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Role of zoledronic acid in nasopharyngeal carcinoma patients with bone-only metastasis at diagnosis

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ABSTRACT

Objective: We aimed to investigate whether zoledronic acid (ZA) can prevent skeletal-related events (SREs) and offer survival benefits for nasopharyngeal carcinoma (NPC) patients with bone-only metastasis at diagnosis.

Materials and Methods: A total of 228 newly diagnosed NPC cases with bone-only metastasis were eligible for this retrospective study. Using the propensity score method (PSM) method, a well-balanced cohort was created for further analysis. Overall survival (OS) was the primary endpoint. The difference in survival was evaluated using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) for allcause mortality were derived from a Cox regression model. Cumulative incidence competing risk analyses using Fine and Gray's method was used to test the cumulative incidence of SREs between the different treatment groups.

Result: In the PSM cohorts, patients in the platinum-based palliative chemotherapy (PCT) + ZA group and PCT alone group achieved similar 3-year OS (57.3% vs. 46.4%; log rank P = 0.188). Multivariate analysis indicated that ZA administration was not an independent prognostic factor (HR, 0.783; 95% CI, 0.267–2.300; P = 0.657). There was no significant difference in acute treatment toxicity between the 2 treatment groups, although the cumulative incidence of bone-related events (SREs) was significantly lower in the PCT + ZA group (Fine-Gray P = 0.026).

Conclusion: ZA combined with PCT could not improve OS in NPC patients with bone-only metastasis at diagnosis. However, the incidence of SREs could be effectively prevented via ZA application.

Introduction

Nasopharyngeal carcinoma (NPC) is a unique malignancy endemic to southern China, particularly in the provinces of Guangdong, Hainan, Guangxi, Hunan, and Fujian [1]. In 2012, approximately 86,700 new cases of NPC were reported, which account for 0.6% of all cancer cases worldwide [2,3]. In contrast to other head and neck cancers, NPC is sensitive to chemotherapy and radiotherapy [4]. Previous clinical trials have recommended concurrent chemoradiotherapy with or without adjuvant chemotherapy (CCRT) as the standard treatment regimen for locoregionally advanced NPC [5,6]. However, 6–15% of NPC patients had developed distant metastasis at the time of the initial diagnosis without any prior treatment, and the most common metastatic site was the bone [7–9]. Once distant lesions have been detected, platinum-based palliative chemotherapy (PCT) becomes the standard treatment method [10–13].

Zoledronic acid (ZA)—a bisphosphonate agent—serves as an inhibitor of osteoclastic bone resorption and can prevent the occurrence of osteoporosis. Based on a previous study, ZA administration markedly reduced skeletal-related events (SREs) (consisting of pathologic fracture, spinal cord compression, radiotherapy for bone pain, and hypercalcemia) in patients with bone metastasis and improved the patients' quality of life [14]. Moreover, as a nitrogen-containing bisphosphonate, ZA has been found to have several antineoplastic effects, including angiogenesis, apoptosis induction, and tumor cell invasion inhibition [15–18]. In cases with breast cancer, the addition of ZA to endocrine therapy has improved disease-free survival in premenopausal patients [19]. Based on these findings, we aimed to investigate the role of ZA in NPC patients with bone-only metastases at diagnosis. Our primary objective was to determine whether PCT + ZA

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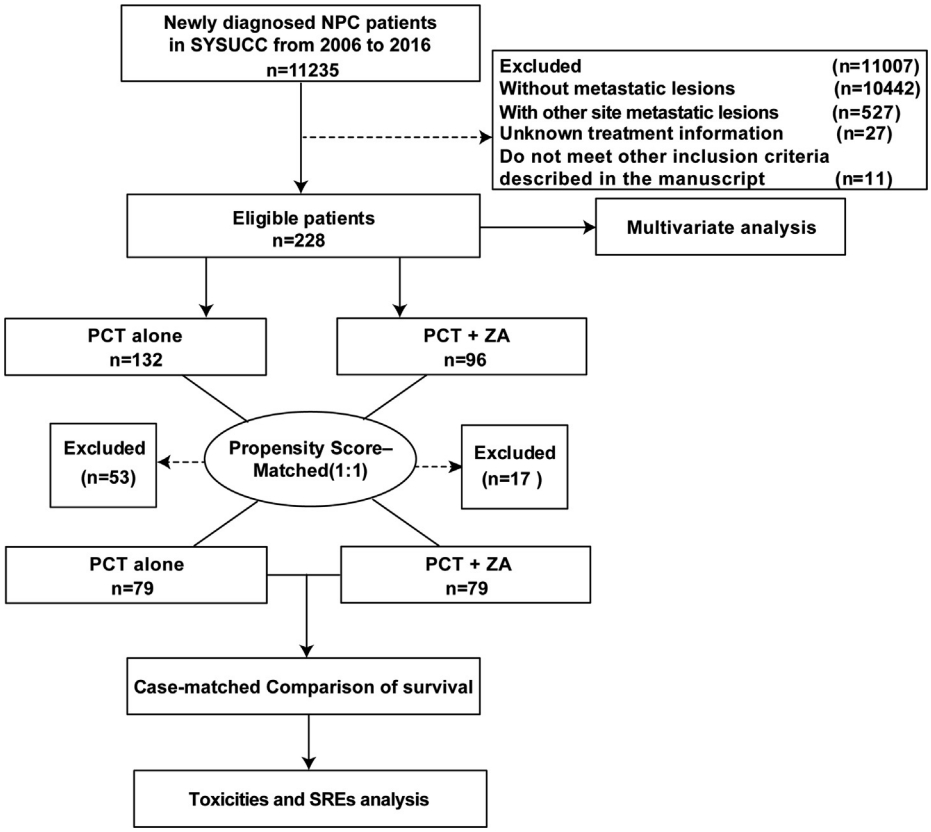

Fig. 1. Flow chart of patient inclusion.

would be superior to PCT alone in the overall survival (OS) of these patients, whereas the secondary objective was to test whether ZA therapy would help reduce the occurrence of SREs.

Patients and Methods

Patient population

In this retrospective cohort analysis, 11,235 newly diagnosed NPC patients were screened at Sun Yat-sen University Cancer Center (SYSUCC) from 2006 and 2016. The eligibility criteria were: (1) histologically confirmed NPC; (2) bone-only metastases at diagnosis; (3) complete treatment information; (4) Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 1; (5) adequate liver and kidney function; and (6) no secondary pregnancy, lactation or other malignant tumors. Flow chart of patient inclusion was shown in Figure 1. The diagnosis of initial only-bone metastasis was mainly based on radiological examination (ECT or PET-CT) before treatment. NPC patients who had radiologically or pathologically confirmed lesions of bone but without any evidence of metastasis in other organs were defined as initial only-bone metastasis. All the diagnostic radiological images were reviewed by two experienced radiologists independently. Finally, 228 patients were involved in this study. This study was approved by the Sun Yat-sen University Cancer Center Clinical Research Ethics Committee. Moreover, each patient signed a written informed consent form.

Quantification of plasma EBV DNA levels

The method of plasma EBV DNA quantification was described in the Supplementary Appendix.

Diagnosis and treatment

Prior to diagnosis, the patients underwent a series of assessments including physical examination, nasopharyngoscopy and pathological biopsy, and magnetic resonance imaging (MRI)/computed tomography (CT) with contrast of the nasopharynx and neck and metastatic lesions. The whole body examination included chest radiography/CT with contrast, abdominal ultrasound/CT with contrast, and emission computed tomography (ECT). Blood routine, biochemical routine, and plasma EBV DNA level measurement were routinely performed. Positron emission tomography-computed tomography (PET/CT) could be used as a substitute for the whole body examination. PCT was applied to all patients undergoing the first line platinum-based regimens. The common chemotherapy regimens were as follows—PF regimen: cisplatin (20–30/m^2 on d1–3) combined with 5-fluorouracil (4–5 g/m^2, 120 h continuous IV infusion); TP regimen: docetaxel (70–80 mg/m^2 d 1) combined with cisplatin (20–25 mg/m^2 d 1–3); TPF regimen: docetaxel (60–70 mg/m^2 d 1) combined with cisplatin (20–25 mg/m^2 d 1–3) plus 5-fluorouracil (3–3.75 g/m^2, 120 h continuous IV infusion); and GP regimen: gemcitabine (0.8–1 g/m^2 d 1,8) and cisplatin (20–30 mg/m^2 d 1–3). Chemotherapy was intravenously administered at 3-week-intervals. ZA was applied with the dose of 4 mg combined with PCT. Locoregional radiotherapy (LRRT) was administered in some patients based on the efficacy of palliative chemotherapy and the patients' own condition. With regard to LRRT, the patient was treated with radiation at a total dose of 68–72 Gy (approximately 2 Gy per fraction, from Monday to Friday, 5 times/week) via two-dimensional conventional radiotherapy (2D-CRT) or intensity-modulated radiotherapy (IMRT).

Outcome and follow-up

OS was the primary endpoint of our study, and was defined as the

time from the date of the pathological diagnosis to death for any cause or patient censoring at last follow-up. Patients returned to the hospital for follow-up at 3-month intervals during the first 3 years, and at 6 months thereafter until death. During follow-up, each patient underwent a series of assessments, including physical examination, nasopharyngoscopy, MRI/CT with contrast of the nasopharynx and neck and metastatic lesions, abdominal ultrasound, and chest radiograph. PET-CT and other examinations were also considered by oncologists, if needed.

Statistical analyses

In the present study, a multivariate logistic regression model was used to calculate propensity scores for each patient, with the following variables: gender, age, T stage, N stage, PCT regimen, PCT cycle, LRRT, number of lesions, and EBV DNA copies. Matching was conducted using a 1:1 matching scheme, with a caliper width equal to 0.05. The time-to-event data were analyzed in different subgroups using Kaplan-Meier curves, and were compared with log rank tests. Cumulative incidence competing risk analyses using Fine and Gray's method were used to test the homogeneity of the cumulative SREs incidence, with modifications to account for deaths without SREs. Univariate and multivariate analyses were used to estimate the OS, along with the hazard ratios (HRs) and 95% confidence intervals (CIs) for the connection between the covariates and OS. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS, Mac version 21.0, Chicago, IL) and Stata Statistical Package 12 (StataCorp LP, College Station, TX, USA). All statistical tests were two-tailed and $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

From 2006 to 2016, 228 patients were involved in this study, including 96 (42.1%) and 132 (57.9%) treated with ZA and without ZA, respectively. After PSM at a ratio of 1:1, a well-balanced cohort of 158 patients was obtained. Among these patients, 79 were assigned to the PCT group and 79 were assigned to the PCT + ZA group. The median patient age was 47 years (range, 18–70 years), with 20 (12.7%) females and 138 (87.3%) males. No significant differences in potential prognostic factors were observed in the 2 groups ($P > 0.05$ for all). The differences in patient characteristics between the PCT and PCT + ZA groups in the whole cohort and PSM cohort were shown in Table 1.

Survival outcomes

In the PSM cohort of 158 patients, the median duration of follow-up was 27.8 months. The OS at 3 years was 46.4% (95% CI, 33.3–59.5%) in the PCT group and 57.3% (95% CI, 45.7–68.9%) in the ZA + PCT group, which were not significantly different (log-rank $P = 0.188$; Fig. 2).

A Cox proportional hazards model was used in all 228 patients. Univariate analysis indicated that the N stage (HR, 2.249; 95% CI, 1.319–3.835; $P = 0.003$), LRRT (HR, 0.442; 95% CI, 0.296–0.661; $P < 0.001$), number of lesions (HR, 2.662; 95% CI, 1.817–3.900; $P < 0.001$), and the EBV DNA levels before treatment (HR, 1.664; 95% CI, 1.132–2.445; $P = 0.010$) were significantly associated with OS. The significant variables in the univariate analysis were considered in the Cox proportional hazards model. As shown in Table 2, the N stage (HR, 1.942; 95% CI, 1.130–3.328; $P = 0.016$), LRRT (HR, 0.530; 95% CI, 0.351–0.801; $P = 0.003$), and the number of lesions (HR, 2.183; 95% CI, 1.450–3.286; $P < 0.001$) were significantly associated with OS.

In the analysis of all 228 patients, after adjusting for N stage, LRRT use, number of lesions, EBV DNA level, and ZA application, an interaction analysis did not show any significant interaction effect between ZA application and N stage (HR, 0.783; 95% CI, 0.267–2.300; $P = 0.657$), ZA application and LRRT (HR, 0.608; 95% CI, 0.272–1.357; $P = 0.224$), and ZA application and the number of lesions on OS (HR, 1.210; 95% CI, 0.555–2.640; $P = 0.632$; Table 3).

Toxicity and SREs incidence

We evaluated the incidence of acute toxicity during treatment in the PSM cohort between the 2 groups. The number of patients with grade 1, 2, 3, and 4 toxicities are shown in Table S1. Intergroup differences in acute toxicities such as leukocytopenia, neutropenia, anemia, and thrombocytopenia, as well as hepatotoxicity and nephrotoxicity, were not significant ($P > 0.05$ for all; Table S1).

There were a total of 16 SREs in the PSM cohort. Cumulative incidence competing risk analyses showed significant differences between the treatment groups in terms of cumulative SREs incidence (Fig. 3). The cumulative incidence of bone-related events was 13.9% in the PCT group, as compared to 6.3% in the PCT + ZA group (HR, 0.314; 95% CI, 0.114–0.870; Fine-Gray $P = 0.026$).

Discussion

In our large cohort from an endemic area, we enrolled 228 NPC cases with bone-only metastasis at primary diagnosis, and assessed the therapeutic value of ZA. We found that, compared with PCT alone, the addition of ZA in NPC patients with *de novo* bone-only metastasis did not yield a marked improvement in OS. However, the incidence of SREs was significantly reduced in the PCT + ZA group. The treatment-related toxicity was comparable in the 2 groups.

CCRT has been established as the standard treatment method for loco-regional advanced NPC. Unfortunately, 7–15% patients exhibit distant metastasis at primary diagnosis, and the bone is the most common metastatic site [7–9]. Once distant metastasis is detected, PCT becomes the primarily treatment method, and yields satisfactory response rates [10–13]. However, the survival time of these patients is limited due to chemotherapy resistance, and second-line chemotherapy is only effective in certain patients [20]. Therefore, new drugs or regimens with tumor inhibiting effect are urgently needed.

ZA has been traditionally regarded as an effective medicine for malignant bone diseases. In other cancers, several studies have been conducted to explore whether adjuvant ZA can improve disease outcomes [21–24]. A randomized clinical study among stage II/III breast cancer cases showed that the application of ZA could reduce the occurrence of bone metastases, with a lower incidence of SREs [21]. However, the disease-free survival (DFS) and invasive DFS did not significantly differ between both arms. Another clinical trial in locally advanced prostate cancer cases indicated similar results, without a significant difference in cancer-specific mortality between the ZA group and non-ZA group [22].

To our knowledge, only 1 study has assessed whether ZA confers survival benefits to NPC patients with bone metastases [25]. The study showed that the ZA combination achieved better OS. However, patients with metastases at other sites were also involved in that study. Moreover, the researchers did not distinguish between patients developing metastases before and after treatment. These factors can both influence the prognosis, but were not considered in the survival analysis in that study.

In the present study, all the NPC patients were diagnosed with bone-only metastasis, and the metastases were detected before any treatment. The PSM method was used to balance the confounding factors. We found that patients treated with ZA + PCT achieved a similar 3-year OS rate, as compared to those treated with PCT alone (57.3% vs. 46.4%; $P = 0.188$). The treatment-related toxicity was also comparable in both arms. In fact, the incidence rate of SREs was significantly lower in the ZA + PCT group, consistent with previous studies.

Thus, our study provides important treatment guidelines for NPC

Table 1
Clinical characteristics.

Characteristic	Entire cohort			Propensity score matching cohort		
	PCT	PCT + ZA maintenance	*P*-value	PCT	PCT + ZA maintenance	*P*-value
	N = 132	N = 96		N = 79	N = 79	
Gender						
Male	110(83.3%)	81(84.4%)	0.858	67(84.8%)	71(89.9%)	0.474
Female	22(16.7%)	15(15.6%)		12(15.2%)	8(10.1%)	
Age (years)						
≤47	73(55.3%)	45(46.9%)	0.229	37(46.8%)	41(51.9%)	0.633
> 47	59(44.7%)	51(53.1%)		42(53.2%)	38(48.1%)	
T stage #						
T1	7(5.3%)	4(4.2%)	0.831	4(5.1%)	3(3.8%)	0.747*
T2	20(15.2%)	12(12.5%)		14(17.7%)	10(12.7%)	
T3	62(47.0%)	51(53.1%)		34(43.0%)	40(50.6%)	
T4	43(32.6%)	29(30.3%)		27(34.2%)	26(32.9%)	
N stage #						
N0	4(3.0%)	3(3.1%)	0.381*	2(2.5%)	2(2.5%)	0.421*
N1	25(18.9%)	17(17.7%)		19(24.1%)	15(19.0%)	
N2	49(37.1%)	46(47.9%)		25(31.6%)	35(44.3%)	
N3	54(40.9%)	30(31.3%)		33(41.8%)	27(34.2%)	
PCT regimen						
TPF	40(%30.3)	25(26.0%)	0.013	30(38.0%)	23(29.1%)	0.521
TP	26(19.7%)	34(35.4%)		17(21.5%)	22(27.8%)	
PF	42(31.8%)	15(15.6%)		17(21.5%)	14(17.7%)	
GP	5(3.8%)	3(3.1%)		4(5.1%)	3(3.8%)	
Others	19(14.4%)	19(19.8%)		11(13.9%)	17(21.5%)	
PCT cycle						
≤4	66(50.0%)	48(50.0%)	1.000	41(51.9%)	40(50.6%)	1.000
>4	55(50.0%)	48(50.0%)		38(48.1%)	39(49.4%)	
LRRT						
No	39(29.5%)	26(27.1%)	0.767	27(34.2%)	22(27.8%)	0.492
Yes	93(70.5%)	70(72.9%)		52(65.8%)	57(72.2%)	
Number of lesions						
≤3	75(56.8%)	58(60.4%)	0.683	47(59.5%)	48(60.8%)	1.000
>3	57(43.2%)	38(39.6%)		32(40.5%)	31(39.2%)	
EBV DNA copies						
≤30000 copies/ml	68(51.5%)	44(45.8%)	0.423	36(45.6%)	40(50.6%)	0.633
>30000 copies/ml	64(48.5%)	52(54.2%)		43(54.4%)	39(49.4%)	

Abbreviations: PCT, palliative chemotherapy; LRRT, locoregional radiotherapy; EBV, Epstein-Barr virus.
According to the 8th edition of the UICC/AJCC staging system.
The P value was calculated using the Pearson χ^2 test or Fisher's exact test (*).

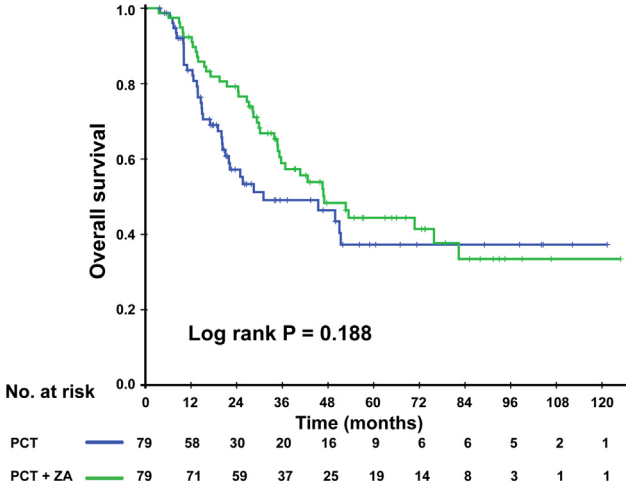

Fig. 2. Kaplan–Meier OS curves in the PSM cohort of patients receiving PCT + ZA or PCT alone.

patients with bone metastasis. Although the application of ZA did not prolong the survival time of NPC patients with bone metastasis, the SREs were better controlled, which further improved the quality of life. Thus, chemotherapy combined with ZA is recommended in clinical practice for these patients. Several recent studies have found that LRRT can further improve patient survival when combined with PCT in metastatic NPC patients [26,27]. In the present study, LRRT was found to be an independent protective factor for OS in multivariate analysis, thus indicating its treatment value towards the primary tumor in *de novo* NPC patients.

However, the overall prognosis of these patients has remained unsatisfactory, with a 3-year OS rate of approximately 50% in our cohort. In order to address this clinical challenge, a novel treatment method is desired. Accordingly, our group has initiated a worldwide, multicenter, phase III study of cisplatin and gemcitabine with or without toripalimab in patients with recurrent or metastatic NPC (NCT 03581786), and we await the findings.

Our study has certain limitations. First, although some confounding factors were balanced via PSM, certain biases could not be completely eliminated due to the retrospective nature of the study. Second, all the patients involved in this study were enrolled from a single treatment center in an endemic area, and a multicenter prospective study may be needed to better evaluate the role of ZA in NPC patients with bone

Table 2
Univariate and multivariate analyses.

	Univariate analyses			Multivariate analyses		
Characteristic	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Gender	1.056	0.637–1.752	0.831			
Age (years)	0.973	0.668–1.417	0.885			
T stage	0.995	0.618–1.603	0.985			
N stage	2.249	1.319–3.835	0.003	1.942	1.130–3.328	0.016
PCT regimens						
TP vs. TPF	0.997	0.584–1.704	0.992			
PF vs. TPF	1.210	0.729–2.011	0.461			
GP vs. TPF	1.580	0.611–4.085	0.346			
Other regimens vs. TPF	1.284	0.719–2.290	0.398			
PCT cycle	1.051	0.721–1.532	0.795			
LRRT	0.442	0.296–0.661	< 0.001	0.530	0.351–0.801	0.003
Number of lesions	2.662	1.817–3.900	< 0.001	2.183	1.450–3.286	< 0.001
EBV DNA	1.664	1.132–2.445	0.010	1.207	0.804–1.811	0.364
ZA application	0.880	0.602–1.287	0.510			

Abbreviations: HR, hazard ratio; CI, confidence interval; ZA, zoledronic acid; PCT, palliative chemotherapy; LRRT, locoregional radiotherapy.
Data are obtained from all 228 patients included in the study.
Hazard ratios were estimated using Cox proportional hazards regression.

Table 3
Interaction between the treatment regimen status and other significant prognostic factors.

Characteristic	Adjusted HR	95% CI	P value
Model 1			
N stage	2.177	1.314–3.318	0.046
ZA application	1.086	0.680–7.745	0.870
ZA application*N stage	0.783	0.267–2.300	0.657
Model 2			
LRRT	0.664	0.377–1.171	0.157
ZA application	1.225	0.638–2.353	0.542
ZA application*LRRT	0.608	0.272–1.357	0.224
Model 3			
Number of lesions	1.980	1.160–3.379	0.012
ZA application	0.794	0.444–1.420	0.436
ZA application*Number of lesions	1.210	0.555–2.640	0.632

Abbreviations: HR, hazard ratio; CI, confidence interval; ZA, zoledronic acid; LRRT, locoregional radiotherapy.
Data are obtained from all 228 patients included in the study.
The multivariable Cox regression model was adjusted for N stage, LRRT use, number of lesions, EBV DNA level, and ZA application.

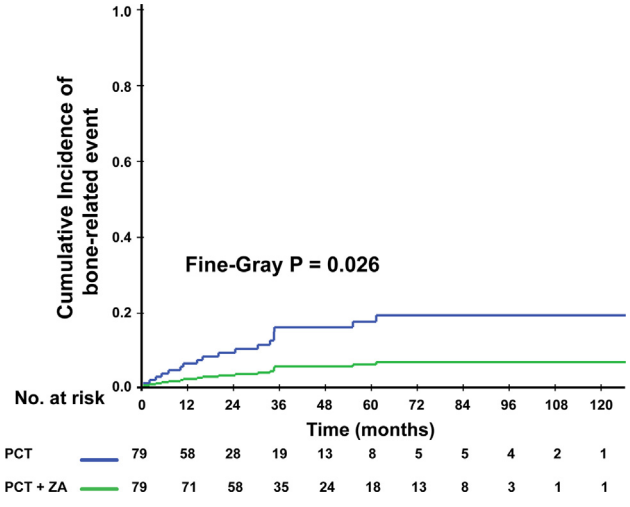

Fig. 3. Adjusted cumulative incidence of bone-related event curves in the PSM cohort of patients receiving PCT + ZA or PCT alone.

metastases.

Conclusion

ZA did not improve the OS in NPC patients with bone-only metastasis at diagnosis. However, the incidence of SREs could be reduced, which could improve the quality of life of these patients.

Author contributions

Study concepts: Hai-Qiang Mai, Lin-Quan Tang, Qiu-Yan Chen
Study design: Xue-Song Sun, Chao Lin, Yu-Jing Liang
Data acquisition: Xue-Song Sun, Chao Lin, Yu-Jing Liang
Quality control of data and algorithms: Xue-Song Sun, Chao Lin, Yu-Jing Liang
Data analysis and interpretation: Xue-Song Sun, Chao Lin, Yu-Jing Liang
Statistical analysis: Xue-Song Sun, Chao Lin, Yu-Jing Liang
Manuscript preparation: Xue-Song Sun, Chao Lin, Yu-Jing Liang
Manuscript editing: Xue-Song Sun, Chao Lin, Yu-Jing Liang
Manuscript review: Hai-Qiang Mai, Lin-Quan Tang, Qiu-Yan Chen

Declaration of Competing Interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary material

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