

# Evaluation of Bone Metastasis by <sup>99m</sup>Tc-MDP Scan in Stomach Cancer Patients

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＝ 국문초록 ＝

## 위암환자에서 <sup>99m</sup>Tc-MDP 스캔에 의한 골전이 평가

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최창운 · 김상은 · 이동수 · 여정석 · 안규리  
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1983년 1월부터 1991년 2월까지 서울대학교 병원에서 진단된 위암환자를 대상으로 시행한 359예의 골스캔을 후향적으로 재검토하여 골전이 빈도와 양상을 관찰하였으며 환자들의 의무기록을 검토하여 위암의 임상상과 비교하였다. 그 결과는 다음과 같았다.

- 1) 359예의 골스캔 중에서 골전이에 부합되는 이상소견은 167예(46.5%)이었다.
- 2) 관찰된 167예의 이상소견 빈도는 척추(66%)에 가장 많이 관찰되었고, 늑골(58%), 골반부(43%), 대퇴골(31%), 두개골(22%)순이었다.
- 3) 척추전이에서 흉추(65.6%)와 요추(64.5%)의 전이빈도는 거의 비슷하였고, 경추(23.6%)는 낮았다.
- 4) 골전이 빈도는 임상적 병기 3기 환자에서 진단 후 1년 이내에 급격히 증가되었고 그 이후는 증가되지 않았다.
- 5) 골전이는 임상적 병기가 증가됨에 따라 증가되었으나, 조직학적 세포형태와는 무관하였다.
- 6) 혈청 alkaline phosphatase 치와 골스캔 상의 골전이 유무와 통계적으로 유의한 상관관계가 관찰되었다.

이상의 결과로 위암환자의 상당 수에서 골전이가 진단되었으며 위암환자, 특히 진행암 환자에서 골전이에 대한 주기적인 추적 검사가 필요할 것으로 생각된다.

## INTRODUCTION

Stomach cancer is the most common malignant disease in Korea that is about 20~25% in registered cancer patients<sup>1)</sup>. The evaluation of metastasis is important in making therapeutic plans and pre-

ling the patients prognosis.

It is well known the bone scan findings of the bone metastases and the usefulness of bone scans in patients with breast cancer, lung cancer and prostate cancer<sup>2-6)</sup>.

But it has not been much reviewed about the findings in bone scans of the patients with stomach

cancer as of yet.

This report is an retrospective evaluation of the incidence and sites of bone lesions detected by <sup>99m</sup>Tc-methylene diphosphonate scans and the correlation with its clinical patterns in patients with stomach cancer.

## MATERIALS AND METHODS

We retrospectively reviewed 359 cases of bone scan of the patient with stomach cancer who were diagnosed at the Seoul National University Hospital since 1983. The number of male patients were 227 (63%) and females were 132 (37%). And their mean age was 53.5 years (Table 1, 2).

The bone scan was performed 2~4 hours after intravenous injection of 555~740 MBq (15~20 mCi) of <sup>99m</sup>Tc-methylene diphosphonate (MDP) using large-field of view gamma camera equipped with low energy, high resolution collimator. Two whole body and 5-view static images with additional views as required were carried out in virtually all patients.

For establishing an individual scan lesions as a bone metastasis, we reviewed the all available correlative radiologic studies, but limited availability of concurrent radiographs of the lesions made the

Table 1. Sex and Age Distribution of the Subjects

	Number	Mean Age
Male	227 (63%)	54.9 (20 - 87)
Female	132 (37%)	51.1 (21 - 76)
Total	359	53.5 (20 - 87)

Table 2. Distribution of Initial Clinical Stage in the Patients with Stomach Cancer

Stage I	13 ( 5.6%)
Stage II	7 ( 3.0%)
Stage III	80 (34.2%)
Stage IV	134 (57.3%)
Total	234

results mainly depend on the scan findings.

The following bone scan findings were excluded from the evidence of bone metastasis<sup>7)</sup>:

- 1) two or more adjacent, aligned rib lesions in a pattern indicative of trauma;
- 2) polyarticular increased uptake in the joint of the extremities;
- 3) diffuse or focal increased uptake in the appendicular skeleton at sites of documented trauma;
- 4) increased uptake in the maxilla or mandible, indicative of dental pathology.

We also reviewed clinical records and biochemical data such as serum calcium, phosphorus and alkaline phosphatase of 242 patients as far as we could evaluate.

## RESULTS

Of 359 cases of bone scans, 167 cases (46.5%) had the bone scan abnormalities that was thought to be metastatic bone lesions (Table 3). The lesions of abnormal bone scans were found most frequently in spine, which was about 66% in 167 patients with

Table 3. Bone Scan Findings in Total Cases

Evidence of Metastasis	167 (46.5%)
No Evidence of Metastasis	192 (53.5%)
Total	359

Table 4. Location of Abnormal Bone Scan Findings

1. Spine	110 (65.9%)
2. Rib	97 (58.1%)
3. Pelvis	71 (42.5%)
4. Femur	51 (30.5%)
5. Skull	36 (21.6%)
6. Shoulder Girdle	28 (16.8%)
7. Sacroiliac Joint	12 ( 7.2%)
8. Humerus	10 ( 6.0%)
9. Sternum	7 ( 4.2%)
10. Tibia	5 ( 3.0%)

In Total 167 Cases of Abnormal Findings

abnormal bone scan. The next was rib, 58% and pelvis (43%) femur (especially in proximal area) (34%) and skull (22%) were followed. The less frequent sites sites were shoulder girdle (17%) such as scapula and clavicle, and sacroiliac joint, humerus (in proximal area), sternum and tibia (Table 4). The distribution of these lesions suggests the bone metastasis in stomach cancer is hematogenous like other bone metastasis. In spinal metastasis, the incidences of thoracic and lumbar spine were equal, and in cervical spine, metastasis was less frequent (Table 5).

In cases with single bone lesion, we were able to most frequently find the abnormal lesion in rib, and spine, femur and pelvis were followed (Fig. 1).

Of the bone scan findings that were performed within two months after diagnosis, in patients with stage 2, although the number of patients were small, there was no case which the evidence of bone metastasis. But in patients with stage 3, 12% were abnormal and in stage 4, 52% were abnormal in bone scan (Table 6). In scans examined in several months or

years later after diagnosis, the incidence of abnormal bone scan was increased. Especially in patients with stage 3, about 11 months later since diagnosis was made, 43% were abnormal in bone scan (Table 7). The cumulated incidence of bone metastases in patients with stage 3 was 26.7% within two months after diagnosis and increased rapidly within 12 months and after then the incidence was not changed (Fig. 2).

There were no statistical differences between the pathologic types of stomach cancer and the inci-

**Table 5. Location of Abnormal Scan Findings in Spine**

Cervical Spine	26 (23.6%)
Thoracic Spine	72 (65.6%)
Lumbar Spine	71 (64.5%)
In Total 110 Cases of Abnormal Spine Findings	

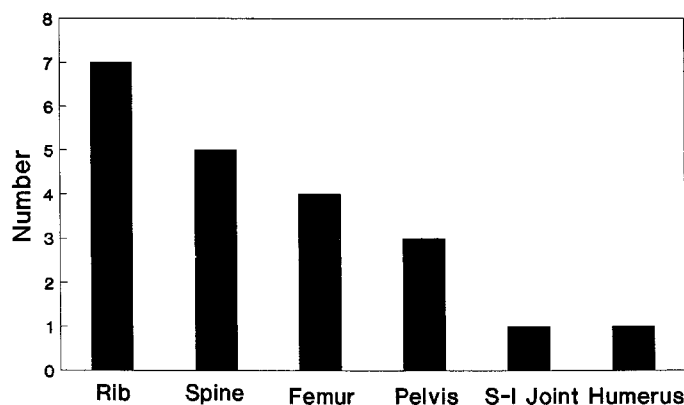
**Table 6. Stages and Abnormal Bone Scan Findings : Cases Within Two Months After Diagnosis**

Stages	Normal	Abnormal
II ( 4)	4	0 ( 0%)
III ( 38)	30	8 (21.1%)
IV ( 84)	40	44 (52.4%)
Total (126)	74	52 (41.3%)

**Table 7. Stages and Abnormal Bone Scan Findings : Total Cases**

Stages	Normal	Abnormal	F/U Month*
II ( 7)	5	2 (28.6%)	14.8
III ( 80)	46	34 (42.5%)	10.9
IV (124)	54	70 (56.5%)	5.4
Total (211)	105	106 (50.0%)	

\* : average follow-up period



**Fig. 1. Location of single bone lesion.**

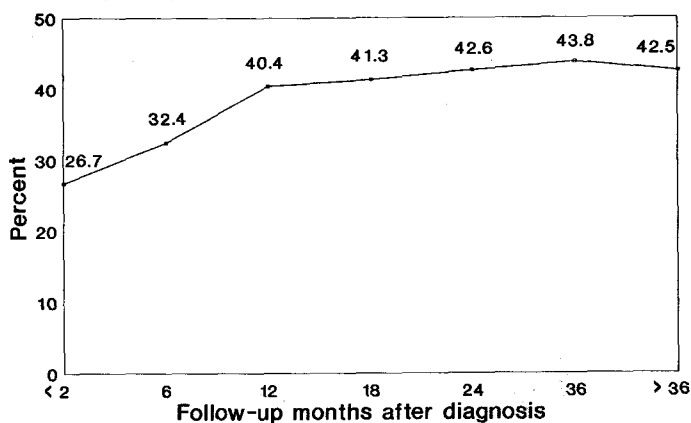


Fig. 2. Cumulated incidence of abnormal bone scan in stage 3.

Table 8. Incidence of Abnormal Bone Scan According to Pathologic Types

Cell type	Number of Patients	Abnormal Bone Scan
Well Differentiation	( 22)	11 (50%)
Moderate Differentiation	( 43)	23 (53%)
Poorly Differentiation	(105)	48 (46%)
Signet Ring Cell	( 20)	11 (55%)
Mucinous Cell	( 3)	2 (67%)

Table 9. Bone Scan Findings and Clinical Parameters

Bone Scan	:	Normal	Abnormal
Mean Age (year)		53 ± 12	54 ± 12
Alk..P* (IU/l)		126 ± 169	288 ± 323
Calcium (mg/dl)		8.2 ± 2.4	8.2 ± 2.5
Phosphorus (mg/dl)		3.7 ± 1.3	3.6 ± 1.3

\* : P < 0.01

dence of abnormal bone scan (Table 8).

The values of serum alkaline phosphatase of the patients who had not the abnormal lesions and the patients with metastatic lesions in bone scan were 126 IU/l and 288 IU/l, respectively. There were statistical differences between the two groups. The normal values of serum alkaline phosphatase in adults was 30~115 IU/l in this study. But mean age, the level of serum calcium and phosphorus were not different in two groups according to the bone scan findings

Table 10. Bone Scan Findings and Alkaline Phosphatase

		Bone Scan	
		Abnormal (114)	Normal (128)
Alkaline Phosphatase	Abnormal* (107)	72	35
	Normal (135)	42	93

P < 0.001, X<sup>2</sup>-test

Abnormal : > 115 IU/L

(Table 9). We also found the correlation between the bone scan findings and serum alkaline phosphatase (Table 10). In cases of normal bone findings with elevated serum alkaline phosphatase, the cause of increased serum alkaline phosphatase were liver disease (metastasis 12, obstructive jaundice 2, hepatitis 1), disseminatron at other sites except bone and liver 8 cases, sepsis 2 cases, bone marrow involvement 1 case, and unidentified cases 8 cases.

## DISCUSSION

The radioisotope bone scan is generally accepted as the initial investigation of choice in the search for bone metastases from most tumors. Metastatic roentgenographic evaluation has been of limited value, since symptoms from bone metastasis occur before there is radiographic evidence of abnormality in some patients. Uptake of the bone scanning agents

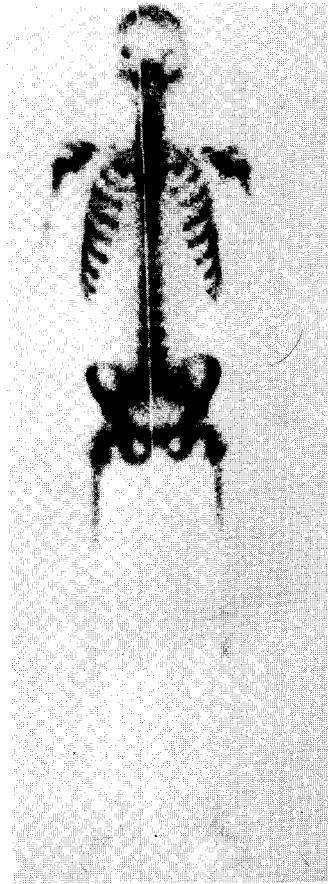


**Fig. 3.** Anterior bone scan of a 57-year-old man shows multiple increased uptake in the axial skeleton and proximal long bones of the upper and lower extremities.

in normal bone depends on both skeletal blood flow and skeletal metabolism, possibly osteoblastic activity<sup>9</sup>).

The increased sensitivity of the bone scan over the bone radiograph for the detection of metastasis due to the fact that invasion of the skeleton by malignant cells will excite metabolic changes such as an increase in local blood flow and reactive bone formation before there is significant structural change<sup>9</sup>). But the changes are nonspecific and the increased uptake in bone scan may be due to other different causes, not due to bone metastasis. We made to apply criteria for differentiation between bone metastasis and other causes.

In 1990, the Korean Ministry of Health and Social



**Fig. 4.** Anterior bone scan of a 49-year old man shows diffuse, increased uptake in the axial skeleton and proximal long bones of the upper and lower extremities. Renal activity is markedly diminished, and a decreased uptake is noted in the greater part of the extremities.

Affair issued the number of patients with stomach cancer occupied 24.0% in all registered cancer patients in Korea. Male patients were 6,650 and females were 3,437 (male to female ratio: 1.93)<sup>11</sup>). In this study, male to female ratio was 1.72.

We were able to find that there were abnormalities suggesting bone metastases in 46.5% of bone scans of the patients with stomach cancer. Many patients had advanced stage, but this suggests that bone metastases are not uncommon in patients with stomach cancer. Seto et. al<sup>10</sup>). and Bussaka et. al<sup>11</sup>). reported the incidence of bone metastases 25% (25 in

60 cases) and 38% (12 in 32 cases) respectively. In our study the incidence was higher than that of those reports. This may be due to the patients population studied. In our study the majority of the patients were advanced cancer patients (91.4%).

The most common site of bone metastases was spine and rib, pelvis, femur and skull were followed. This distribution of metastatic lesions suggests stomach cancer metastasizes hematogenously in bone like other malignancies such as breast, lung, prostate cancer. This was similar to the other results<sup>10,11</sup>.

Bone metastases in patients with stomach cancer or colorectal cancer were not significantly related with the presence of liver metastases<sup>10,11</sup>. Even in patients without liver metastases, bone metastases had been found. These suggested the presence of non-portal routes such as the vertebral venous (Batson's) plexus in metastatic spread in gastrointestinal malignancies<sup>10,12</sup>.

Single bone lesion was found 21 cases (12.6%) in 167 bone metastases. A single abnormality, however, has a significant probability of being due to a non-malignant lesion. Mc Neil<sup>13</sup> states that in the case of solitary rib lesions the frequency of malignant cause has estimated to vary between 1% and 17%, while around 80% of vertebral lesions are malignant. Isolated joint abnormalities are likely to be due to arthritis<sup>13-16</sup>. But we have the clue to differentiate the rib lesion between metastasis and fracture in bone scan. The fracture presents focal increased uptake in most cases, but the metastatic lesion is found linear increased uptake in more than half of the cases in bone scan<sup>17</sup>. All bone scan abnormalities should be correlated with the results of other, more specific investigations. Initially a radiograph of the area showing the hot spot should be obtained. This may either show a benign cause for the scan appearance, confirm the presence of metastases or be normal at the site of scan abnormality. Skeletal metastases develop in the medulla of the bone and only involve

the cortex at a late stage. When standard radiographs are normal, computed tomography of bone<sup>18</sup> or percutaneous bone biopsy<sup>19</sup> can be valuable in evaluating the significance of a scan abnormality.

Of these 167 patients with bone metastases, 14 patients showed the findings of diffuse increased uptake on bone scan, namely "superscan". This was found in patients with breast carcinoma, prostate carcinoma, prostate carcinoma and other patients with extensive bone metastases and also found in stomach cancer patients<sup>7,20,21</sup>.

The incidence of bone metastases in patients with clinical stage 3 was 21.1% within 2 months after diagnosis but increased to 42.5% in bone scans performed after 11 months of mean follow-up period. The cumulated incidence of bone metastasis was rapidly increased within 12 months after diagnosis was made and after then the incidence was not significantly changed, even decreased slightly after 36 months. This suggests that regular examination should be done at least for 12 months after diagnosis was made, for evaluation of bone metastasis in patients with advanced stomach cancer.

The poorly differentiated cell type was the most common (54%). But there was no significant differences among the pathological cell types and the frequencies of bone metastases.

Serum alkaline phosphatase was elevated in 63% (72 in 114) of patients with bone metastasis. Seto et al<sup>10</sup>. also reported the relationship between the bone metastasis and elevation of serum alkaline phosphatase in patients with stomach cancer and Bellevue and Spencer<sup>22</sup> stated there was correlation between level of serum alkaline phosphatase and bone metastases in other malignancies. But serum alkaline phosphatase was elevated in various clinical conditions such as liver disease including liver metastasis, infarction of internal organs, gastrointestinal diseases and even produced by neoplasm itself<sup>23</sup>. Although it is unreasonable to say that the elevated serum alkaline phosphatase means

bone metastasis, the measurement of serum alkaline phosphatase can give the physicians some guidelines for making treatment plans. There was no correlation between the bone metastasis and serum calcium. Ralston et al<sup>24)</sup>. reported the development of hypercalcemia in malignancy is not directly related to the presence or extent of metastatic bone disease. It was suggested that the development of hypercalcemia may depend on an alternative mechanism, such as the production of a humoral substance by tumor tissue, having its effect on calcium metabolism at sites or organs distant from local areas of tumor involvement.

### CONCLUSION

We retrospectively reviewed the 359 bone scans of the stomach cancer patients who were diagnosed at Seoul National University Hospital. We were able to find the following guidelines to be useful in evaluation of bone metastasis in stomach cancer.

1) There were abnormal bone scans, suggesting bone metastases, in 167 of 359 cases (46.5%)

2) The most common site was spine and followed by rib, pelvis, femur and skull like other malignant disease such as lung carcinoma or breast carcinoma.

3) The incidence of bone metastasis was increased according to the increased period after diagnosis in stage 3.

4) Bone metastasis was increased by the degree of clinical stage but not related to the pathologic cell types.

5) There was relationship between the bone scan findings and serum alkaline phosphatase. The measurement of serum alkaline phosphatase will give the useful information in diagnosis of metastasis.

Bone metastasis of stomach cancer is not unusual and regular follow-up for evaluation of bone metastasis is necessary, especially in patients with advanced stomach cancer.

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