Prognostic value of hypertension in patients with nasopharyngeal carcinoma treated with intensity-modulated radiation therapy

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Research

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Abstract

Purpose

To investigate the prognostic value of hypertension in patients with nasopharyngeal carcinoma (NPC) treated with intensity-modulated radiation therapy (IMRT).

Methods and Materials:

A total of 1057 patients with nonmetastatic, histologically proven NPC who were treated with IMRT were retrospectively reviewed. Associations between hypertension and overall survival (OS), loco-regional relapse-free survival (LRRFS) and distant metastasis-free survival (DMFS) were estimated by Cox regression.

Results

Among 1057 patients, 94 (8.9%) had hypertension. Compared to normotensive patients, the hypertensive patients were generally older, had higher body fat, were more likely to be alcohol consumers, were more often in the early stage and usually received radiotherapy alone. Compared to normotension, hypertension was significantly associated with worse OS (hazard ratio (HR), 2.20; 95% confidence interval (CI), 1.41–3.42; $P = 0.000$), LRRFS (HR, 2.13; 95% CI, 1.12–4.03; $P = 0.021$) and DMFS (HR, 1.82; 95% CI, 1.09–3.05; $P = 0.023$) after adjusting for covariates. Moreover, the association with OS remained unchanged regardless of smoking, body mass index (BMI), N stage and chemotherapy, whereas it was limited in the subgroup of patients who were older than 50 years, male, not alcohol consumers, in advanced T stage and in advanced clinical stage. Compared with treated hypertension, untreated hypertension was associated with increased risks for death ($P = 0.221$; HR, 1.88; 95% CI, 0.69–5.15), locoregional recurrence ($P = 0.073$; HR, 3.29; 95% CI, 0.89–12.09) and distant metastasis ($P = 0.640$; HR, 1.30; 95% CI, 0.44–3.83). The patients with more severe levels of hypertension had worse survival and locoregional control, although there was no statistically significant difference ($P > 0.05$).

Conclusions

Hypertension is an independent adverse prognostic factor in NPC patients treated with IMRT. The NPC patients with untreated hypertension had similar survival as those with treated hypertension. The severity of hypertension did not influence the prognosis.

Introduction

Nasopharyngeal carcinoma (NPC) is endemic in certain regions, especially in southern China and Southeast Asia [1]. The annual incidence of NPC is 15–50 cases per 100,000 people [2]. NPC is unresectable due to its proximity to the skull base and high radiosensitivity, so radiation therapy remains the mainstay treatment modality for locoregionally confined stages of NPC, and the TNM staging system is the most reliable method for guiding treatment decisions and predicting prognosis. However, the TNM staging system classifies the extent of the disease chiefly on the basis of anatomical information, and it is inadequate for the assessment of prognosis [3]. Therefore, it is of great clinical value to identify novel prognostic indicators to improve outcome prediction and optimize the treatment of patients with NPC.

Hypertension has been reported to be the most common comorbidity encountered in patients with tumours, with an occurrence rate of 37% [4]. Many studies have suggested that hypertension is associated with an increased risk of cancer, such as renal cell carcinoma [5], breast cancer [6], and urinary bladder cancer [7]. In addition, renal cancer [8], pancreatic cancer [9] and oesophageal cancer patients [10] with hypertension have poorer prognoses than normotensive patients.

To the best of our knowledge, only one study has reported an association between hypertension and the survival of NPC patients [11], and the study population covered not only non-metastatic NPC patients but also metastatic patients. Since the biological behaviours and therapeutic principles were obviously different between these two groups, it is reasonable to discuss the prognostic indicators separately. Furthermore, it is well known that intensity-modulated radiation therapy (IMRT) provides excellent local control and is now the mainstream radiation therapy [12]. However, the prognostic value of hypertension in NPC patients treated with IMRT is unclear. Hence, in this report, we conducted a retrospective analysis of existing patient data to evaluate the prognostic impact of hypertension on the outcome of non-metastatic NPC patients treated with IMRT.

Materials And Methods

Patient cohort

We reviewed the medical records of all patients with NPC treated with IMRT at the Affiliated Cancer Hospital & Institute of Guangzhou Medical University between February 2010 and October 2016. We included all patients with newly diagnosed, non-metastatic, histologically confirmed disease, and 1057 patients were eventually enrolled in this study. All patients underwent a physical examination, fibreoptic examination, chest X-ray, abdominal ultrasonography, magnetic resonance imaging (MRI) of the neck and nasopharynx, and a whole-body bone scan using single-photon emission computed tomography (SPECT) prior to treatment. The medical records and imaging studies were analysed retrospectively, and all patients were restaged according to the 8th edition of the Union for International Cancer Control/American Joint Committee on Cancer staging system for NPC. The study was reviewed and approved by the ethics committee of the Affiliated Cancer Hospital & Institute of Guangzhou Medical University, and informed consent was obtained from all patients.

Hypertension Assessment

All patient medical records were thoroughly reviewed. In our study, pretreatment hypertension was defined as an average systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg measured three times on a different day without the use of antihypertensive drugs, as well as having a history of hypertension or receiving anti-hypertension medication treatment. Furthermore, hypertension was categorized as Grade 1 (BP ≥ 140/90 mmHg), Grade 2 (BP ≥ 160/100 mmHg) or Grade 3 (BP ≥ 180/110 mmHg). The pretreatment hypertension treatment status was also recorded.

Treatment

Radiotherapy

All patients were treated with definitive IMRT at the Affiliated Cancer Hospital & Institute of Guangzhou Medical University. A high-resolution planning computed tomography scan with contrast was taken from the vertex down to 2 cm below the sternoclavicular joint. The target volumes were delineated in accordance with the International Commission on Radiation Units and Measurements reports 50 and 62. The planning target volumes (PTVs) and planning organ at risk volumes (PRVs) were generated by adding a margin of 3 mm to the respective clinical target volumes (CTVs) and corresponding structures, such as the spinal cord and brainstem. The prescribed dose was 68–70 Gy to the PTV of gross tumour volume of the primary (GTV-P), 64–66 Gy to the PTV of nodal gross tumour volume (GTV-N), 60–66 Gy to the PTV of clinical target volume-1 (CTV-1; i.e., high-risk regions), and 54–56 Gy to PTV of CTV-2 (i.e., low-risk regions) and CTV-N (i.e., neck nodal regions) in 30–33 fractions. All targets were treated simultaneously using the simultaneous integrated boost technique. The irradiation was delivered once daily 5 days per week.

Chemotherapy

Institutional guidelines recommended no chemotherapy for patients in the early stage and induction, concurrent and adjuvant chemotherapy or combined treatment for those in the locoregionally advanced stage. Induction or adjuvant chemotherapy consisted of platinum with 5-fluorouracil, platinum with taxane or triplet therapy with platinum and 5-fluorouracil plus taxane every 3 weeks for one to three cycles. Concurrent chemotherapy consisted of platinum given weekly or on weeks 1, 4 and 7 of radiotherapy. Deviation from the institutional guidelines occurred as a result of organ dysfunction, treatment intolerance and/or patient refusal.

Follow-up

The follow-up duration was calculated from the first day of treatment to either the day of death or the day of the last examination. Each patient was assessed every 3 months during the first 2 years and every 6 months during years 3–5 after radiotherapy. Endoscopy, computed tomography or MRI scans of the head and neck were performed every 3 months during the first year and annually during years 2–5. The median follow-up period for the whole group was 54.1 months (range 2.9–120.4 months).

Statistical analysis

Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL, USA) was used for analysis. The primary end point was overall survival (OS), defined as the time from treatment to death resulting from any cause. The secondary end points were loco-regional relapse-free

survival (LRRFS) and distant metastasis-free survival (DMFS), defined as the time from treatment to the first locoregional relapse and distant metastasis, respectively.

The baseline characteristics between the two groups were compared and analysed using the chi-square test. The actuarial rates were estimated using the Kaplan–Meier method, and the differences were compared using the log-rank test. Multivariate analyses with the Cox proportional hazards model were used to test the independent significance of different explanatory variables. Two-tailed *P*-values < 0.05 were considered statistically significant.

Results

Patient baseline characteristics

In total, 94/1057 patients were found to be hypertensive. Of the 94 hypertension patients, 42 (44.7%) had grade 1 hypertension, 31 (33.0%) had grade 2 hypertension, and 21 (22.3%) had grade 3 hypertension. Furthermore, 72 (76.6%) were treated for hypertension, while 22 (23.4%) were not.

The characteristics of the 1057 NPC patients are summarized in Table 1. There were no differences in the distributions of sex, smoking, T stage, N stage or clinical stage between the two groups ($P > 0.05$). However, the hypertension group had a higher percentage of patients who were older ($P = 0.000$), consumed alcohol ($P = 0.016$), were overweight ($P = 0.000$), and were in an early clinical stage ($P = 0.044$), and the proportion of hypertensive patients who received chemotherapy along with RT was lower than that of patients without hypertension ($P = 0.000$).

Table 1
Baseline characteristics of NPC patients with or without hypertension.

Characteristics	Without hypertension	With hypertension	*P*
	No. (%)	No. (%)	
Total	963	94	
Age			0.000
< 50	577(59.9)	19(20.2)	
≥ 50	386(40.1)	75(79.8)	
Gender			0.308
Male	690(71.7)	72(76.6)	
female	273(28.3)	22(23.4)	
Smoking			0.385
Yes	396(41.1)	43(45.7)	
No	567(58.9)	51(54.3)	
Drinking			0.016
Yes	136(14.1)	22(23.4)	
No	827(85.9)	72(76.6)	
BMI(kg/m^2)			0.000
< 18.5	79(8.2)	4(4.3)	
18.5–22.9	477(49.5)	19(20.2)	
22.9–27.5	338(35.1)	50(53.2)	
≥ 27.5	69(7.2)	21(22.3)	
T stage*			0.889
T1	166(17.2)	18(19.1)	
T2	134(13.9)	15(16.0)	
T3	520(54.0)	48(51.1)	
T4	143(14.9)	13(13.8)	
N stage*			0.252
N0	114(11.8)	16(17.0)	
N1	552(57.3)	57(60.7)	
N2	227(23.6)	16(17.0)	
N3	70(7.3)	5(5.3)	
Clinical stage*			0.044
I	34(3.5)	9(9.7)	
II	185(19.2)	18(19.1)	
III	538(55.9)	49(52.1)	
IV	206(21.4)	18(19.1)	
Chemotherapy			0.000

Abbreviations: NPC, nasopharyngeal carcinoma; BMI, Body Mass Index.

* According to the 8th AJCC/UICC staging system.

Characteristics	Without hypertension	With hypertension	*P*
	No. (%)	No. (%)	
No	41(4.3)	14(14.9)	
Yes	922(95.7)	80(85.1)	
Abbreviations: NPC, nasopharyngeal carcinoma; BMI, Body Mass Index.			
* According to the 8th AJCC/UICC staging system.			

Failure pattern

The patterns of treatment failure and causes of death are shown in Table 2. Thirteen of 94 patients in the hypertension group (13.8%) and 78 of 963 patients in the normotensive group (8.1%) experienced locoregional failure, and 19 of 94 patients in the hypertension group (20.2%) and 134 of 963 patients in the normotensive group (24.3%) developed distant metastases. Moreover, 31 of 94 patients in the hypertension group (33.0%) and 134 of 963 patients in the normotensive group (13.9%) died; the majority of deaths (74.2% and 85.8%, respectively) were attributed to NPC. There was no significant difference noted with regard to the percentage of non-cancer-related deaths between hypertensive and normotensive patients (25.8% vs 14.2%; $P = 0.115$) (Table 2).

Table 2
Patterns of treatment failure and causes of death for patients with or without hypertension.

Failure pattern	Without hypertension	With hypertension	*P*
	No. (%)	No. (%)	
Local only	41(21.5)	4(14.8)	0.586
Local + regional	2(2.1)	0(0.0)	1.000
Local + distant	8(4.2)	3(11.1)	0.285
Local + regional + distant	2(1.0)	0(0.0)	0.466
Regional only	14(7.3)	4(14.8)	0.343
Regional + distant	11(5.8)	2(7.4)	1.000
Distant only	113(59.2)	14(51.9)	0.471
Total Locoregional	78(40.8)	13(48.1)	0.471
Total distant	134(70.2)	19(70.4)	0.982
Total failure	191	27	
Causes of death			0.115
cancer	115(85.8)	23(74.2)	
Non cancer	19(14.2)	8(25.8)	
Total	134	31	

Prognostic value of hypertension in patients with NPC

Hypertension history in NPC patients was associated with a significant increase in the risk of death (Fig. 1A). The 5-year OS rate was 66.6% for patients with hypertension compared with 85.4% for those without hypertension ($P < 0.0001$; HR, 2.54; 95% CI, 1.68–3.83). This remained unchanged after adjusting for other important prognostic factors, including age, sex, smoking, alcohol consumption, body mass index (BMI), T stage, N stage, clinical stage and chemotherapy. Compared with patients without hypertension, the NPC patients with hypertension had a multivariate HR of 2.20 ($P = 0.000$; 95% CI, 1.41–3.42) for death (Table 3).

Table 3
Multivariate analysis of prognostic factors for patients with NPC

Endpoint	Variable	*P*	HR	95% CI
OS	age	0.000	2.32	1.63–3.31
	hypertension	0.000	2.20	1.41–3.42
	chemotherapy	0.009	0.47	0.26–0.82
	T_{1-2} vs T_{3-4}	0.031	2.05	1.07–3.93
	N_{0-1} vs N_{2-3}	0.000	1.94	1.36–2.78
LRFS	hypertension	0.021	2.13	1.12–4.03
DMFS	hypertension	0.023	1.82	1.09–3.05
	N_{0-1} vs N_{2-3}	0.000	2.33	1.61–3.38
PFS	age	0.012	1.41	1.08–1.84
	hypertension	0.001	1.94	1.31–2.87
	T_{1-2} vs T_{3-4}	0.040	1.69	1.02–2.79
	N_{0-1} vs N_{2-3}	0.000	1.87	1.39–2.51

The results for the risk of locoregional relapse (Fig. 1B) and distant metastasis (Fig. 1C) were similar to those for death. In univariate analysis, hypertension was associated with worse LRRFS ($P = 0.027$; HR, 1.95; 95% CI, 1.08–3.51) and DMFS ($P = 0.048$; HR, 1.62; 95% CI, 1.00-2.62). In multivariate analysis, the adjusted HRs for LRRFS and DMFS were 2.13 ($P = 0.021$; 95% CI, 1.12–4.03) and 1.82 ($P = 0.023$; 95% CI, 1.09–3.05), respectively (Table 3).

The grade and treatment status of hypertension

We found that the three grades of hypertension were associated with a significant increase in the risk of death with adjusted HRs of ascending grades of 1.59, 2.30 and 2.86, respectively, when compared with normotensive individuals (Table 4). The patients with more severe levels of hypertension had worse survival and locoregional control; however, there was no statistically significant difference ($P > 0.05$).

Table 4
Multivariate analysis for the grade and treatment status of hypertension.

	Total(No.)	OS			LRFS			DMFS		
		Events(No.)	HR(95%CI)	*P*	Events(No.)	HR(95%CI)	*P*	Events(No.)	HR(95%CI)	*P*
The grade of hypertension										
0	963	120	1.00		74	1.00		130	1.00	
1	42	11	2.08(1.09–3.98)	0.026	4	1.59(0.56–4.49)	0.380	5	1.12(0.45–2.80)	0.813
2	31	10	2.27(1.17–4.41)	0.016	5	2.30(0.90–5.90)	0.083	10	2.64(1.35–5.16)	0.004
3	21	7	2.29(1.04–5.05)	0.041	4	2.86(0.99–8.26)	0.053	4	1.79(0.64–4.97)	0.266
The treatment status of hypertension										
0	963	120	1.00		74	1.00		130	1.00	
treated	72	22	2.06(1.26–3.59)	0.004	9	1.84(0.88–3.86)	0.105	14	1.68(0.93–3.02)	0.085
untreated	22	6	2.87(1.24–6.63)	0.014	4	3.17(1.13–8.94)	0.029	5	2.35(0.95–5.83)	0.066

In addition, we examined the effect of antihypertensive drug intake on prognosis. After adjusting for known confounders, both treated hypertension ($P = 0.004$; HR, 2.06; 95% CI, 1.26–3.59) and untreated hypertension ($P = 0.014$; HR, 2.87; 95% CI, 1.24–6.63) were associated with

an increased risk for death compared with normotension (Table 4). Compared with treated hypertension, untreated hypertension was associated with increased risks for death (P = 0.221; HR, 1.88; 95% CI, 0.69–5.15), locoregional recurrence (P = 0.073; HR, 3.29; 95% CI, 0.89–12.09) and distant metastasis (P = 0.640; HR, 1.30; 95% CI, 0.44–3.83), although statistical significance was not reached.

Subgroup analysis based on various prognostic factors

We assessed the prognostic value of hypertension in different NPC subgroups, which were stratified by other potential predictors of patient outcome (Fig. 2). Multivariate analyses showed that hypertension was significantly correlated with worse OS regardless of smoking, BMI, N stage and chemotherapy. In addition, the effect of hypertension on increasing the risk of death was observed among older individuals (HR, 2.16; 95% CI, 1.34–3.49; P = 0.002), males (HR, 2.36; 95% CI, 1.44–3.87; P = 0.001), and non-alcohol consumers (HR, 2.47; 95% CI, 1.52–4.02; P = 0.000). Moreover, hypertension was also significantly associated with OS among patients with advanced T stage (HR, 2.33; 95% CI, 1.45–3.74; P = 0.000) and advanced clinical stage (HR, 2.33; 95% CI, 1.47–3.69; P = 0.000), whereas this did not occur in those with early T stage and stage I/II disease.

Discussion

To our knowledge, this is the largest and most detailed report to evaluate the impact of hypertension on the prognosis of non-metastatic NPC patients treated with IMRT. We demonstrated that hypertension was associated with a significant increase in the risk of death, locoregional relapse and distant metastasis in nonmetastatic NPC patients treated with IMRT, and the result remained unchanged after adjusting for known prognostic factors.

In our study, the incidence of hypertension was 8.9%, which was lower than that in a previous study (17.8%) [11]. A possible explanation for this difference may be the stricter patient selection criteria employed in the present study, that is, only nonmetastatic NPC patients who received IMRT were included. The hypertensive patients in our study tended to be elderly, obese and alcohol consumers, which reflected unhealthy lifestyles and metabolic discordance, and these clinical features were similar to those reported in other literature [11]. In addition, we found that hypertensive patients were more likely to be in the early clinical stage and receive radiotherapy alone. One reason for this was probably that patients with hypertension are generally under closer medical supervision for treatment than those without such a profile, which may increase the probability of early detection of malignancy and consequently lead to a lower proportion of chemotherapy being added to RT for NPC in patients with hypertension. The other reason was probably that hypertension is a kind of comorbidity, and the risk increased with age; older people with complications were considered to be less able to receive chemotherapy than the rest of the population.

Various potential mechanisms have been reported to link hypertension to carcinogenic processes. Chronic hypoxia and vascular endothelial growth factor (VEGF) have been considered to be partly responsible for the increased cancer mortality in patients with hypertension [10, 13]. It is well known that hypertension leads to angiosclerosis and artery stenosis, resulting in insufficient blood supply to tissues and hypoxia. Hypoxic tumour cells exhibit increased resistance to radiotherapy, which may result in treatment failure, local relapse and metastasis [14, 15], especially for NPC, which is mainly treated by radiation therapy. On the other hand, VEGF was found to be increased in hypertensive patients [16], and it was also confirmed to promote tumour angiogenesis [17], thus possibly causing tumour cell proliferation and metastasis in cancer patients with hypertension. Furthermore, studies have reported that there is a close relationship between hypoxia and VEGF expression in tumours and that hypoxia can induce an increase in VEGF expression [18, 19]. Our results indicate that NPC patients with hypertension had HRs of 2.20, 2.13 and 1.82 for death, locoregional relapse and distant metastasis, respectively, which was similar to the findings reported by other research groups, including the study by Yang et al. [11], in which multivariate analysis indicated that hypertension is an independent risk factor and results in poorer survival outcomes in patients with NPC. Similarly, Eytan DF et al. [20] analysed the effect of hypertension on the survival of head and neck cancer patients and found a 7–19% increased risk in cancer mortality in those with hypertension compared with those without hypertension. However, the prognostic value of hypertension in ovarian cancer (Stocks T et al. [9] and Minlikeeva AN et al. [21]) and breast cancer (Schairer C et al. [22] and Braithwaite1 D et al. [23]) patients remains controversial. This may be due to differences in the biology and pathology of NPC vs. ovarian and breast cancers. In addition, only two studies, including ours, have reported the poor prognostic value of hypertension in NPC patients. More research should be performed to evaluate the impact of hypertension on the survival outcome of NPC patients.

Previous research has reported that the severity of hypertension can significantly influence prognosis [11]. Stocks T et al. [9] found that the risk of cancer mortality increased, with an HR of 1.12 (95% CI: 1.08–1.15) for men and 1.06 (95% CI: 1.02–1.11) for women for every 10 mmHg increase in hypertension. Harding JL et al. [24] also noted a 23% increased risk for mortality in those with the highest grade of hypertension compared with those with the lowest. We then examined the effects according to the severity of hypertension; no significant decrease in OS, LRRFS or DMFS with increasing severity was observed. Further investigations are required because this non-significant difference in survival seemed to be driven by the small sample size of cases with different grades hypertension among NPC patients in our study.

Our results did not explicitly support a benefit of antihypertensive medications for the prognosis of NPC patients treated with IMRT. Previous study results suggested a potential favourable prognostic role of β-blockers for several tumours [25–26]. Moreover, a meta-analyse found that bevacizumab-induced hypertension may represent a prognostic factor in patients with metastatic colorectal cancer [27]. However, no report has thus far addressed the relationship between antihypertensive medications and NPC prognosis. Therefore, whether improvement in NPC survival with antihypertensive medications is because of only blood pressure-lowering effects or additional anticancer mechanisms is still unknown, and further validation of our findings will be required.

In our subgroup analysis, we found that the effects of hypertension were restricted in elderly patients. No interaction between age and hypertension was shown, and a higher proportion of patients received radiotherapy alone in the elderly group than in the young group. Moreover, there were a low proportion of patients and few events in the group of young people with hypertension. These findings may partially explain the lack of effects of hypertension in young patients. In addition, we found that the effect of hypertension was restricted in male patients and non-alcohol consumers. This may partly have been because of the small number of patients in the individual subgroups. Moreover, the poor prognostic effect of hypertension was observed only in T3-4 patients, and there were significant interactions between T stage and hypertension. Patients with early T stage disease exhibit better survival than those with T3-4 stage disease. Therefore, it is likely that the poor prognostic value of hypertension is not applicable to early T stage patients.

The results of the current study provide the first evidence of the unfavourable prognostic impact of hypertension on the prognosis of patients with NPC who received IMRT. Therefore, researchers conducting clinical trials in patients with NPC should pay attention to the hypertension rates in different treatment arms. Conversely, although antihypertensive status in the current study was not associated with survival, we cannot conclude that antihypertensive therapy for patients with NPC is unnecessary due to the retrospective nature of the current study, and high blood pressure can damage arteries and kidneys, causing stroke, kidney disease and other illnesses, resulting in a reduced ability to receive chemotherapy and an increase in non-cancer-related death rates. It is current practice in the tumour population to control blood pressure within reasonable limits before antitumour therapy, which is similar to treatment in the noncancer population.

Limitations

This study had some limitations. One limitation of our study was the nonrandomized study design due to the retrospective nature of the study. However, we attempted to reduce any potential bias by using univariate and multivariate analyses, as well as subgroup stratification, to achieve more homogeneous patient groups. The other limitation was that we only focused on pretreatment hypertension. Hypertension that may occur during the follow-up interval was not included because we could not judge the reliability of the information accurately through outpatient or telephone follow-up. Third, we did not have information about the type or dose of antihypertensive medications that participants were taking and therefore could not explore the role of specific antihypertensive treatments on prognosis.

Conclusion

In the current study, hypertension was found to be an independent poor prognostic factor for non-metastatic NPC patients receiving IMRT. The NPC patients with untreated hypertension had similar survival as those with treated hypertension. The severity of hypertension did not influence the prognosis.

Abbreviations

NPC: Nasopharyngeal carcinoma; IMRT: Intensity-modulated radiation therapy; MRI: Magnetic resonance imaging; SPECT: Single-photon emission computed tomography; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; PTVs: Planning target volumes; PRVs: Planning organ at risk volumes; CTV: Clinical target volume; OS: Overall survival; LRRFS: Loco-regional relapse-free survival; DMFS: Distant metastasis-free survival; HR: Hazard ratio; CI: Confidence interval; BMI: Body mass index; VEGF: Vascular endothelial growth factor.

Declarations

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Availability of supporting data

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YWJ, MW and XM participated in the design of the study and drafted the manuscript. LJQ and CDP performed the statistical analyses. QB and WMY collected data. YF conceived of the study and participated in its design. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Informed consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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References

1. Chan AT, Teo PM, Johnson PJ. Nasopharyngeal carcinoma. Ann Oncol. 2002;13(7):1007–15.
2. Wee JT, Ha TC, Loong SL, Qian CN. Is nasopharyngeal cancer really a "Cantonese cancer"? Chin J Cancer. 2010;29(5):517–26.
3. Guo R, Tang LL, Mao YP, Du XJ, Chen L, Zhang ZC, et al. Proposed modifications and incorporation of plasma Epstein-Barr virus DNA improve the TNM staging system for Epstein-Barr virus-related nasopharyngeal carcinoma. Cancer. 2019;125(1):79–89.
4. Piccirillo JF, Tierney RM, Costas I, Grove L, Spitznagel EL Jr. Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA. 2004;291(20):2441–7.
5. Sanfilippo KM, McTigue KM, Fidler CJ, Neaton JD, Chang Y, Fried LF, et al. Hypertension and obesity and the risk of kidney cancer in 2 large cohorts of US men and women. Hypertension. 2014;63(5):934–41.
6. Han H, Guo W, Shi W, Yu Y, Zhang Y, Ye X, et al. Hypertension and breast cancer risk: a systematic review and meta-analysis. Sci Rep. 2017;7:44877. doi:10.1038/srep44877.
7. Kok VC, Zhang HW, Lin CT, Huang SC, Wu MF. Positive association between hypertension and urinary bladder cancer: epidemiologic evidence involving 79,236 propensity score-matched individuals. Ups J Med Sci. 2018;123(2):109–15.
8. Grossman E, Messerli FH, Boyko V, Goldbourt U. Is there an association between hypertension and cancer mortality? Am J Med. 2002;112(6):479–86.
9. Stocks T, Van Hemelrijck M, Manjer J, Bjørge T, Ulmer H, Hallmans G, et al. Blood pressure and risk of cancer incidence and mortality in the metabolic syndrome and cancer project. Hypertension. 2012;59(4):802–10.
10. Liang J, Li G, Xu J, Wang T, Jia Y, Zhai Q, et al. Hypertension predicts a poor prognosis in patients with esophageal squamous cell carcinoma. Oncotarget. 2018;9(18):14068–76.
11. Yang P, Elhalawani H, Shi Y, Tang Y, Han Y, Zhao Y, et al. A large-scale retrospective study of the overall survival outcome in nasopharyngeal carcinoma with hypertension in Chinese population. Oncotarget. 2017;8(43):75577–86.
12. Du T, Xiao J, Qiu Z, Wu K. The effectiveness of intensity-modulated radiation therapy versus 2D-RT for the treatment of nasopharyngeal carcinoma: A systematic review and meta-analysis. PLoS One. 2019;14(7):e0219611. doi:10.1371/journal.pone.0219611.
13. Sharifi N, Farrar WL. Perturbations in hypoxia detection: a shared link between hereditary and sporadic tumor formation? Med Hypotheses. 2006;66(4):732–35.
14. Carlson DJ, Yenice KM, Orton CG. Tumor hypoxia is an important mechanism of radioresistance in hypofractionated radiotherapy and must be considered in the treatment planning process. Med Phys. 2011;38(12):6347–50.

15. Bjork-Eriksson T, West C, Karlsson E, Mercke C. Tumor radiosensitivity (SF2) is a prognostic factor for local control in head and neck cancers. Int J Radiat Oncol Biol Phys. 2000;46(1):13–9.
16. Belgore FM, Blann AD, Li-Saw-Hee FL, Beevers DG, Lip GY. Plasma levels of vascular endothelial growth factor and its soluble receptor (SFlt-1) in essential hypertension. Am J Cardiol. 2001;87(6):805–7.
17. Apte RS, Chen DS, Ferrara N. VEGF in Signaling and Disease: Beyond Discovery and Development. Cell. 2019;176(6):1248–64.
18. Morfoisse F, Kuchnio A, Frainay C, Gomez-Brouchet A, Delisle MB, Marzi S, et al. Hypoxia induces VEGF-C expression in metastatic tumor cells via a HIF-1alpha-independent translation-mediated mechanism. Cell Rep. 2014;6(1):155–67.
19. Jensen RL, Ragel BT, Whang K, Gillespie D. Inhibition of hypoxia inducible factor-1alpha (HIF-1alpha) decreases vascular endothelial growth factor (VEGF) secretion and tumor growth in malignant gliomas. J Neuro-Oncol. 2006;78(3):233–47.
20. Eytan DF, Blackford AL, Eisele DW, Fakhry C. Prevalence of Comorbidities and Effect on Survival in Survivors of Human Papillomavirus-Related and Human Papillomavirus-Unrelated Head and Neck Cancer in the United States. Cancer. 2019;125(2):249–60.
21. Minlikeeva AN, Freudenheim JL, Cannioto RA, Szender JB, Eng KH, Modugno F, et al. History of Hypertension, Heart Disease, and Diabetes and Ovarian Cancer Patient Survival: Evidence From the Ovarian Cancer Association Consortium. Cancer Causes Control. 2017;28(5):469–86.
22. Schairer C, Gadalla SM, Pfeiffer RM, Moore SC, Engels EA. Diabetes. Abnormal Glucose, Dyslipidemia, Hypertension, and Risk of Inflammatory and Other Breast Cancer. Cancer Epidemiol Biomarkers Prev. 2017;26(6):862–68.
23. Braithwaite D, Tammemagi CM, Moore DH, Ozanne EM, Hiatt RA, Belkora J, et al. Hypertension is an independent predictor of survival disparity between African-American and white breast cancer patients. In J Cancer. 2009;124(5):1213–9.
24. Harding JL, Sooriyakumaran M, Anstey KJ, Adams R, Balkau B, Brennan-Olsen S, et al. Hypertension, Antihypertensive Treatment and Cancer Incidence and Mortality: A Pooled Collaborative Analysis of 12 Australian and New Zealand Cohorts. J Hypertens. 2016;34(1):149–55.
25. Baek MH, Kim DY, Kim SO, Kim YJ, Park YH. Impact of Beta Blockers on Survival Outcomes in Ovarian Cancer: A Nationwide Population-Based Cohort Study. J Gynecol Oncol. 2018;29(6):e82. doi:10.3802/jgo.2018.29.e82.
26. Zhao Y, Wang Q, Zhao X, Meng H, Yu J. Effect of antihypertensive drugs on breast cancer risk in female hypertensive patients: Evidence from observational studies. Clin Exp Hypertens. 2018;40(1):22–7.
27. Cai J, Ma H, Huang F, Zhu D, Bi J, Ke Y. Correlation of bevacizumab-induced hypertension and outcomes of metastatic colorectal cancer patients treated with bevacizumab: a systematic review and meta-analysis. World J Surg Oncol. 2013;11:306. doi:10.1186/1477-7819-11-306.

Figures

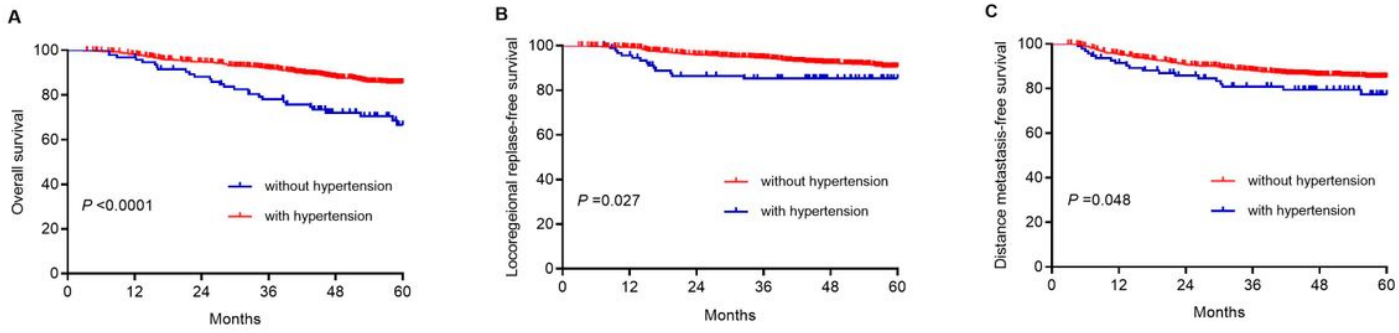

Figure 1

Kaplan-Meier survival curves are shown for (A) overall survival, (B) locoregional recurrence-free survival, and (C) distance metastasis-free survival in nasopharyngal carcinoma patients with or without hypertension.

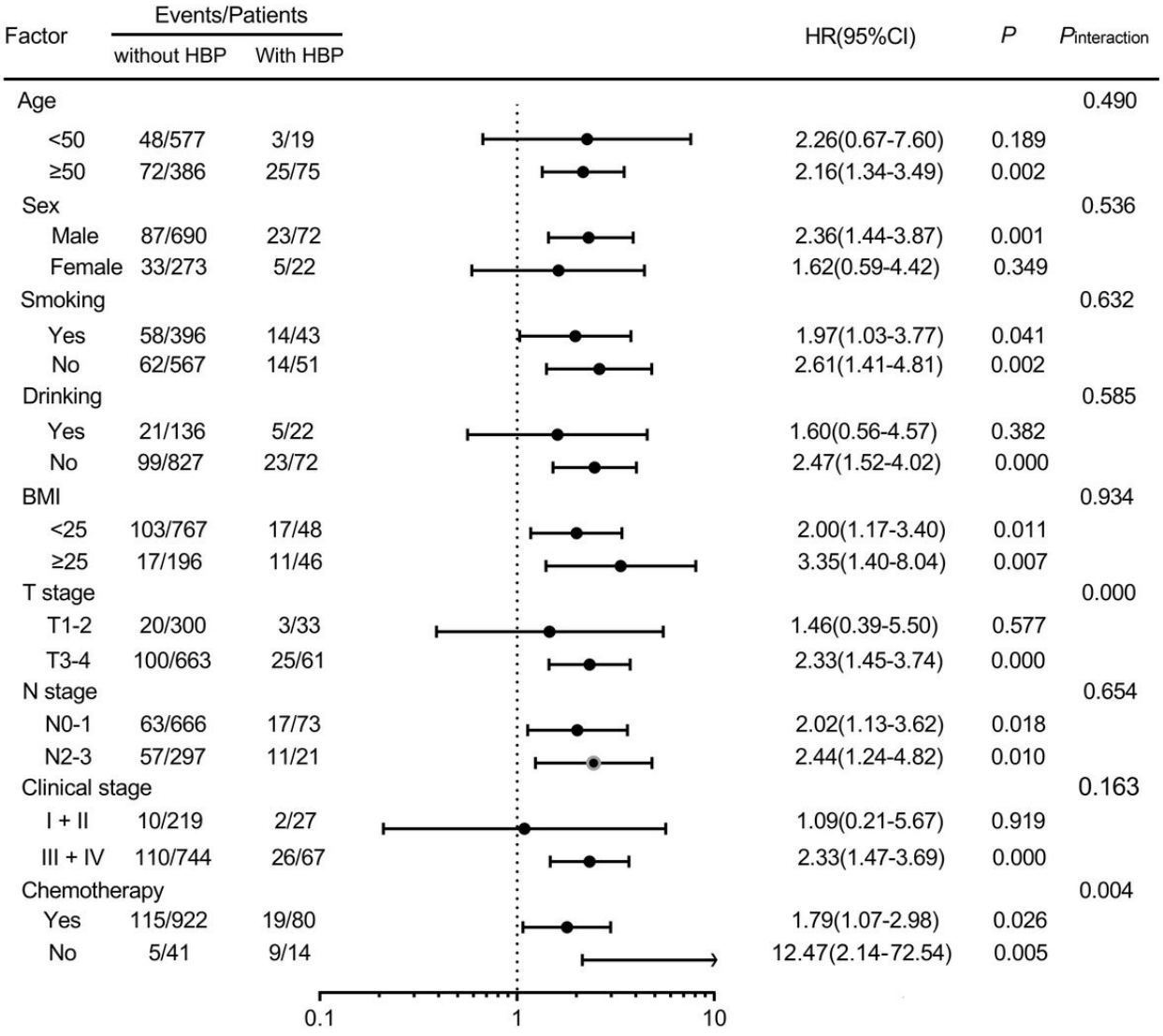

Figure 2

Subgroup analysis of overall survival by patients' characteristics in terms of with or without hypertension. Abbreviations: HBP, high blood pressure; HR, hazard ratio; CI, confidence interval.