

Analysis of the Factors Affecting Bone Metastasis in Breast Cancer

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Abstract Objective To explore the factors affecting bone metastasis in breast cancer. **Methods** The clinical data of 136 breast cancer patients with bone metastasis treated in the First Affiliated Hospital of Chongqing University of Medical Sciences, from January 1990 to April 2005, were analyzed retrospectively. **Results** ①All the cases were confirmed with X-ray, CT, MRI, or ECT and most of them (2/3) were diagnosed with two or more of the above methods; ②Since diagnosis of bone metastasis, the patients had been followed up from 2 months to 15 years and 5 months (mean value of 27.2 months); ③The occurrence rate of bone metastasis was 9.9% and the mean occurrence duration was 34.0 months after operation; ④The occurrence of bone metastasis was positively related with high clinic staging, poor pathological type, axillary lymph node metastasis and long following-up duration; ⑤29.4% cases of bone metastasis were axillary lymph node-negative, with chronic duration and certain features; ⑥the death rate of patients with bone metastasis accompanied with other visceral or soft tissue metastasis was 80.4% (45/56), while that of simple bone metastasis was 20.0% (16/77) ($\chi^2=45.38$, $p<0.001$). **Conclusions** The main factors affecting bone metastasis in breast cancer were clinic staging, pathological type, axillary lymph node metastasis and following-up duration. Certain ratios of breast cancer patients with negative axillary lymph node metastasis, suffered from bone metastasis, indicated that systemic treatment such as chemotherapy played an important role in the prevention and treatment of bone metastasis in breast cancer.

Key Words breast cancer; bone metastasis; affecting factor

Breast cancer is one of the most common malignant tumors in women, and about 70% breast cancer patients at advanced stage suffered from tumor bone metastasis, which might occur in the places like vertebra, pelvis, rib and skull. The initial symptoms of bone metastasis are bone ache and osteoporosis, and 15% of the patients with bone metastasis may have pathological fracture, which may result in severe pains, limitation to mobility and paralysis even, and may vitally impact living quality and shorten survival duration, and is one of the most important factors arousing death of breast tumor patients at late stage. It is many factors that affect bone metastasis, and there are still many problems having no last words. This article is to explore the characteristics and influence factors of bone metastasis in breast cancer, according to the clinical data of 136 breast cancer patients with bone metastasis treated in the First Affiliated Hospital of Chongqing University of Medical Sciences during 15 years.

MATERIALS AND METHODS

Clinical data

General data: In the First Affiliated Hospital of Chongqing University of Medical Sciences from January 1990 to April 2005 have continuously received 1920 breast cancer patients, who had radical operations with pathological diagnoses. 1370 cases have been followed recently, and 136 cases have bone metastasis, whose occurrence rate is 9.9%. All of them were confirmed with X-ray, CT, MRI, or ECT and most of them (2/3) were diagnosed with two or more of the above methods. Radiological aggregation in ECT can't confirm the diagnosis except for with other image proofs. All the cases were osteolytic without osteoclastic destruction. One case underwent surgical resection and was confirmed with pathology.

Age: The patients' age was from 24 to 80 years old with mean of 47.5 years old, and 3 patients of them were from 24 to 29 years old; 21 patients from 30 to 39; 62 patients from 40 to 49;

32 patients from 50 to 59; 15 patients from 60 to 69; 3 patients from 70 to 80. The peak occurrence age of bone metastasis ranged from 40 to 49 years.

Clinical staging: Stage I: 9 cases; Stage II a: 26 cases; Stage II b: 55 cases; Stage III: 40 cases; Stage IV: 6 cases.

Pathological type: There were 128 cases (94.1%) of invasive non-specific breast cancer (including 52 cases of invasive ductal carcinoma; 34 of medullary carcinoma; 17 of simple carcinoma; 8 of scirrhous carcinoma; 6 of adenocarcinoma; 11 of invasive lobular carcinoma), 4 cases of invasive specific carcinomas (including 2 of mucinoid carcinoma, 2 of medullary carcinoma with infiltration of large amount of lymph node cells), and 4 cases of intraductal early infiltration carcinomas.

RESULTS

Number of regional lymph node metastasis: Of 136 cases, there were 129 cases with detailed notes about lymph nodes, among which the number of dissected lymph nodes was 2441 with mean of 18.9 lymph nodes in each case. There were 40 cases

without lymph node metastasis, 7 cases with 1 lymph node metastasis, 11 cases with 2 lymph nodes metastasis, 7 cases with 3 lymph nodes metastasis, 64 cases with 4 or more lymph nodes metastasis.

Occurrence time of bone metastasis: 4 cases of bone metastasis were found before operation and the other 132 cases were found from 1 month to 19 years after operation, with the mean time of 34.0 months. 85 cases (64.4%) and 101 cases (76.5%) occurred within 3 years and 4 years respectively after operation; and 8 cases (6.1%) occurred from 9 to 19 years after operation (seen in table 1).

Relationship between the number of metastatic lymph nodes and occurrence time of bone metastasis (seen in table 2)

Bone metastasis occurred in 40 cases of N₀ stage, including 22 cases (55.0%) within 2 years after operation, 3 cases (7.5%) within 3-4 years, 7 cases (17.5%) within 5-6 years, 4 cases (10.0%) within 7-8 years, 4 cases (10.0%) within 9-19 years (seen in Fig.1).

Bone metastasis occurred in 89 cases with lymph node metastasis, including 46 cases (51.7%)

Table 1 Occurrence time of bone metastasis

Occurrence time of postoperative bone metastasis	~1 year	~2 year	~3 year	~4 year	~5 year	~6 year	~7 year	~8 year	~9 year	10~19 year	Totle
Cases	40	25	20	16	7	5	4	7	2	6	132

Table 2 Relationship between the number of metastatic lymph nodes and occurrence time of bone metastasis

Number of metastatic lymph nodes	cases	Occurrence time of bone metastasis												
		~1 year	~2 year	~3 year	~4 year	~5 year	~6 year	~7 year	~8 year	~9 year	~10 year	~15 year	~19 year	
0	40	13	9	1	2	6	1	1	3		2	1		1
1	7	2	1	2	2									
2	11	4	2	2	1			1	1					
3	7	2			1	1		1			1		1	
≥4	64	21	14	12	9		3	2	2				1	
total	129*	42	26	17	15	7	4	4	6	1	3	1	2	1
%	100	32.6	20.2	13.1	11.6	5.4	3.1	3.1	4.7	0.8	2.3	0.8	1.5	0.8

* 7 cases with lymph node metastasis were not listed in this table for unclear metastatic numbers

△ The numbers of bone metastasis within 4 years after operation in cases with no less than 4 or more lymph nodes metastasis were significantly different from that with no more than 3 or less lymph node metastases ($\chi^2=8.89$, $p<0.01$).

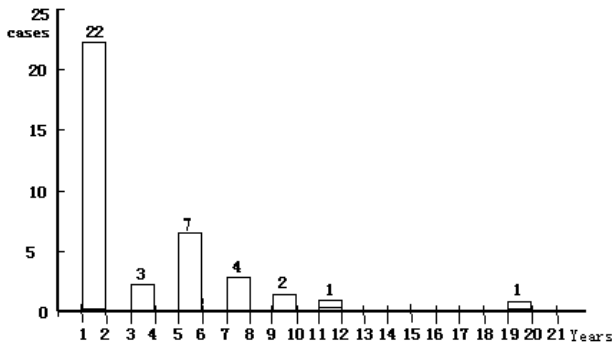


Fig.1 Occurrence time of bone metastasis in N0 cases

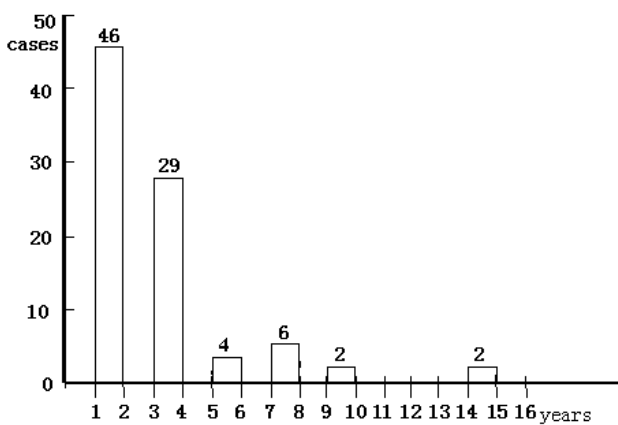


Fig.2 Occurrence time of bone metastasis in cases with lymph nodes metastasis

within 1-2 years after operation, 29 cases (32.6%) within 3-4 years, 4 cases (4.5 %) within 5-6 years, 6 cases (6.7 %) within 7-8 years, 4 cases (4.5 %) within 9-15 years (seen in Fig. 2).

Site of bone metastasis: There have been 622 bone metastatic sites in 136 cases with bone metastasis, altogether, with mean value of 4.6 (ranging from 1 to 25) bone metastatic sites in each case, including 23 sites in skull, 3 in maxilla, 21 in cervical vertebrae, 79 in thoracic vertebrae, 190 in ribs, 17 in sternum, 12 in clavicles, 70 in humerus and scapula bones, 116 in lumbar vertebrae, 31 in sacrum metastasis, 21 in ilia, 35 in femoral and hip bone, 5 in ischium and pubis, 1 in metatarsal bones.

Simple bone metastasis and complicated with other site metastasis with other sites: Of 136 cases with bone metastasis, there were 80 cases (58.8 %) of simple bone metastasis and 56 cases (41.2 %) of complicated bone metastasis with 75 sites of other

organ metastasis, including 27 sites of lung metastasis, 13 sites of liver metastasis, 7 sites of brain metastasis, 10 sites of thoracic soft tissue metastasis, 13 sites of supraclavicular lymph node metastasis, 1 site of inguinal lymph node metastasis, 1 site of pancreas metastasis, 1 site of kidney metastasis, 1 site of eye fundus metastasis. Of 56 cases complicated bone metastasis, there were 46 cases with positive axillary lymph node metastasis and 10 cases with negative axillary lymph node metastasis, in which the occurrence time of bone metastasis was respectively 4 years and 2 months, 10 years and 10 months, 4 years and 8 months, 4 years and 8 months, 4 years and 10 months, 6 years and 5 months, 10 months, 19 years, 2 years and 3 months and as well as 7 years and 11 months after operation, with the mean value of 67.3 months. While all the 136 cases the mean value of occurrence durationtime was 34.0 months after operation.

Following-up: Of 136 cases with bone metastasis, 135 cases (99.3 %) had been followed up. The following-up durations were from 5 months to 15 years and 5 months, with the mean of 27.2 months for each case. 63 cases died and the mean survival duration was 15.3 months. Of 61 patients who died of this disease, there were 16 cases of simple bone metastasis with the mortality rate of 20.0% (16/77) and 45 cases complicated bone metastasis with the mortality rate of 80.4% (45/56). The two mortality rates were significantly different ($\chi^2=45.38$, $p < 0.001$). Main death causes of them were as following: 25 cases were died for lung metastasis and respiratory failure, 11 cases for liver metastasis with ascites and hepatic failure, 5 cases for brain metastasis, 3 cases for systemic multiple organ failure, 16 cases for paralysis, 1 case with rheumatic heart disease died for heart failure and 1 case died of suicide.

Statistics All the data were treated with statistics and analyzed by chi-square test.

DISCUSSION

Diagnosis and morbidity of bone metastasis: It is reported that the morbidity of postoperative bone metastasis of breast cancer ranged from 3.1% to 70.0% or even higher [1-4], the great disparity is related to diagnostic measures and following-up durations. It is suggested that breast cancer patients at high risk of bone metastasis should have ECT scan for bone, which is of high sensitivity, and be

re-examined within a short period when they have local or suspicious symptoms; While those at low risk of bone metastasis should also have a regular ECT examination^[5]. However, bone metastasis cannot be diagnosed only by ECT, which has certain rate of false positive result^[6]. While X-ray, though with high accuracy, can not confirm the diagnosis of bone metastasis at early stage and is not helpful for treatment. In recent years it has been generally accepted that diagnostic accuracy of bone metastasis by MRI is higher than that only by CT, X-ray or ECT, and diagnostic accuracy will be improved when ECT is combined with X-ray, CT or MRI. In the latest time it has been reported that systemic examination by PET is superior to that by ECT in sensitivity, specificity and accuracy^[10], but it is too expensive and difficult to be popularized. There are more osteolytic changes than osteoblastic ones in bone metastasis^[7], and all the cases in our report are osteolytic metastasis.

In addition, the longer the follow-up duration is, the larger the number of bone metastasis is. In this report, the postoperative bone metastatic rate of breast cancer is 9.9% and their mean occurrence time after operation is 34.0 months, and about 62.0% occurred within 3 years after operation, 76.5% within 4 years and 6.1% within from 9 to 19 years, which indicated that patients with this disease should be followed up for whole lives.

Relation between bone metastasis and clinical staging of breast cancer: Our data was in accordance with the reports^[7], i.e. with the increasing of clinical staging of breast cancer, the chance of postoperative bone metastasis increased. It is notable that bone metastasis can also occur in breast cancer at early stage such as clinical stage I. In our report, 9 cases (6.6%) with bone metastasis belong to clinical stage I.

Relationship between bone metastasis and pathological type: There are different opinions in different reports about the relationship between bone metastasis and pathological type^[8,9]. It is usually believed that pathologic types of bone metastasis are not invasive specific breast cancers but invasive non-specific, such as invasive ductal carcinoma, medullary carcinoma, simple carcinoma, scirrhous carcinoma, adenocarcinoma and invasive lobular carcinoma^[4]. The results in this report are similar to those of majority documents. In theory, distant metastasis cannot occur in intraductal carcinoma, while in clinical practice we actually found 4 cases

of early infiltrative intraductal carcinoma appeared bone metastasis, which indicated that the diagnosis of intraductal carcinoma should be made carefully and patients with early infiltration carcinoma should have systemic treatment for the risk of distant metastasis.

Relationship between bone metastasis and the amount of lymph node metastasis: It is reported that the larger the number of lymph node metastasis is, the bigger the extent of bone metastasis is^[2]. In this paper, we compared in detail the relationship between bone metastasis occurrence time and the number of lymph node metastasis: within 4 years after operation, of 64 cases with 4 or more lymph node metastasis, there were 56 cases (87.5%) with bone metastasis; of 25 cases with 3 or less lymph node metastasis, there were 19 cases (76.0%) with bone metastasis; of 40 cases with negative lymph node metastasis, 25 cases (62.5%) with bone metastasis. There were significant differences between them ($\chi^2=8.89$, $p<0.01$). It has been proved that the more the lymph nodes metastasis are, the earlier and more the bone metastasis are.

Features of bone metastasis in breast cancer patients with negative axillary lymph node metastasis (N_0): Bone metastasis can also occur in N_0 breast cancer patients. In our reports, there were 40 cases (29.4%) of N_0 breast cancer with bone metastasis. The features of bone metastasis in N_0 breast cancer patients were as following: ① Bone metastatic rate of N_0 breast cancer was at the lowest level in the 3rd and 4th year after operation (Figs.1 and 2) and the reason may be related to following factors: Metastasis in N_0 breast cancer mostly belongs to hematogenous without lymph route, and such patients usually have accepted chemotherapy in the first two years after operation, which inhibits hematogenous metastasis to certain extent. While breast cancer with positive lymph node metastasis usually have both hematogenous and lymph metastasis with relatively high load of carcinoma cells, and its chemotherapy effect is possibly inferior to that in the patients with only hematogenous metastasis. Therefore, those patients doesn't appear the lowest level of bone metastatic rate in the 3rd and 4th year after operation. ② Bone metastatic rate of N_0 breast cancer in the first 4 postoperative years was 62.5%, which is lower than that of breast cancer with positive lymph node metastasis (84.3%). However, bone metastasis still appeared in 15 patients of N_0 breast cancer (37.5%) during from 5 to

19 years after operation. Its reason is still unclear. But it may at least imply that hematogenous metastasis usually occurs in breast cancer and systemic treatment for breast cancer is necessary for the prevention of bone metastasis.

Simple bone metastasis and those complicated with other site metastasis: It is reported that prognosis of breast cancer with bone, visceral and soft tissue metastasis is poorer than that of breast cancer with simple bone metastasis^[11]. In our reports, there were 80 cases of simple bone metastasis and 56 cases (41.2%) of complicated bone metastasis. It was 61 patients that died of this disease: 16 cases (20.0%) died of simple bone metastasis and 45 cases (80.4%) died of bone metastasis complicated with visceral and soft tissue metastasis. Their mortality rates were significantly different ($\chi^2=45.38$, $p<0.001$), which suggested that prognosis of breast cancer with simple bone metastasis is better than that of breast cancer with bone, visceral and soft tissue metastasis.

Features of bone metastatic sites: Some scholars believed that bone metastasis of breast cancer were, mainly axial bone, such as vertebra and pelvis instead of limbs^[11]. Some scholars also reported that prognosis of axial bone metastasis is poorer than that of limbs metastasis. In our reports, bone metastatic sites are mainly ribs, thoracic vertebra, lumbar vertebra, proximal humeral and scapula, implying that bone metastatic sites scatter from the center of breast cancer focus, instead of among main axial bones only.

In short, the occurrence rate of bone metastasis in our reports was 9.9% and the mean time of postoperative occurrence was 34.0 months, and it was positively related to high clinic staging, poor pathological type, axillary lymph node metastasis and long following-up duration. Some proportion of breast cancer patients with negative axillary lymph node metastasis (29.4%) suffered from bone metastasis, suggesting that hematogenous route is vital for bone metastasis and systemic treatments (such as chemotherapy and endocrinotherapy) play an important role in the prevention and treatment of bone metastasis in breast cancer.

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