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ADDITIONAL INFORMATION FROM QUANTITATIVE 24-HOUR ^{99m}Tc-MDP BONE SCINTIGRAPHY IN PATIENTS WITH PROSTATIC CARCINOMA

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Abstract

Quantitative bone scintigraphy was performed at 4 and 24 h after injection of ^{99m}Tc-MDP. The lower thoracic and all the lumbar vertebrae were recorded in 37 patients with prostatic carcinoma before orchiectomy as well as two weeks, two and six months postoperatively. Fourteen patients had normal bone scintigrams. By means of the measured variation in the count rate between normal vertebrae, the criterion for a vertebra to be considered as abnormal was determined using the 4 h-uptake values. For patients with normal scintigrams the count rate at 24 h was below the 4 h level and the mean 24 h/4 h ratio was determined to be 0.85 ± 0.09 (1 SD). Normal vertebrae in patients with skeletal metastases had only slightly lower count rate values at 24 h than at 4 h. Abnormal vertebrae showed a higher count rate at 24 h, especially two weeks postoperatively, while a tendency towards lower values than at 4 h was seen after 6 months. If the 24 h/4 h ratio is used as an extra criterion to the count rate at 4 h, the vertebrae will be more accurately defined as normal or abnormal.

Key words: Prostatic carcinoma, skeletal metastases, quantitative bone scintigraphy.

Bone scintigraphy is normally performed 3–4 h after injection of ^{99m}Tc-labeled phosphate complexes. Most of the information about differences in ^{99m}Tc methylene diphosphonate (MDP) uptake has been shown to be available already during the first hour after injection (1). Reduction of activity in blood may thereafter improve the visualization of both tumours and the normal skeleton (2). In a previous study, patients with prostatic carcinoma were investigated with quantitative bone scintigraphy 4 h after injection of ^{99m}Tc-MDP (3). The value of bone scintigraphy extended up to 24 h after injection with determination of the 24 h/4 h ratio has earlier been studied, but without quantitative uptake measurements (4).

The aim of this study was to investigate if the count rate per unit administered activity at 24 h and the ratio between the 24 h and 4 h-values will provide additional information to the 4 h count rate value to further distinguish between abnormal and normal vertebrae in patients with prostatic carcinoma.

Material and Methods

Thirty-seven men (aged 60–81 years, mean age 74 years) with recently discovered, cytologically confirmed, prostatic carcinoma were included in the study. The patients were referred for routine whole-body scintigram before treatment with orchiectomy. In addition, the patients underwent quantitative 4- and 24-h bone scintigraphy of the lower thoracic and all the lumbar vertebrae. The whole-body scintigrams were visually reviewed by one experienced observer to get a standardized evaluation. If there was a doubt whether an increased uptake was due to benign or malignant disease, conventional radiography, computed tomography or bone biopsy were performed. The patients, who received no other therapy than orchiectomy, were investigated with bone scintigraphy also 2 weeks, and 2 and 6 months after operation.

Bone scintigraphy. Approximately 500 MBq ^{99m}Tc-MDP was injected intravenously. The activity in the syringe was measured before and after injection. With the patients supine, posterior images of the lower thoracic and all the lumbar vertebrae were recorded with a large-field (39.0 cm diameter) gamma camera equipped with a high-resolution, parallel-hole collimator. Pictures taken 4 and 24 h after

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injection were digitized in 128 × 128 matrices. A region of interest (ROI) was defined over each vertebra from T10 to L5. The count rate per pixel and unit injected activity, corrected for radioactive decay, was calculated for each ROI and measurement period. To correct for soft tissue activity in front of and behind the vertebrae, a background ROI between the projection of the kidney and crista iliaca was chosen. A correction factor for the varying depths of the different vertebrae was calculated to compare the count rate in any vertebra from T10 to L5 (3). By normalizing the count rate to the mean value of all the investigated vertebrae in the patients with normal bone scintigrams, the following correction factors were determined (3): 0.83 (T10), 0.90 (T11), 0.98 (T12), 1.09 (L1), 1.15 (L2), 1.13 (L3), 1.06 (L4) and 0.96 (L5).

Statistical analyses. For the vertebrae in patients with normal bone scintigrams Student's t-test was used for statistical analysis of the ^{99m}Tc-MDP count rate, as the count rate values were found to be normally distributed. A non-parametric Wilcoxon's signed rank-test was used for the vertebrae in patients with skeletal metastases, for which the count rate values were not normally distributed, this being due to the selection criterion. Differences in count rate between the groups of patients with normal and abnormal vertebrae, respectively, were evaluated by means of the Mann-Whitney test.

Results

Normal bone scintigrams. Fourteen patients (aged 60–80 years, mean age 74 years) had normal bone scintigrams prior to orchiectomy as well as 2 weeks, 2 and 6 months after operation. The upper level for the normal count rate was defined as the mean value plus two standard deviations at 4 h for all patients with normal bone scintigrams. This level was determined to be $130 \cdot 10^{-5}$ counts pixel^{-1} s^{-1} MBq^{-1} (Table 1). The count rate at 24 h was significantly lower ($p < 0.001$) than the count rate at 4 h. The mean of the 24 h/4 h ratio for 112 vertebrae at the four different investigations was determined to be 0.85 ± 0.09 (1 SD). The upper level for the normal 24 h/4 h ratio was defined as 1.03, corresponding to the mean value of the ratio plus two standard deviations.

Abnormal bone scintigrams. Twenty-three patients (aged 62–81 years, mean age 74 years) were found to have skeletal metastases prior to operation. According to the above defined criterion for normal count rate, 77 vertebrae were considered normal and 107 vertebrae abnormal in the preoperative investigation (Tables 1 and 2). The abnormal vertebrae were equally distributed among the investigated vertebrae (T10—L5) and no change in the mean count rate was seen between the different vertebrae. The groups of preoperatively defined normal and abnormal vertebrae were kept unchanged during the following postoperative investigations.

The normal vertebrae in the patients with skeletal metastases showed at 24 h slightly lower count rate values than at 4 h. The 24 h/4 h ratio was found to be 0.95 (median) before operation, and 0.95, 0.93 and 0.90 two weeks, two and six months, respectively, after operation (Table 2).

In the abnormal vertebrae the count rate at 24 h was higher than the count rate at 4 h, especially two weeks

Table 1

^{99m}Tc-MDP count rate (in units of 10^{-5} pixel^{-1} s^{-1} MBq^{-1}) in 112 vertebrae for 14 patients with normal bone scintigrams (A) and in 107 abnormal vertebrae for 23 patients with skeletal metastases (B) preoperatively (I), two weeks (II), two months (III) and six months (IV) after operation. SD = one standard deviation; range = the 10th–90th percentiles

	A				B			
	I	II	III	IV	I	II	III	IV
4 h after injection								
mean	98.3	98.6	98.1	96.6	235.0	287.8	221.5	178.3
SD	16.1	14.8	17.2	15.0	87.3	123.9	95.1	67.8
median	96.6	97.0	96.0	94.9	209.7	259.9	199.6	171.3
range	79.2–117.6	82.2–117.8	76.3–119.0	76.9–116.5	143.4–352.8	153.0–448.6	123.8–361.2	107.0–273.4
24 h after injection								
mean	83.5	81.6	84.5	82.8	244.1	310.2	229.6	175.8
SD	13.9	14.3	16.0	15.0	96.4	142.2	108.1	74.3
median	79.7	78.0	84.3	81.7	214.0	285.1	206.9	168.4
range	67.9–103.7	66.8–103.6	63.4–104.7	64.7–104.8	141.0–388.4	149.0–503.2	115.9–375.1	92.7–283.6
24 h/4 h ratio								
mean	0.85	0.83	0.86	0.86	1.03	1.07	1.02	0.97
SD	0.09	0.08	0.10	0.10	0.08	0.11	0.11	0.11
median	0.86	0.83	0.85	0.87	1.03	1.05	1.01	0.97
range	0.75–0.97	0.71–0.92	0.77–0.97	0.73–0.99	0.95–1.12	0.94–1.21	0.89–1.16	0.85–1.08

Table 2

^{99m}Tc-MDP count rate (in units of 10^{-5} pixel^{-1} s^{-1} MBq^{-1}) for 23 patients with skeletal metastases in 77 vertebrae considered normal according to one criterion, the count rate at 4 h (C_1), and in 66 vertebrae considered normal according to two criteria, the count rate at 4 h and the 24 h/4 h ratio (C_2), preoperatively (I), two weeks (II), two months (III) and six months (IV) after operation. SD = one standard deviation; range = the 10th–90th percentiles

	C_1				C_2			
	I	II	III	IV	I	II	III	IV
4 h after injection								
mean	106.6	116.4	115.3	110.3	105.6	106.2	106.1	102.0
SD	13.0	35.4	37.6	31.8	13.2	17.4	14.6	15.1
median	106.9	106.7	103.9	101.6	105.6	101.3	103.3	99.8
range	87.3–122.6	89.6–156.8	92.1–136.9	86.8–147.8	86.5–122.6	89.1–130.8	91.3–123.1	85.6–121.0
24 h after injection								
mean	103.1	112.4	109.4	102.8	99.2	100.5	98.4	92.1
SD	17.2	42.4	44.5	42.2	13.8	16.7	17.1	16.3
median	100.6	99.1	98.1	92.9	97.5	95.1	96.5	90.6
range	82.4–122.5	82.7–150.4	82.8–128.1	74.4–135.6	81.8–118.3	82.4–126.4	82.2–117.6	72.7–110.7
24 h/4 h ratio								
mean	0.97	0.96	0.94	0.92	0.94	0.96	0.93	0.90
SD	0.09	0.07	0.08	0.09	0.08	0.04	0.07	0.07
median	0.95	0.95	0.93	0.90	0.95	0.94	0.92	0.90
range	0.89–1.07	0.86–1.04	0.84–1.05	0.82–1.00	0.88–0.99	0.86–1.04	0.84–1.03	0.82–0.99

postoperatively, while a tendency towards lower count rate values was seen six months after operation. The 24 h/4 h ratio was found to 1.03 (median) before operation, and 1.05, 1.01 and 0.97 two weeks, two and six months, respectively, after operation (Table 1). The count rate after 6 months was significantly lower ($p < 0.001$) than the preoperative measurements.

The 'flare phenomenon', with an increase in count rate 2 weeks after operation followed by a decrease 2 and 6 months postoperatively, was seen 24 h as well as 4 h after injection.

As mentioned previously, an abnormal vertebra was defined as having a count rate above $130 \cdot 10^{-5}$ counts pixel^{-1} s^{-1} MBq^{-1}. If an additional criterion, an abnormal 24 h/4 h ratio above 1.03, was used for selecting abnormal vertebrae, eleven of the 77 vertebrae with normal count rate in patients with skeletal metastases would be considered abnormal (Table 2; Fig. 1a and b). When studying these individual vertebrae, 9 of 11 vertebrae passed the level for abnormal count rate at the investigation carried out two weeks postoperatively. Seven vertebrae, from two patients, remained abnormal at 2 and 6 months after operation. These two patients showed a clinical progression of their disease.

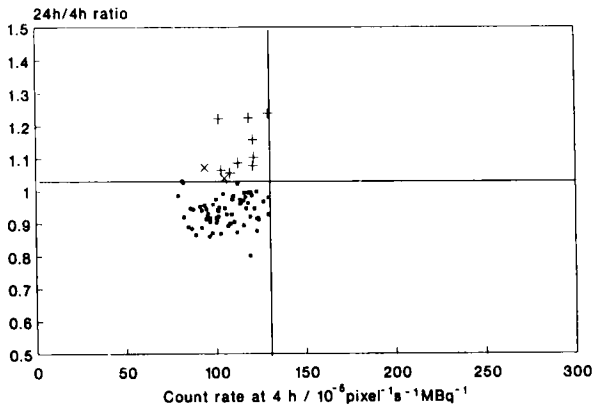
Throughout the study, patients with skeletal metastases showed for their normal vertebrae significantly lower values ($p < 0.001$) in count rate (at 4 h and 24 h) and ratio (24 h/4 h) compared with their abnormal vertebrae and significantly higher values ($p < 0.001$) compared with the vertebrae in patients with normal bone scintigrams. This was found independently using either one or two criteria to define abnormal vertebrae. The largest relative changes in count rate between the different measurements were seen at 24 h.

Background ROI. The count rate in the background ROI at 24 h was lower than 4 h (Table 3). Slightly higher values at 4 h and 24 h were found in patients with skeletal metastases than in patients with normal bone scintigrams.

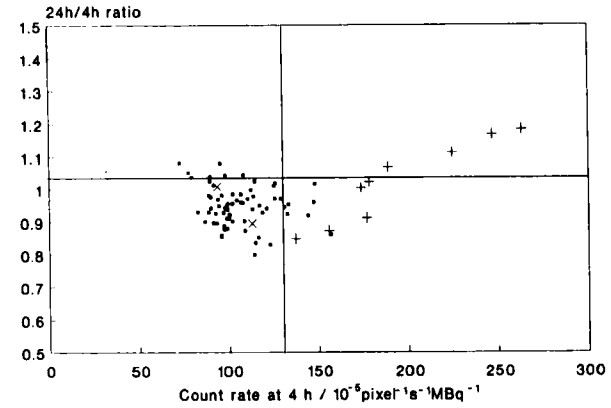
Discussion

The lesion-to-non-lesion count rate ratios at 4 h and 24 h as well as the 24 h/4 h ratios have earlier been studied in individual patients to differentiate between degenerative and metastatic changes, especially in single lesions (4). Over 40% of the patients with prostatic carcinoma may have skeletal metastases at the time of discovery (5). Frequently, the metastases appear first in the lumbar vertebrae and progressively involve the axial skeleton (6). Without quantification of the ^{99m}Tc-MDP uptake it may be difficult to select a normal vertebra as a reference. Therefore, in the present study, the count rate was measured and expressed as a function of the administered activity.

Vertebrae in patients with normal bone scintigrams showed a higher count rate at 4 h than at 24 h. The count rate probably reaches its maximum just after 4 h, as the count rate increased only slightly between 3 h and 4 h as shown in a previous study (1). The 24 h/4 h ratio was found to be 0.85. Thus, approximately 15% of the MDP content has been released from the vertebrae during this



(a)



(b)

Fig. 1. ^{99m}Tc-MDP count rate at 4 h and 24 h/4 h ratio for 77 vertebrae with normal count rate in patients with skeletal metastases a) preoperatively and b) two weeks after operation. Vertebrae with 24 h/4 h ratio above 1.03 in the preoperative investigation and with abnormal (+) and normal (×) count rate respectively, two weeks after operation.

20-h period. No changes in uptake values were seen after orchiectomy. Patients with normal bone scintigrams seem to have an MDP metabolism more like normal subjects, initially appearing to lose disphosphonate from the skeleton more rapidly than those with changed skeletal metabolism (7).

The normal vertebrae in patients with skeletal metastases were found to have higher count rate values at 4 h and 24 h as well as a higher 24 h/4 h ratio than patients with normal bone scintigrams. This is probably due to involvement of metastases that are impossible to detect by using non-quantitative bone scintigrams. This is an important result, which may have implications for the selection of 'normal' areas in quantitative bone scintigraphy. It may also be of interest when studying the metastatic process itself.

In the abnormal vertebrae the flare phenomenon, with an initial increase in count rate after operation followed by a decrease, was seen in reponse to therapy. Six months after operation the count rate was actually below the preoperative level. This was seen both at 4 h and 24 h, with the greatest difference at 24 h. The flare phenomenon was more pronounced at 24 h indicating that this was due to active bone uptake, rather than to ^{99m}Tc-MDP in the vascular phase, as the total fraction of the injected activity remaining in the blood at 24 h is very small (8). Performing bone scintigraphy additionally at 24 h after injection may add clinically useful information helping to distinguish abnormal vertebrae from normal. Most of the vertebrae which were considered to have a normal count rate at 4 h but had an increased 24 h/4 h ratio at the preoperative investigation, were found to have abnormal count rates in the following investigations. Thus, with this additional criterion on the 24 h/4 h ratio, skeletal metastases will be identified more accurately than in the primary investigation.

Table 3

^{99m}Tc-MDP count rate (in units of 10^{-5} pixel^{-1} s^{-1} MBq^{-1}) in the background ROI for 14 patients with normal bone scintigrams (A) and 23 patients with skeletal metastases (B) preoperatively (I), two weeks (II), two months (III) and six months (IV) after operation. SD = one standard deviation; range = the 10th–90th percentiles

	A				B			
	I	II	III	IV	I	II	III	IV
4 h after injection								
mean	16.9	16.7	16.4	15.7	18.1	17.7	17.1	16.3
SD	3.5	2.9	2.9	3.1	4.9	4.7	4.3	4.0
median	16.1	16.4	17.1	16.5	18.9	17.3	17.2	16.3
range	13.1–20.9	12.8–20.0	12.9–19.5	10.7–20.2	12.4–25.5	11.6–24.3	9.8–23.0	11.5–20.2
24 h after injection								
mean	10.5	12.2	11.2	11.1	14.2	16.3	14.4	13.5
SD	2.7	2.6	2.7	2.9	4.2	3.7	3.3	3.8
median	10.2	11.7	11.0	10.7	14.6	15.6	15.6	13.3
range	7.2–15.1	9.7–15.1	7.2–14.0	8.0–15.7	8.3–19.6	11.6–21.7	9.9–18.3	8.7–18.7

During recent yèars there has been a growing interest in the use of the beta-emitting radionuclide strontium-89 (^{89}Sr) in palliation of bone pain associated with prostatic carcinoma (9, 10). At the time of ^{89}Sr therapy, patients also receive a small amount of ^{85}Sr to follow the uptake, distribution and retention of ^{89}Sr. To determine whether painful lesions will accumulate ^{89}Sr or not, ^{99m}Tc-MDP bone scintigrams have been found to be a valuable tool (11). Therefore, quantitative 24-h ^{99m}Tc-MDP bone scintigraphy may be of special importance in estimating absorbed doses to skeletal metastases as well as in evaluating response to ^{89}Sr therapy.

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