The value of Serial Quantitative Technetium-99m Methylene Diphosphanate in Assessment of the Response of Metastatic Skeletal Lesions to Different Types of Treatment Modalities.

H. Moustafa, SH. El-Haddad, G. Ziada and A. Fawzi
Nuclear Medicine Department, Faculty of Medicine, Cairo University, Egypt

خلاصة

اشتملت هذه الدراسة على 95 مريضا يعانون من انتشار المرض بثانويات في العظام تم اختبارهم بالتحليل الكمي لالتقاط العظام المصابة لمادة ميثلين ثنائي الفوسفات قبل وبعد العلاج على فترات تتراوح بين 6 شهور واثني عشر شهرا وقد تم اجراء الفحص دوريا كل ثلاثة شهور.
وقد تبين أن نسبة (ت.ف.) بين 24 ساعة/ 4 ساعات مؤشر للاستجابة للعلاج بالطرق المختلفة وقد كان هناك تغير بصورة واضحة في نسبة (ت.ف.) بعد العلاج بستة شهور في المرضى الذين تم علاجهم بالاشعاع والعلاج الكيميائي معا وكذا في المرضى الذين تم علاجهم بالاشعاع لنصف الجسم بينما وجد ارتفاع مطرد في نسبة (ت.ف.) بعد ستة شهور في المرضى الذين لم يأخذوا أي علاج. وكانت نسبة الاستجابة لثانويات العظام متساوية تقريبا سواء في الفقرات أو العظام المفلطحة أو العظام الطويلة ولكن هناك تغير العظام الطويلة بعد العلاج الاشعاعي.

Abstract

The study included 95 patients having metastatic bone lesions, subjected to serial quantitative skeletal scintigraphy before and after treatment every 3 months for 6 months.
To study the fate of metastatic bone lesions under the effect of different treatment modalities, an objective index was used. This index was introduced in 1985 by Israel et al. (1), and was designated TF. A significant drop in TF ratio was observed 6 months following therapy in the groups who received combined localized radiotherapy together with systemic therapy and those who received half body irradiation. In contrast, a marked increase in TF ratio was observed in the patients who did not receive any specific treatment. The response of metastatic skeletal lesions

was nearly similar whatever the site of involvement whether in the spine, flat or long bones except for an initial response in the long bones with drop of TF ratio after localized radiotherapy.

Introduction :

In the majority of patients presenting with skeletal secondaries, the metastatic lesions are usually multifocal. Furthermore, the development of new lesions on sequential studies is considered to be one of the most important prognostic factors.

According to previous investigators, changes in intensity of uptake within bone lesions of less than 40% are not likely to be dectected visually [2]. In contrast, quantitative measurements allow objective assessment of serial changes in skeletal lesion uptake [3, 4]. In addition, estimation of lesion to non lesion radioactivity uptake at 4 and 24 hours with calculation of the TF ratio [24/4 hours ratio] was found to be a useful method to differentiate between solitary metastatic and degenerative vertebral lesions [1, 5].

The aim of this work is to study the fate of metastatic bone lesions under the effect of different treatment modalities using serial TF ratio estimations as a quantitative means for assessment of skeletal lesions.

Materials and Methods:

The present study included 95 patients having metastatic bone disease referred to the Nuclear Medicine Department of NEMROCK center in the period from July 1990 to July 1991. This group was formed of 76 females and 19 males, with the mean age of 46.2 ± 12.6 years. It should be remembered that some of these patients had multiple lesions, and this made the number of lesions included in the present study to be 156 lesions.

After obtaining a full clinical history with details of treatment, the patients were subjected to a thorough clinical examination with special reference to sites of pain and tenderness. X-rays and bone biopsy were performed if other diagnostic tests were inadequate.

Following the intravenous injection of 240 - 555 MBq of ^{99m}Tc- MDP, the patients were encouraged to drink plenty of fluids to ensure proper

hydration. They were also instructed to evacuate the bladder to minimize the radioactivity in the bladder and establish maximum bone to soft tissue

Imaging was performed using a large field of view gamma camera with a parallel hole high resolution collimator linked with an IMAC computer. The acquired data was stored on 128 x 128 matrix.

For quantitative assessment a total count of 600,000 was collected at 4 hours and 150,000 counts at 24 hours post dose for each image. Then, a region of interest was drawn over the involved site or lesion [L], as well as over an equal area of normal bone in the same region [cervical, dorsal, lumbar ... etc] and this was designated as non-lesion [NL]. This enabled calculation of the ratio of counts in lesion / non-lesion at both 4 and 24 hours. Division of the ratio obtained at 24 hours by that of the 4 hours gave the TF ratio [1].

$$TF = \frac{\text{L/NL ratio at 24 hours}}{\text{L/NL ratio at 4 hours}}$$

Regarding the distribution of the patients according to the method of treatment adopted, 39 lesions were subjected to localized radiotherapy alone, whereas, 34 received localized radiotherapy as well as systemic-treatment. A further group of 24 lesions was subjected to half body irradiation. In addition, systemic treatment was given to 39 lesions. In contrast, 20 lesions received non-specific treatment [Table 1].

The study was repeated every 3 months for a period of 6 months in all patients.

Analysis of the data was done using the standard statistical methods with TF ratio [24/4 hours ratio] as an index in the follow up of response to different treatment modalities in metastatic bone lesions.

Results :

The study included 95 patients with histologically proven malignancy associated with bone metastases as evident in skeletal scintigraphy. Some patients had multiple sites of involvement and this raised the number of lesions to 156. The commonest site of involvement was the vertebral column

[49.3%]. This was followed by flat bones and the long bones, with an incidence of 37.8% and 12.9% respectively [Table 1].

The mean value of TF ratio obtained before treatment for the different groups investigated amounted to 1.35 + 0.2, 1.25 + 0.16, 1.36 + 0.18, 1.25 ± 0,09 and 1.37 + 0.16 in the groups receiving localized radiotherapy alone, localized radiotherapy and systemic treatment, half body irradiation, systemic therapy and non-specific treatment respectively [Table 2, Figure 1].

There was no significant change in TF ratio at 3 months after treatment in all groups except for a slight initial rise in patients receiving systemic treatment whether alone or with radiotherapy. On the other hand, statistically significant drop of TF ratio was observed following therapy among the lesions subjected to combined localized radiotherapy and systemic therapy and those who received half body irradiation with TF ratio of 1.19 + 0.13 and 1.19 + 0.16 in both groups [$P < 0.05$]. Also, there was marked increase in TF ratio in the patients who did not receive any specific treatment with TF ratio rising to 1.58 + 0.19 [$P < 0,01$] [Table 2, Figure 1].

Vertebral lesions and lesions of flat bones seem to respond to all types of treatment with drop of TF ratio. However, the lesions receiving combined localized radiotherapy together with systemic treatment and those receiving half body irradiation only achieved statistically significant drop of TF ratio at the end of 6 months after treatment [$P < 0.05$] [Table 3].

Similar changes were seen in long bones, but additional initial significant drop in TF ratio with mean TF ratio of 1.13 ± 0.17 was evident following localized radiotherapy 3 months after treatment.

In contrast, a remarkable rise was observed in TF ratio of vertebrate and long bones lesions in the patients who received non specific treatment [Table 3].

Discussion :

Multiple bone lesions are usually the hallmark of metastatic disease, with the axial skeleton being the commonest site of bone secondaries. Clain [16] reported 69% of cases with vertebral deposits followed by 41% and 25% in pelvic bones and femori. Similarly, in the present work vertebral

lesions represented 49.3% followed by flat bones and long bones in 37.8% and 12.9% respectively.

Radionuclide skeletal scanning using ^{99m}Tc-MDP is essentially a visual display of skeletal function. The radiopharmaceutical is adsorbed on metabolically active bone with intact blood supply, thus measurement of radionuclide accumulation provides a sensitive and objective methods of quantifying bone metabolism [7].

Flare phenomenon described by Rossleigh et al. [8]. Which showed higher radioactivity accumulation in bone lesions following systemic therapy was explained by osteoblastic response which may occur with bone metastases healing. Also, Dlrichman et al. [9] documented flare phenomenon in the first few months after starting systemic therapy. In this study, slight early rise in TF ratio at 3 months was observed in the patients who received systemic therapy alone or combined with radiotherapy [Table 2, Figure 1]. This observation may be attributed to flare phenomenon.

Quantitative assessment using lesion to non-lesion uptake at 4 hours and 24 hours with calculation of TF ratio was found to be useful in separating solitary metastatic from degenerative lesions in the spine [1]. Similar results were reported by Ziada et al. [5] with a significant drop in

Table I: Distribution of treated skeletal lesions according to the different modalities of treatment.

Treatment modality	Vertebrae	Flat bones	Long bones	Total
Localized Radiotherapy	20	12	7	39
Localized Radiotherapy & Systemic therapy	20	9	5	34
Half body irradiation	12	11	1	24
Systemic therapy	17	19	3	39
Non specific treatment	8	8	4	20
Total	77	59	20	156
Incidence	49.3%	37.8%	12.9%	100%

Table [2]: Serial quantitative assessment of metastatic skeletal lesions using TF ratio in relation to different treatment modalities.

Treatment modality	Mean TF1	Mean TF2	Mean TF3
Localized Radiotherapy	1.35 ± 0.20	1.34 ± 0.13	1.30 ± 0.26
Localized Radiotherapy & Systemic therapy	1.25 ± 0.16*	1.35 ± 0.14	1.19 ± 0.13*
Half body irradiation	1.36 ± 0.18§	1.33 ± 0.20	1.19 ± 0.16§
Systemic therapy	1.25 ± 0.09	1.29 ± 0.13	1.23 ± 0.11
Non Specific treatement	1.37 ± 0.16°	1.35 ± 0.21	1.58 ± 0.19°

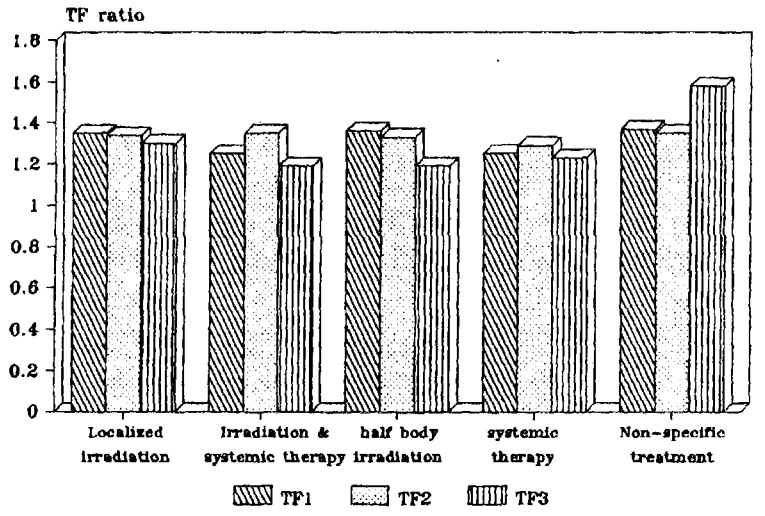
* $P < 0.05$ § $P < 0.05$ ° $P < 0.01$

Table [3]: Correlation between treatment modalities and site of disease involvement using serial TF ratio.

Treatment Modality		Vertebral bodies	Flat bones	Long bones
Localized Radiotherapy	TF1	1.31 ± 0.11	1.39 ± 0.10	1.38 ± 0.12*
	TF2	1.35 ± 0.21	1.34 ± 0.09	1.13 ± 0.17*
	TF3	1.23 ± 0.20	1.32 ± 0.21	1.26 ± 0.20
Localized Radiotherapy & Systemic therapy	TF1	1.28 ± 0.12*	1.35 ± 0.18#	1.36 ± 0.13*
	TF2	1.34 ± 0.09	1.27 ± 0.14	1.35 ± 0.19
	TF3	1.17 ± 0.16*	1.16 ± 0.09#	1.18 ± 0.11*
Half body irradiation	TF1	1.36 ± 0.14#	1.32 ± 0.13*	1.39 ± 0.15#
	TF2	1.30 ± 0.21	1.38 ± 0.14	1.34 ± 0.13
	TF3	1.13 ± 0.19#	1.14 ± 0.09*	1.10 ± 0.13#
Systemic therapy	TF1	1.30 ± 0.14	1.33 ± 0.17	1.32 ± 0.19
	TF2	1.33 ± 0.12	1.34 ± 0.13	1.30 ± 0.13
	TF3	1.24 ± 0.14	1.27 ± 0.14	1.24 ± 0.09
Non specific treatment	TF1	1.35 ± 0.18@	1.37 ± 0.14	1.23 ± 0.13°
	TF2	1.37 ± 0.13	1.28 ± 0.18	-----
	TF3	1.54 ± 0.16@	1.39 ± 0.24	1.95 ± 0.17°

* $P < 0.05$ # $P < 0.05$ @ $P < 0.01$ ° $P < 0.01$

Figure (1): Serial quantitative assessment of metastatic skeletal lesions using TF ratio in relation to different treatment modalities.



TF ratio of 1.36 $\pm$ 0.2 before treatment to 1.14 + 0.09 following localized radiotherapy.

In this study, serial quantitative assessment of metastatic skeletal lesions showed remarkable change after half body irradiation as well as after combined localized irradiation and systemic therapy [Table 2, Figure 1], whereas, there was a remarkable rise in the group of metastatic patients receiving non specific treatment for 6 months. This serial quantitative skeletal scanning is essential for assessment of skeletal lesions to different modalities of treatment.

The response of metastatic skeletal lesions was nearly similar whatever the site of involvement in the spine, flat bones or long bones with siginificant change in the TF ratio 6 months after therapy in those who have received half body irradiation together with systemic therapy [Table 3]. In

addition, an initial response was evident in long bones after 3 months after localized radiotherapy.

So, quantitative analysis of radionuclide uptake of bone lesions is a sensitive objective method for the evaluation of the fate of metastatic bone lesions.

References

[1] Israel, O.; Front, F.; Frenkel A. and Kleinhaus, U. (1985): 24 hours / 4 hours ratio of technetium-99m methylene diphosphonate uptake in patients with bone metastases and degenerative bone changes. J. Nucl. Med., 26: 237 - 240.

[2] Condon, B.R.; Buchanan, R. and Garvie, N.W. (1980): Assessment of progression of secondary bone lesions following cancer of the breast or prostate using serial radionuclide imaging. Br. J. Radiol., 54: 18 - 23.

[3] Pfeifer, J.P.; Hill, W.; Bull, V.; Burkhardt, R. and Kirsch, C.M. (1983): Improvement of bone scintigraphy by quantitative evaluation compared with X-ray studies and iliac crest biopsy in malignant disease. Eur. J. Nucl. Med. 8: 342 - 345.

[4] Pitt, W.R. and Sharp, P.E. (1985): Comparison of quantitative and visual detection of new focal bone lesions. J. Nucl. Med., 26: 230 - 236.

[5] Ziada, G.; Moustafa, H.; Saber, R.; Moustafa, A. and El-Haddad, SH. (1990): Evaluating 24/4 hours ratio of ^{99m}Tc-MDP - A method of analysis for differentiation between bone metastases and degenerative bone lesions. Eur. J. Nucl. Med., 16: 556 [Poster].

[6] Clain, A. (1965): Secondary malignant disease of bone. Br. J. Cancer, 19:15 - 29.

[7] Holmes, R.A. (1978): Quantitation of skeletal ^{99m}Tc- labelled phosphates to detect metabolic bone disease. J. Nucl. Med., 19: 330 - 331.

[8] Rossleigh, M.A.; Lovegrove, F.T.A.; Reynold, P.M. and Byrne M.J. (1982): Serial bone scans in the assessment of response to therapy in advanced breast carcinoma. Clin. Nucl. Med., 7: 397 - 402.

[9] Dlrichman, A.; Decker, A.; Al-Sarraf, M.; Vaitkevicius, V.K. and Muz, J. (1984): Computerized bone scan. A potentially useful technique to measure in prostatic carcinoma. Cancer, 53: 1061 - 1065.