局部野放射治疗鼻咽癌骨转移病灶对患者生存风险的影响

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摘 要:【目的】评估根治性放疗后骨转移鼻咽癌患者在其骨转移病灶接受局部放射治疗的生存结果。【方法】选取2001 年 2 月至 2004 年 12 月期间,在中山大学肿瘤防治中心接受治疗的 231 例鼻咽癌骨转移病人纳入这项研究,分别采用单因素和多因素分析,对比有无接受骨转移病灶放射治疗病人的生存差异,并确定其独立预后因素。【结果】与没有接受骨转移放射治疗的一组对比(中位生存时间: 15 个月),接受骨转移病灶放射治疗的一组总生存时间明显延长(中位生存时间:25 个月,$P < 0.001$)。与年轻组(≤ 45 岁)、孤立性骨转移(单个或两个病灶),和不合并其他器官转移一样,骨转移灶放疗是本组患者的独立保护性预后因素(危险比:0.705;95%置信区间:0.536–0.928;$P = 0.013$)。进一步亚组分析表明,不管在孤立性骨转移、多发性骨转移、单个器官转移、多个器官转移,还是在大龄组(> 45 岁),接受骨转移病灶放射治疗组的总生存时间始终优于没有接受骨转移放射治疗组($P < 0.05$),但是在年轻组中例外($P = 0.403$)。【结论】对根治性放疗后骨转移鼻咽癌患者实施骨转移灶放疗可能会给患者带来生存获益,但是这个结论需要配对均衡的病例对照或随机试验进一步证实。

关键词:鼻咽癌;骨转移;放射治疗;化疗;预后因素
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Impact of Local Radiotherapy of Bone Lesions on the Survival Risk in Nasopharyngeal Carcinoma Patients with Bone Metastasis

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Abstract:【Objective】To evaluate survival outcomes of local radiotherapy of bone metastasis (bmRT) in patients with bone metastatic nasopharyngeal carcinoma (bmNPC) after radical radiotherapy.【Methods】A total of 231 bmNPC patients treated in Sun Yat-sen University Cancer Center (SYSUCC) between February 2001 and December 2004 were enrolled into this study. Univariate and multivariate analyses were conducted to compare the survival difference between the patients received bmRT or not and identify the independent prognostic factors. 【Results】 The group received bmRT after bone metastasis exhibited significantly better overall survival (OS) compared with another group without bmRT (median survival time [MST], 25 vs. 15 months; $P < 0.001$)). bmRT, as well as younger age group (≤ 45 years), oligo bone lesions (single or two lesions), and absence of other organ metastasis, was found to be an independent protective prognostic factor (hazard ratio [HR], 0.705; 95% CI, 0.536-0.928, $P = 0.013$). Further subgroups analysis still showed that bmRT was associated with better OS regardless of in subgroup of oligo or multiple bone lesions, single or multiple metastatic organ sites, or old age group (> 45 years) ($P < 0.05$), except in younger age group ($P = 0.403$).【Conclusions】 bmRT may bring the survival benefit for bmNPC patients after radical radiotherapy. However, a well-balanced case-matched or randomized study is expected to identify the survival value of bmRT in bmNPC.

Key words: nasopharyngeal carcinoma; bone metastasis; radiotherapy; chemotherapy; prognostic factors
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Nasopharyngeal carcinoma (NPC) is an endemic Epstein-Barr virus (EBV)-related neoplasm occurs commonly in southern China, southeastern Asia, and northern Africa[1-5]. It is highly sensitive to radiotherapy with the 5-year overall survival (OS) of 90% in early NPC[4] and 68%-74.5% in locally advanced NPC[6-7]. However, 22%-47% NPC patients developed metachronous distant failure after primary radical radiotherapy, which made distant metastasis the leading cause of death in NPC patients [8-9]. Among those bmNPC patients, bone was the most common metastatic site with the incidence of 60%-80% compared to other metastatic organs such as liver (21.9%), lung (26.9%), and extraregional lymph nodes (22.7%)[9]. Bone metastases will lead to severe cancer pain which seriously affects the patient's quality of life. Furthermore, bone metastases can cause a lot of skeletal-related events (SREs) including: pathological fractures, spinal cord compression, bone radiotherapy, bone surgery and hypercalcemia. Furthermore, these bone metastatic lesions may also promote the further metastases in the liver, lungs and other vital organs and accelerate the patient's death. It is crucial to control the bone metastasis in mNPC patients. Currently, the main treatment for bone metastases is systemic chemotherapy, combined with bisphosphonate therapy or not, but mainly is palliative treatment with the 3-year overall survival of 43.4%[10] Local radiotherapy of bone metastasis (bmRT) was limitedly applied for analgesic treatment or prevention of pathologic fracture or spinal cord compression. A lot of studies have demonstrated that bmRT is effective for the relief of uncomplicated metastatic bone pain and SREs[11-13]. However, few reports were available to evaluate the impact of bmRT on survival in bmNPC patients. The current retrospective study was conducted to evaluate the therapeutic effect on survival and identify the prognostic value of bmRT in bmNPC patients.

1 Patients and Methods

1.1 Patients

Between February 2001 and December 2004, 231 consecutive NPC patients with bone metastases treated in Sun Yat-sen University Cancer Center (SYSUCC) were included in this study. The diagnostic criteria of bone metastasis including that: (1) Pathologically confirmed NPC, or bone lesion biopsy or cytology diagnosis of malignant bone metastases; (2) Plain X-ray, bone scan, MR scan, CT scan, or/and PET-CT scanning evidence of bone metastasis at the index site. Based on the recorded clinical and radiological data, all those patients were retrospectively classified into T1-4 and N0-3 at initial time, following the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) TNM classification (6th edition, 2002). Informed consent was obtained and chart reviews were performed after approval by the local Ethics Committee.

According to our institutional guideline for palliative treatment of bmNPC, cisplatin-based systemic chemotherapy was first provided to all patients as the basic treatment, combined with bisphosphonate therapy or not. Local radiotherapy was administered as local symptomatic control or a part of multidisciplinary treatment to local recurrence, or metastatic lesions, including the bone metastasis.

Bone radiation was delivered with a ^{60}Co or linear accelerator using 6-15 MV photons and 9, 12, and 16 MeV electron beam irradiation. The protocol specified use of photon or electron RT as appropriate. The radiation field was designed according to the illuminated area of the lesion, and some principles should be considered such as: (1) the upper and lower vertebrae, including each vertebral body, of the affected area are included in the radiation field for vertebral metastasis; (2) osteopathy radiotherapy was required for long or flat bone metastases. The spine was to be treated with direct fields prescribed to 5 cm depth (D5); ribs with direct fields to applied dose (D_{max}); other sites with parallel opposed fields to mid-plane, three-field irradiation, or IMRT irradiation technique. Conventional fractionated irradiation, namely 2 Gy/times, 5 times a week, DT: 36-60

Gy; or low fractionated irradiation, high-dose short course of radiation therapy, 3-5 Gy/times a week, 3 to 5 times, DT: 20~30 Gy.

1.2 Statistical analysis

Overall survival (OS) is defined as the survival time from the first diagnosis of bone metastasis to the time of death (or to the most recent follow-up). OS was analyzed and compared between different subgroups. The actuarial rates and estimated median survival time were calculated using the Kaplan-Meier method and the differences were compared by log-rank test. To evaluate the independent contribution of each variable to mortality, covariates significantly associated ($P < 0.05$) with prognosis detected by univariate analyses were included in the multivariate analyses. All analyses were performed with SPSS software (version 16.0, SPSS Inc., Chicago, IL) and a two-tailed $P < 0.05$ was considered to be statistically significant.

2 Results

2.1 Clinicopathological characteristics of bmNPC patients

The clinicopathological characteristics were summarized in Table 1. Among all 231 NPC patients, more than half patients (162/231, 70.2%) had multiple metastatic lesions, and only 41 cases (17.7%) had single metastatic lesion and the rest 28 cases (12.1%) had two lesions; almost half of them (101/231, 43.7%) combined with metastasis in liver, lung, or/and other organs; and only 39 patients (16.9%) had bone metastasis alone with single lesion in current series. 93 patients (40.3%) received local radiotherapy of bone metastasis, combined with systemic chemotherapy (median, 6 circles) and other anticancer treatments.

2.2 bmRT is associated with better OS in bmNPC patients

At the cutoff of January 2012, the median follow-up time was 16 months (range: 1-132 months). After multidisciplinary treatment, 192 (83.1%) patients died, and the estimated median survival time (MST) was 18 months (95% CI, 15.7 to 20.3). At 1, 2, 3, and 5 years, the OS rates were 64.8%, 34.1%, 17.4%, and 12.3%, respectively. (Fig.1A) The survival of bmRT was significantly higher than that

Table 1 Univariate analysis of patients characteristics for overall survival ($n = 231$)

Parameters	n	Overall survival		P
		Median/Months	95% CI	
Sex				0.081
Female	41	20	17.7-22.3	
Male	190	17	14.0-20.0	
Age				0.026
≤ 45 years	103	21	18.0-24.0	
> 45 years	128	16	13.0-19.0	
Pathological type				0.619
WHO I/II	9	19	13.2-24.8	
WHO III	222	18	15.5-20.5	
Karnofsky Performance Scale				0.917
< 90	35	16	10.6-21.4	
≥ 90	196	19	16.8-21.2	
T Classification				0.256
T1-2	131	19	15.8-22.2	
T3-4	100	17	13.1-20.9	
N Classification				0.159
N0-1	72	21	15.6-26.4	
N2-3	159	17	13.9-20.1	
DFI				0.214
≤ 24 months	176	17	13.9-20.1	
>24 months	55	21	16.5-25.5	
Bony metastatic lesion				
Single	41	26	17.1-34.9	
Two	28	18	15.6-20.4	0.685[1)]
Multiple	162	17	13.5-20.5	0.006[1)]
Combined other organ metastasis				0.012
No	130	20	16.2-23.8	
Yes	101	15	11.7-18.3	
Combined loco-regional recurrence				0.838
No	186	18	15.7-21.3	
Yes	45	19	11.6-28.4	
Chemotherapy				0.878
≤ 6 circles	110	18	14.4-24.9	
> 6 circles	121	18	14.9-29.1	
Local radiotherapy of bone metastasis				<0.001
No	138	15	11.9-18.1	
Yes	93	25	18.4-31.6	

1) compared with single bone lesion.

without bmRT (1-, 2-, 3-, 5-year OS rates: 72.8%, 51.5%, 28.6%, 19.5%, vs. 65.4%, 20.6%, 8.8%, and 5.9%; $P < 0.001$; Fig.1B). Besides bmRT, better survival was also associated with younger age group, single/two bone metastasis, and absence of other organ metastasis rather than bone lesion ($P < 0.01$). However, it was not associated with sex, pathological type, Karnofsky Performance Scale (KPS), T and N classification, DFI, or chemotherapy circles (Table 1).

2.3 bmRT is one of independent prognostic factors in OS of bmNPC patients

Among all potential prognostic factors that were taken into account by adjusted COX model, Age group, number of bone metastatic lesions, whether combined with other organ metastasis or not, and bmRT were revealed as the independent prognostic factors. In particular, bmRT was associated with a 29.5% reduction in the risk of death (Table 2; hazard ratio [HR], 0.705; 95% CI, 0.536-0.928; $P = 0.013$).

2.4 bmRT is associated with significantly better survival in subgroup analysis

To eliminate the selection bias of patient assignment to bmRT in this respective study, we repeated the univariate analysis to evaluate the impact of bmRT on OS in each subgroup of the rest 3 independent prognostic factors. Finally, bmRT is observed to be still associated with better OS regardless of in subgroup of oligo, multiple bone lesions, single, multi metastatic organ sites, or old age group, respectively ($P < 0.05$), except one of younger age group ($P = 0.403$) (Fig.2).

3 Discussion

Although the molecular mechanism of bone metastasis remained unknown, the treatment of bone metastases had received more and more attention[14]. As normally multiple metastases were involved at the same time once the bone metastasis was discovered in nasopharyngeal carcinoma patients. It is difficult to impose aggressive local treatments, such as radiotherapy, which is technically difficult to carry out to all metastatic sites and lesions. New techniques, Tomotherapy, make it enable to give multi sites and lesions synchronous radiation[15], but extensive radiation may seriously affect bone marrow function and eventually affect the subsequent chemotherapy. In current study, among 231 cases of patients with bone metastases, 70.2% of them had multiple bone lesions, 43.7% combined with other organ metastasis, and only 16.9% had bone metastasized alone with single lesion. Even for oligo bone metastasis, undetectable micrometastases of bmNPC have been considered the main obstacle to

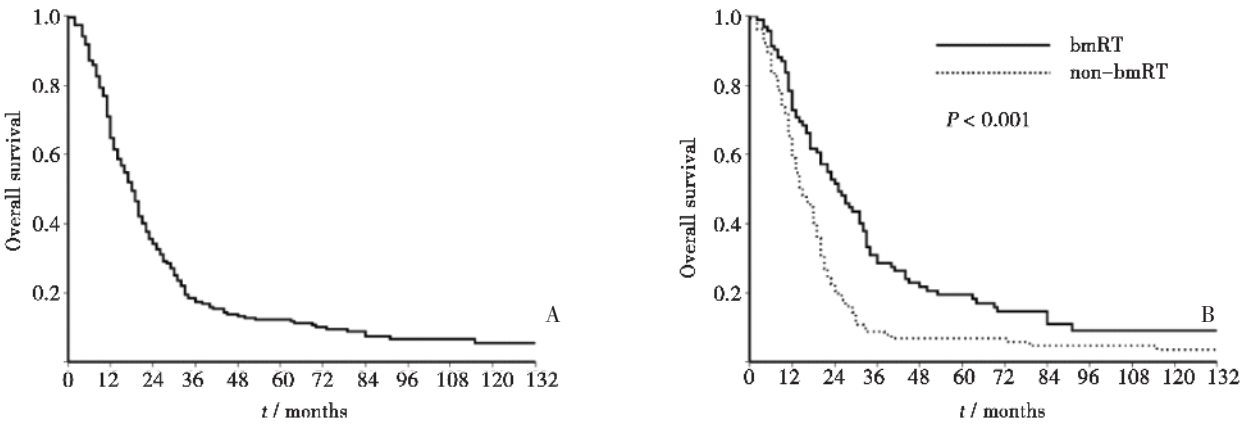

Fig.1 The overall survival in bone metastatic NPC and comparison of survival of patients treated with or without bmRT

Survival curves were plotted as estimated from the Kaplan-Meier method. At 1, 2, 3, and 5 years, the OS rates were 64.8%, 34.1%, 17.4%, and 12.3%, respectively (Panel A). The survival of bmRT was significantly higher than that without bmRT (1-, 2-, 3-, 5-year OS rates: 72.8%, 51.5%, 28.6%, 19.5%, vs. 65.4%, 20.6%, 8.8%, and 5.9%; $P<0.001$) (Panel B).

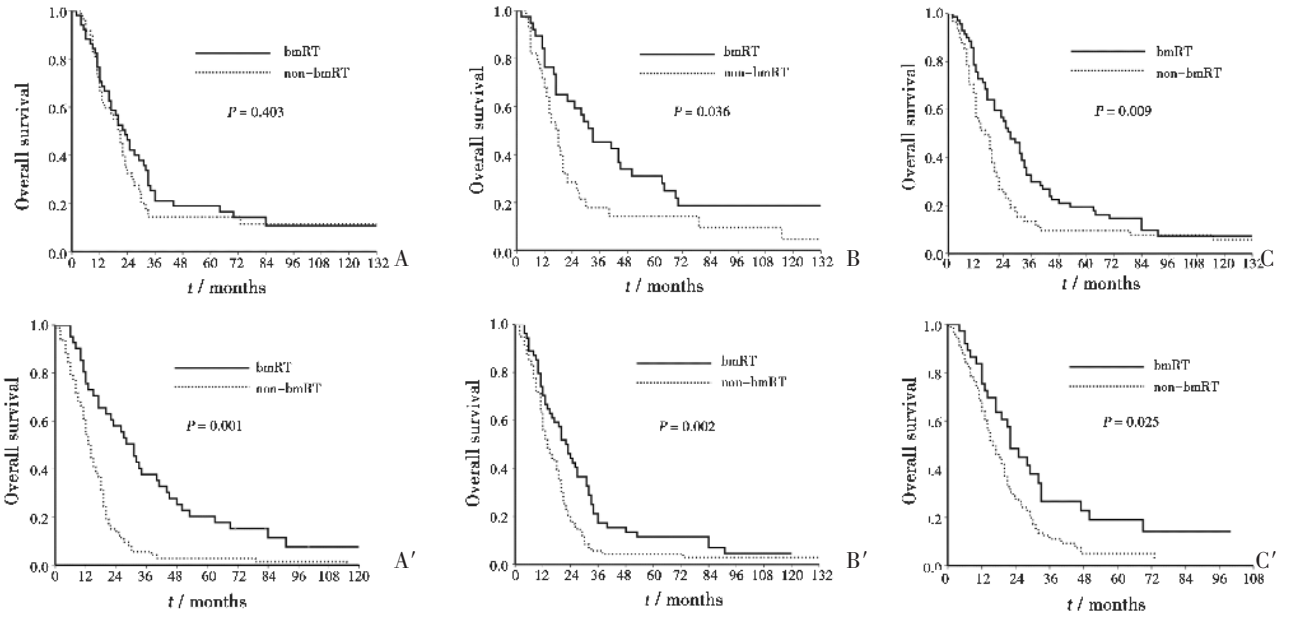

Fig.2　The comparison of survival of patients treated with or without bmRT in subgroups with different clinical characteristics

bmRT is observed to be associated with better OS regardless of in subgroup of oligo ($P = 0.036$, Panel B), multiple bone lesions ($P = 0.002$, Panel B'), single ($P = 0.009$, Panel C), multi metastatic organ sites ($P = 0.025$, Panel C'), or old age group ($P < 0.001$, Panel A'), respectively ($P < 0.05$), except the younger age group ($P = 0.403$, Panel A).

gain a survival benefit after aggressive local treatments to visualized metastatic lesions. Therefore, local radiotherapy were recommended as analgesic treatment and usually applied in those patients with severe cancer pain in metastatic bone lesions.

Pain is the most common symptom in cancer patients with bone metastases, radiation therapy provides significant pain relief of symptomatic bone metastases. Between 50% and 80% of patients will have significant improvement of pain after radiotherapy. Almost 50% of patients with bone metastases will require radiotherapy, normally using external beam radiotherapy to control their pain, representing about 30% –40% daily practice of a radiotherapy department [11–13]. Numerous randomized trials have evaluated the potential benefits of certain dose fractionations of external beam RT[11–13]. However, because of the varying endpoints used, different results can be obtained from each trial, making comparisons among trials extremely difficult. In 2002, the International Bone Metastases Consensus Working Party published its first consensus on palliative RT in an attempt to encourage investigators to adopt a common set of endpoints for future clinical trials in bone metastases[16]. This initiative involved an international faculty representing the American Society for Radiation Oncology (ASTRO), the European Society for Therapeutic Radiology and Oncology (ESTRO), the Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists (RANZCR), and the Canadian Association of Radiation Oncology (CARO). The participating members from these groups collaboratively formulated a framework for palliative RT trials in patients with bone metastases. For pain control, different radiotherapy schedules had been employed: 40 Gy in 20 fractions, 30 Gy in 10 fractions and single fraction of 8 Gy, 6 Gy, or 4 Gy. Several randomized prospective trials and meta –analyses have reported the same results in pain relief when comparing single doses vs protracted treatments [11–14]. In current study, conventional fractionated irradiation (namely 2 Gy/times, 5 times a week, DT: 36 ~ 60 Gy), or low fractionated irradiation, high –dose short course of radiation therapy (3 ~ 5 Gy/times a week, 3 to 5 times, DT: 20 ~ 30 Gy) was used at the discretion of the

Table 2 Summary of multivariate analysis of prognostic factors in bmNPC patients

Variable	*P* value	HR	95% CI for HR
Sex(Female vs male)	0.218	0.802	0.564–1.140
Age(>45 vs ≤45 years)	0.038	1.314	1.016– 1.700
Bone metastatic lesions(Multiple vs. single/two)	0.019	1.413	1.057–1.889
Combined other organ metastasis(Yes vs no)	0.049	1.297	1.008–1.699
Local radiotherapy of bone metastasis(Yes vs no)	0.013	0.705	0.536–0.928

HR: hazard ratio

attending radiation oncologists.

Lim et al [17] recently had reported that a more than 5 years disease-free survival in a newly bmNPC patient with a solitary bone metastasis treated with concomitant chemoradiotherapy of loco -regional tumor and bone metastatic lesion. This interesting phenomenon led to our thinking: whether bone metastases radiotherapy be helpful to prolong the survival of patients with bmNPC? A growing number of studies have reported some encouraging results of aggressive local treatment in liver or lung lesions, including surgical removal, microwave ablation, or other methods [17-23]. Pan's study had reported 12 patients with a solitary liver metastasis after primary radiotherapy underwent surgical resection or radiofrequency ablation and got a median survival time of 47 months which was obviously longer than that of the entire series (16.5 months)[17]. Surgical resection or other local treatments, combined with systemic chemotherapy or not, also showed to be a promising approach for those with pulmonary metastases[20-23]. Recently, Cao Xun and his colleagues had found that the median survival time (MST) of bmNPC patients combined with radiotherapy was significantly longer than that of patients underwent chemotherapy alone (n, 57 vs 59 cases; MST, 50.7 vs 22.8 months; $P < 0.001$)[24]. However, which sites under radiation, primary site or distant lesion, were not stated in details in this studies.

In current study, we found that the group received bmRT exhibited significantly better OS (MST, 25 months) after bone metastasis compared with another group without bmRT (MST, 15 months) using larger series (n,93 vs 138 cases). Furthermore, bmRT, as well as metastasis status, the number of bone lesions, and whether combined with other organ metastasized, was found to be an independent prognostic factor. This result indicated that bmRT may be helpful to prolong survival more than pain treatment. To further eliminate the bias of patients selection on the other prognostic factors, we repeated the analysis in the subgroups with different clinicopathological characteristics and found that bmRT was still associated with better OS regardless of in subgroup of oligo, multiple bone lesions, single, multi metastatic organ sites, or old age group, respectively ($P < 0.05$). Those results suggested that the positive impact of bmRT is relatively independent to metastatic status. However, in the subgroup of younger age group, patients underwent bmRT didn't presented better OS than those without bmRT ($P = 0.162$). An independent study focused on the impact of bmRT on survival in younger patients with bmNPC is expected to use larger series in the future.

bmRT may improve the survival of bmNPC. Nevertheless, in consideration of the limitations of respective study such as the bias of patients selection for bmRT, a well-balanced case-matched or randomized study is expected to identify the survival value of bmNPC.

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