0.024		
Unmarried/Unknown	41 (45.1%)	563 (41.4%)				Reference	
Married	50 (54.9%)	798 (58.6%)				1.09 (0.68-1.73)	0.732
Histology			1.000	0.000	0.012		
Non-squamous carcinoma	32 (35.2%)	478 (35.1%)				Reference	
Squamous carcinoma	59 (64.8%)	883 (64.9%)				1.31 (0.80-2.13)	0.271
Tumor grade			<0.001				

Grade I-II	17 (18.7%)	103 (7.57%)	-0.111	0	Reference	
Grade III-IV	42 (46.2%)	869 (63.9%)	0.177	-0.021	2.72 (1.38-5.20)	0.003
Unknown	32 (35.2%)	389 (28.6%)	-0.066	0.021	1.46 (0.72-2.87)	0.282
T category			0.935	0.010	0.023	0.026
T1	22 (24.2%)	316 (23.2%)			Reference	
T2-3	69 (75.8%)	1045 (76.8%)			1.89 (1.07-3.29)	
N category			<0.001	0.247	0.006	
N0	34 (37.4%)	173 (12.7%)			Reference	
N1-2	57 (62.6%)	1188 (87.3%)			3.98 (2.36-6.72)	<0.001

Abbreviation: IPTW, inverse probability of treatment weighting; OR, odds ratio; CI, confidence interval.

Table 2. Effect of chemotherapy versus no chemotherapy in the survival of stage III NPC.

Cohorts and events	HR or SHR (95% CI)	P value	5-year mortality rate (%)	
			Chemotherapy	No chemotherapy
All stage III NPC				
All-cause mortality				
Crude	0.51 (0.38-0.70)	0.001	31.6 (28.7-34.4)	48.4 (35.1-59.0)
IPTW-adjusted	0.58 (0.39-0.86)	0.007	32.1 (29.2-34.9)	48.9 (30.6-62.4)
Cancer-specific mortality				
Crude	0.58 (0.39-0.85)	0.005	26.4 (23.6-29.1)	37.8 (24.8-48.6)
IPTW-adjusted	0.62 (0.42-0.92)	0.017	32.7 (29.3-35.9)	35.7 (23.9-45.7)
Node-negative stage III NPC				
All-cause mortality				
Crude	0.87 (0.51-1.50)	0.618	41.5 (32.5-49.2)	41.6 (20.6-57.0)
IPTW-adjusted	0.89 (0.45-1.76)	0.746	41.9 (22.9-49.8)	42.5 (16.8-60.3)
Cancer-specific mortality				
Crude	0.98 (0.51-1.88)	0.960	35.3 (26.5-43.0)	32.2 (13.0-47.2)
IPTW-adjusted	1.01 (0.52-1.96)	0.982	33.7 (25.4-41.1)	31.2 (12.9-45.7)
Node-positive stage III NPC				
All-cause mortality				
Crude	0.44 (0.30-0.65)	<0.001	30.2 (27.1-33.1)	53.5 (35.1-66.7)
IPTW-adjusted	0.63 (0.39-0.99)	0.048	30.4 (27.3-33.3)	42.8 (20.8-57.9)
Cancer-specific mortality				
Crude	0.50 (0.31-0.80)	0.003	25.1 (22.2-28.0)	42.0 (23.3-56.2)
IPTW-adjusted	0.54 (0.33-0.87)	0.012	24.3 (21.4-27.0)	39.0 (21.8-51.8)

Abbreviation: NPC, nasopharyngeal carcinoma; HR, hazard ratio; CI, confidence interval; IPTW, inverse probability of treatment weighting.

Note: Hazard ratios (HRs) for all-cause mortality were estimated using univariable unweighted and IPTW-weighted Cox proportional hazards models. Sub-hazard ratios (SHRs) for cancer-specific mortality were estimated using Fine and Gray proportional subdistribution hazards models with noncancer mortality as the competing event.

Figures

Figure 1

Patient selection diagram. (Abbreviations: NPC, nasopharyngeal carcinoma; SEER: Surveillance, Epidemiology, and End Results.)

Figure 2

General dominance of independent predictors for receiving chemotherapy in patients with stage III NPC.

Figure 3

(i) Patients with Stage III NPC: crude (A) and IPTW-adjusted (B) cumulative incidence of ACM for patients receiving chemotherapy vs. receiving no chemotherapy; the cumulative incidence of CSM without (C) or with (D) competing risk for patients receiving chemotherapy vs. receiving no chemotherapy.

(ii) Patients with node-negative Stage III NPC: crude (E) and IPTW-adjusted (F) cumulative incidence of ACM for patients receiving chemotherapy vs. receiving no chemotherapy; the cumulative incidence of

CSM without (G) or with (H) competing risk for patients receiving chemotherapy vs. receiving no chemotherapy. (iii) Patients with node-positive Stage III NPC: crude (I) and IPTW-adjusted (J) cumulative incidence of ACM for patients receiving chemotherapy vs. receiving no chemotherapy; the cumulative incidence of CSM without (K) or with (L) competing risk for patients receiving chemotherapy vs. receiving no chemotherapy. (Abbreviations: IPTW, inverse probability of treatment weighting; ACM: all-cause mortality; CSM: cancer-specific mortality.)

Figure 4

Balance between treatment groups in patients with stage III nasopharyngeal carcinoma evaluated by standardized mean difference (SMD) before and after inverse probability of treatment weighting (IPTW) adjustment. A SMD less than 0.1 indicates good balance.

Hazard Ratio

Figure 5

Results for the subgroup analyses for all-cause mortality are summarized in a forest plot.

Supplementary Files

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- [SupplementaryMaterials.pdf](#)