RESEARCH ARTICLE

Retrograde Analysis of Clinical Characteristics of Bone Metastasis in 1,031 Cases of Preliminarily Diagnosed Nasopharyngeal Carcinoma

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Abstract

Purpose: To explore the clinical characteristics of bone metastasis (BM) in a large sample of preliminarily diagnosed nasopharyngeal carcinomas (NPCs). Methods: The sample consisted of 1,031 patients diagnosed with NPC at first visitg clinics between October 1989 and June 2012. Several parameters including metastasis locus, T/N staging, diagnosis, therapy and prognosis of BM were analyzed retrospectively. Results: In 70 patients who had been preliminarily diagnosed with BM, the incidence of BM in N0, N1, N2 and N3 stage was 5.7%, 17.2%, 50.2%, and 25.7%, respectively, while the incidence in T0, T1, T2 and T3 stage was 0%, 23.8%, 47.6% and 28.6% respectively. BM occurred in most common in vertebral column, rib, sternum, ilium and femur. Positive rate of Epstein-Barr virus antibody was 77.6%. The median survival time was 12 months. Conclusion: The incidence of BM in NPC preliminarily diagnosed is about 7% and it is related to N classification but not T classification.

Keywords: NPC - bone metastasis - clinical characteristics

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Introduction

Distant metastasis is the most important prognostic factor in nasopharyngeal carcinoma (Zhang et al., 1989; Tang et al., 2010; Pan et al., 2012; Peng et al., 2013). Generally, 30% patients with NPC will eventually develop distant metastasis, but only one-sixth patients with metastasis are diagnosed at their initial diagnosis, and another one-third are identified within 3 months after diagnosis (Tang et al., 1990; Lee et al., 1992; Teo et al., 1996). In deadly cases with NPC, 36% patients were diagnosed with distant metastasis when they were alive and the most common metastasis location was bone, followed by distant lymph node, liver and lung. Anatomy for patients with NPC showed distant metastasis occurred in 51% patients (Ahmad et al., 1986). Bone metastasis (BM) significantly affected the survival time of these patients (Gregory., 2002). Owing to the significant effect of BM on prognosis and living quality, lots of researches mainly focused on BM in tumors such as breast carcinoma and prostate carcinoma, only few researches focused on BM in NPC.

Although the overall mortality NPC has consistently decreased in China over the past three decades, particularly in women and old in adults (Huang, 2012), but the NPC is one of the most common malignant tumor in south China region. In order to further explore the clinic characteristics of BM in patients with NPC, this study reviewed the clinical data of BM among 1031 patients with NPC.

Materials and Methods

Patients

We reviewed 1031 consecutive cases with NPC for first visiting of hospital from October 1989 to June 2012. The average age of the patients (697 men and 334 women) at the time of first visiting was 58.9 (20-94) years. For those patients with BM, several parameters including the characteristics, metastasis locus, tumor and lymph node (TN) staging, diagnosis, therapy and prognosis were further analyzed. Patients with a diagnosis of other cancer prior to NPC diagnosis were excluded from this study. The hospital ethics committee approved this study.

Pathology and TNM Staging System (TNM) classification

Histological classification of NPC was performed according to the method recommended by World Health Organization (WHO) (Shanmugaratnam et al., 1991). TNM classification was performed according to the 2002 stage-classification of International Union Against Cancer (UICC) .

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Table 1. Characteristic of 70 NPC Patients with BM

Characteristic	n
Patients	70
Male	25
Female	45
Age	29-81 years old
Pathology	70
Differentiated non-keratinizing carcinoma	63
Undifferentiated carcinoma	4
Keratinizing squamous cell carcinoma	3
Epstein-Barr virus	70
Positive	55
Negative	15

Table 2. T Classification and N Classification of 70 NPC Patients with BM

T classification and N classification	
T classification	
T1	0
T2	17
T3	33
T4	20
N classification	
N0	4
N1	12
N2	36
N3	18

Table 3. Distribution of BM and Other Metastasis Locations in 70 NPC Patients with BM

Distribution of BM and other metastasis	
BM	
Mandible	2
Maxilla	6
Sternum	20
Cervical vertebrae	4
Thoracic vertebrae	25
Lumbar vertebrae	32
Lumbosacral vertebrae	4
Shoulder joint	13
Ilium	20
Sacrum	4
Ribs	27
Cacroiliac joint	17
Calvaria	1
Occipital bone	2
Scapula	6
Femur	18
Hip joint	2
Os pelvicum	4
Humerus	2
Phalanges of toes	5
Other metastasis locations	
Lung metastasis	13
Liver metastasis	10
Lung and liver metastasis	6

Epstein-Barr virus (EBV) test

Enzyme linked immunosorbent assay (ELISA) was use to detected epstein-barr virus-viral capsid antigen-immunoglobulin M (EBV-VCA-IgM) antibody.

Diagnosis

Emission computed tomography (ECT), positron emission tomography-computed tomography (PET-CT), computed tomography (CT), magnetic resonance imaging (MRI) and X-ray examination were utilized for diagnosis. Treatment Radiating pain induced by BM was treated with radiotherapy or chemotherapy. Low dose, fractionation dolichotherapy (DT30Gy) was recommended to those who were alive for at least one year after diagnosis of NPC; while high dose, fractionation brachytherapy (4~5Gy a time, three times a week, total 24~30Gy) was adminstrated for patients with bad prognosis. For BM in vertebral column, percutaneous vertebroplasty (PVP) was an adjuvant treatment. Zoledronic acid was administrated at 4 mg intravenous injection, once a month.

Results

Diagnosis

In the 1031 patients, 70 patients (6.79%) were diagnosed with BM in preliminary diagnosis of NPC, including 7 patients whose primary symptom was BM. The characteristics, T and N classification of those 70 patients were presented in table 1 and table 2, respectively. In 70 patients with BM, the incidence of BM in N0, N1, N^2 and N^3 stage was 5.7%, 17.2%, 50.2%, and 25.7%, respectively, while the incidence in T0, T1, T2 and T3 stage was 0%, 23.8%, 47.6% and 28.6%, respectively (Table 2). The most common location of BM was thoracic vertebrae, lumbar vertebrae, sternum, ribs, ilium and femur (Table 3). Among those 70 patients, 3 patients underwent rib fracture, femur fracture and spinal cord compression respectively, 34 patients occurred combined metastasis in other location, mainly including lung and liver or both of them (Table 3).

Treatment outcomes

Thirty-three patients received chemotherapy, including 21 patients treated with Cisplatin+5-Fu therapy and 12 patients treated with Cisplatin+paclitaxel therapy. 12 patients received local radiotherapy showed better effect in relieving pain than anodyne.

In 16 patients with serious thoracic and lumbar spine metastasis, 5 patients were treated with PVP to increase vertebral stability and relieve pain, 11 patients were given zoledronic acid to relieve pain. Nine patients received 89Sr treatment (a pure β-ray emission with the maximum energy of 1.43 MeV and half-life of 50.5 days) by a dose of 1.48~2.22 MBq/kg intravenously injection to give medicine and observe for 4-6 months, with repetition after 6 months, if necessary. The main side effects were mild bone marrow suppression.

Prognosis

Two patients had paraplegia. Three patients had bone marrow syndrome due to bone marrow failure, manifested as thrombocytopenia, severe anemia and low white blood cells and died within a short time. The median survival time is 12 months.

Discussion

In the 1031 patients with preliminary diagnosis of NPC, the incidence of BM was about 7%. All the 70 cases were combined with lymph metastasis (N1-N3), indicating BM was related to lymph metastasis. High-risk (N2-N3) factor should be fully staged with bone scan. In terms of staging, MRI is able to detect marrow infiltration by tumors, whereas CT cannot detect this kind of infiltration unless there is associated bone erosion. This kind of marrow infiltration has been suggested to be associated with an increased risk of distant metastases (Cheng et al., 1998). The role of PET in the detection of distant metastases in other malignancies has been established (Nakamoto et al., 2003), but its application in the staging of NPC has not been ascertained. FDG-PET stages N and M disease of NPC more accurately and sensitively than does the conventional workup. Patients with advanced node disease, particularly N3 disease, would benefit the most from FDG-PET (Chang etal., 2005). SPECT is the main method for BM detection, with significantly higher positive rate and detective rate than X-ray. SPECT is thought to be superior to MRI, CT and X-ray, and could clarify diagnose 3-6 months earlier than other method, thus is suggested as the routine examination for NPC. Part of patients having BM before treatment or after routine radiotherapy was ignored, which could significantly affected patients' prognosis. Recent studies have shown that 18F-FDG PET/CT may enhance our diagnosis of tumor bone metastasis and provide more information for cancer treatment (Liu, 2013).

In this study, BM also occurred in 22.4% patients with negative EBV antibody. Serum EBV DNA level was thought to be vital in estimating therapeutic efficacy and recurrence rate. One year follow-up visit indicated that if serum EBV DNA segment increased to ten times, the relative risk of local recurrence and distant metastasis would be 4.5 (95% confidence interval was 1.9-10.4) (Lo et al., 2005) . A study has reported that the level of post-treatment EBV DNA compared with pretreatment EBV DNA is a good predictor of progression-free survival (Chan et al., 2005). Our study showed that even if the EBV was negative, attentions should also be paid to BM.

BM mainly occurs to thoracic vertebrae, lumbar vertebrae, sternum, ribs, and ilium, and multiple locations metastasis is more common in these cases. However, 48% BM was co-occurrence of lung and/ or liver metastasis. Prognosis was considerably bad in those patients with multiple systemic metastases. Thus, liver and lung examination is also important in BM patients.

Among treatments of BM in NPC, chemotherapy is essentially palliative, although long-term disease-free survivors have been reported (Fandi et al., 2000). For selected patients with few metastases, additional locoregional treatment could delay the disease development. In cases where there has been little spread to the mediastinal node, the addition of radiotherapy to chemotherapy could also result in protracted tumor control (Kwan et al., 1997; Cao et al., 2011). Our study showed that positive treatment could improve living quality and survival time, thus should be recommended to all tolerant patients. Paclitaxel and cisplatin are the routine chemotherapeutic medicine while capecitabine is an effective salvage therapy in patients with recurrent and metastatic NPC. Cisplatin-based combination chemotherapy is the most effective treatment for metastatic NPC, and therefore, cisplatin and infusional 5-fluorouracil has become the standard treatment with a 66-76% response rate (Wang et al., 1991).

Radiotherapy is considered to be an effective method to relieve pain. Intractable pain is the common syndrome for BM patients and local radiotherapy could fleetly relieve pain in 80%-90% patients and could last for a longer time. PVP for thoracic and lumbar spine transfer is an effective treatment, can effectively prevent fractures and reduce pain, improve quality of life and extend the survival time to some extent. 89Sr which targets and treats all lesions, can effectively reduce pain and delay the progress of bone metastases, and is an effective method.

The survival time after BM is 6-24 months with median of 12 months. The median survival time for patients accepted alleviative treatment is merely 4 months. Survival time would significantly decrease if BM combined with multiple organs metastasis. Chemotherapy and radiotherapy could prolong the median survival time of BM patients, but simple anodyne could never prolong median survival time, despite the improvement in living quality.

Solid cancers with bone marrow metastases are dismal and incurable diseases, The median overall survival was 49 days (Hung, 2014) and bone marrow metastasis in the patients, patients in a short time of death, The median overall survival was 32 days.

In conclusion: The occurrence of BM in NPC was about 7% at first visiting of hospital. In 21 patients who had been preliminarily diagnosed with BM, BM in N0, N1, N2 and N3 stage was 5.7%, 17.2%, 50.2%, and 25.7%, respectively, respectively, while the incidence in T0, T1, T2 and T3 stage was 0%, 23.8%, 47.6% and 28.6% respectively78.3% patients occurred BM within 2 years after diagnosis with NPC, indicating the importance of regular recheck. Positive rate of EBV in BM patients was 77.6%, showing the high association of BM with EBV. Combination treatment could improve patients' living quality and survival time. In addition to palliative chemotherapy, radiotherapy of BM, PVP and 89Sr were effective treatment methods. Attention should be paid to the prevention of fractures and the incidence of bone marrow failure syndrome.

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