

Relationship of uptake of ^{99m}Tc -MIBI in bone metastases to efficiency of strontium-89 therapy in prostate cancer patients

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Abstract

BACKGROUND: Although the pharmacokinetic profiles and clinical efficiency of $^{89}\text{SrCl}_2$ as an agent of choice in extensive metastatic bone disease have been studied widely, the relationship of its efficiency to perfusion of metastases remains unresolved. Hence we aimed to compare the clinical and radiological manifestations of regression of metastatic bone disease in prostate cancer with results of pre-treatment scanning with ^{99m}Tc -MIBI as a blood flow marker.

MATERIALS AND METHODS: Sixteen patients with bone metastatic spread of prostate cancer (on average 9 s.d. 3 bone metastases on ^{99m}Tc -MDP scan) were treated with $^{89}\text{SrCl}_2$ (Metastron, Amersham plc) and studied during post-injection follow-up. In each patient whole-body ^{99m}Tc -MDP (3–4h post-injection of 510 MBq) and ^{99m}Tc -MIBI (10 min post-injection of 510 MBq) scans were performed before injection of 150 MBq of $^{89}\text{SrCl}_2$ and 3 and 6 months after. Mean count ratio (metastasis/normal bone) was calculated for ^{99m}Tc -MDP scans for all metastases. ^{99m}Tc -MIBI uptake was employed as a marker of local neoplastic blood flow in metastases, and quantified in a manner similar to ^{99m}Tc -MDP study as (metastasis/normal bone) pixel count ratio. MRI T1 and T2 scanning were used for anatomic follow-up of metastases.

RESULTS: All patients demonstrated substantial improvement in severity of pain syndrome with full release from pain in ten. The ^{99m}Tc -MDP follow-up revealed a decrease in the number of «hot» metastatic uptake sites from 9 s.d. 3 to 5 s.d. 3 ($p < 0.01$) with a simultaneous decrease of normal bone ratio in remaining hot spots on ^{99m}Tc -MDP scans from 2.79 s.d. 0.45 to 1.83 s.d. 0.18 ($p < 0.05$) after 3 months and further to 1.44 s.d. 0.43 ($p < 0.05$) after 6 months. Metastases with ^{99m}Tc -MIBI pre-treatment (metastasis/background) index over 1.5 and anatomic cross-dimensions below 19 mm demonstrated near-full regression when studied using ^{99m}Tc -MDP and MRI 3 and 6 months after injection of $^{89}\text{SrCl}_2$. A significant correlation was observed between pre-treatment ^{99m}Tc -MIBI (Mts/Bg) ratio and decrease in ^{99m}Tc -MDP metastatic uptake ($r = 0.84$, $p < 0.005$).

CONCLUSION: Metastases with anatomic dimensions smaller than 20 mm and persistent blood supply can be effectively cured with ^{89}Sr . The ^{99m}Tc -MIBI scan of bone metastases is of predictive value for prognosis of success of systemic ^{89}Sr therapy in prostate cancer.

Key words: Strontium-89, bone metastases, ^{99m}Tc -MIBI, therapy, prognosis

Introduction

The last decade has witnessed progredient growth of primarily generalised clinical forms of prostate cancer, so that at the moment of first diagnosis more than 60% of all prostate cancer patients demonstrate distant metastases, mainly to the skeleton (1). Bone metastases, the most frequent pattern of metastatic spread in prostate cancer, usually appear together with persistent pain syndrome, which drastically aggravates the quality of life in the patients and demands either high-dose analgesic treatment with morphine analogues (2) or external irradiation (3). Both chemotherapy and external irradiation are not satisfactorily efficient in cure of bone metastases (3, 4).

A great advancement in the cure of pain syndrome in bone metastatic disease was achieved with the introduction of system-

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ic radiotherapy with $^{89}\text{SrCl}_2$ (5, 6). Once intravenously injected, ^{89}Sr , as metabolic analogue to calcium, is actively extracted from blood by peri-metastatic osteoblastic bone regions and remains there for more than 100 days (7, 8). As ^{89}Sr is a pure β -emitter with $t_{1/2}=50,6$ days, emitting 1.46 MeV electrons, it delivers the radiation dose inside the range of 7–8.5 mm thin perimetastatic area and provides effective local suppression of bone pain (8). Nowadays the main indication for use of $^{89}\text{SrCl}_2$ remains palliation of pain syndrome in extensive metastatic bone spread of prostate cancer (9). It has clearly been shown that suppression of pain manifests in a relatively short time after injection of $^{89}\text{SrCl}_2$ and lasts for 3 months to 1 year (6). Although the pharmacokinetic profiles and clinical efficiency of $^{89}\text{SrCl}_2$ as the agent of choice in extensive metastatic bone disease have been studied widely, the changes in the anatomic structure of metastases in the course of $^{89}\text{SrCl}_2$ therapy are not well known. Some essential pathophysiological mechanisms ensuring the efficiency of $^{89}\text{SrCl}_2$ therapy, in particular, the relationship between blood supply to metastases and regress induced by $^{89}\text{SrCl}_2$, also remain unresolved. Hence in this study we have followed up the condition of bone metastases in prostate cancer patients treated with $^{89}\text{SrCl}_2$ in order to compare the clinical and radiological manifestations of regress of the metastatic bone disease to results of pre-treatment scanning with $^{99\text{m}}\text{Tc-MIBI}$.

Patients and Methods

Patients

This study was a prospective one. Sixteen patients with prostate cancer and documented metastatic spread were referred for the study. The mean age of the patients was 63 ± 7 years. Earlier all these patients had been treated using various combined schemes, all of which comprised total androgen blockade, chemotherapeutic treatment and distant irradiation of painful metastatic regions. In all cases the treatment was appraised as partially or entirely non-effective when evaluated by the group of consultants supervising the Department of General Oncology at the Institute. In all patients the mono- or multifocal pain syndrome was progressively increasing during the months prior to the start of $^{89}\text{SrCl}_2$ therapy. The time span between previous stage of therapy and injection of $^{89}\text{SrCl}_2$ was more than four weeks in all patients, during which time the patients received the analgesics only. In all patients except one the pain syndrome before the start of $^{89}\text{SrCl}_2$ therapy demanded continuous treatment with morphine and morphine analogues, owing to the entirely ineffective conventional analgesic treatment.

$^{89}\text{SrCl}_2$ (Metastron, by Amersham plc, UK, in 10 cases, and « $^{89}\text{SrCl}_2$ solution», by Medradiopreparat, Russia, in 6 cases) was injected intravenously to the patients as a single dose, at activity 150 MBq (4 mCi). The injection was performed via G19 “butterfly” canula with subsequent slow flushing with 20–30 ml of saline. The total androgen blockade, chemotherapy and systemic hypothermia treatment were not discontinued.

The imaging study in patients referred for $^{89}\text{SrCl}_2$ treatment comprised whole body scan with $^{99\text{m}}\text{Tc-MDP}$, $^{99\text{m}}\text{Tc-MIBI}$ and MRI scanning of metastatic $^{99\text{m}}\text{Tc-MDP}$ hot spots before the treatment and $^{99\text{m}}\text{Tc-MDP}$ and MRI scanning 3 and 6 months afterwards.

Whole-body $^{99\text{m}}\text{Tc-MDP}$ scanning

Whole-body $^{99\text{m}}\text{Tc-MDP}$ scanning was performed using single-head large field-of-view gamma-camera Gemini-700 (by Technicare Co., US), linked on-line to a dedicated computer system SCINTI 4.0 (IBM PC compatible, Intel Xeon processor based, by Gelmos Ltd, Russia). The $^{99\text{m}}\text{Tc-MDP}$ whole body bone scanning was performed 3 hours after injection of 570–740 MBq of the agent (“Technefor” kits, by Diamed Ltd, Russia). A group of planar scans covering the whole of the patient’s body, both in anterior and posterior views, was acquired using 128×128 matrix, each 4 min long, with total acquisition of 1400000–1500000 counts/scan. In order to avoid masking of pelvic and low lumbar metastases by bladder activity, the urine was withdrawn via canula 15–20 min before the study.

Bone scanning with $^{99\text{m}}\text{Tc-MIBI}$

$^{99\text{m}}\text{Tc-MIBI}$ (Technetryle, by Diamed Ltd, Moscow, 510 MBq) was injected via 19 G butterfly canula into the vein of the hand and flushed with 15–20 ml of saline. Static images of metastatic regions were acquired almost immediately, 4–5 min after injection, i.e. over a time interval shorter than the mean transit time of $^{99\text{m}}\text{Tc-MIBI}$ over the biliary tree, for 5 min each using 128×128 matrix, with acquisition of up to 500000 counts/frame. A Gemini 700 SPECT LFOV (Technicare Co., Ohio) gamma-camera together with a SCINTI 4.0 (Gelmos Ltd, Moscow) computer system were employed for all these studies.

MRI studies

Magnetic resonance tomographic study was performed using low-field system Magnetom Open (by Siemens Medical). Multiple 6 mm thin slices of metastatic areas, primarily detected on $^{99\text{m}}\text{Tc-MDP}$ scans were obtained in T1 (TR=600 ms, TE=15 ms) and T2 (TR=4000 ms, TE=117 ms) modes.

Analysis

Both nuclear medicine and MRI studies were first reported qualitatively, by two doctors not aware of clinical data, who provided descriptions of the scans independently, pointing out the number of hot spots on the $^{99\text{m}}\text{Tc-MDP}$ planar scintigram or abnormal intraosseous nodes on the MRI multislice scan. In each case the dimensions of bone metastases were measured using planimetric programs included in the standard software of the scintigraphic systems. For every metastasis, both for $^{99\text{m}}\text{Tc-MDP}$ and $^{99\text{m}}\text{Tc-MIBI}$ studies, the uptake index (metastasis/intact bone) was calculated as a ratio of the average count rates in the metastatic region to the contralateral or — in the case of spinal metastases or bilateral metastatic involvement — to the adjacent proximal equiareal bone region. In bone MRI scans the metastases were analysed in a cognate manner with calculation of geometric dimensions of each one and also of the ratios of average T1 signals (metastasis/intact bone). For final quantitative analysis only the data from the metastases not superimposed with liver, gallbladder, myocardium, and urinary bladder were used. A typical case of an analysis of $^{99\text{m}}\text{Tc-MIBI}$ scan is shown in Figure 1.

Statistics

Evaluation of the significance of differences during the follow-up was carried out using Student’s paired t-criterion. Correlation between variables employed in the study was quantified using linear correlation analysis.

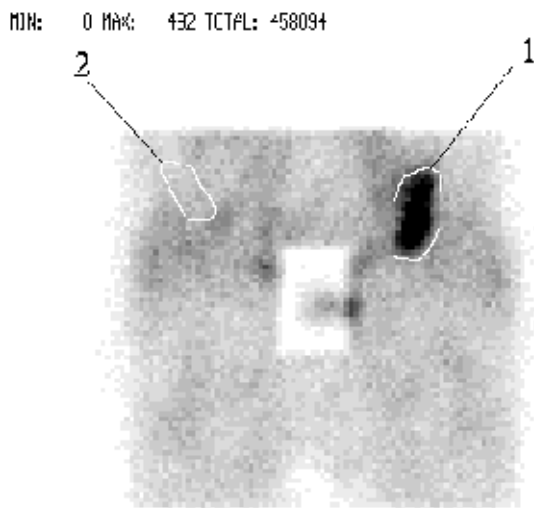


Figure 1A. Typical drawing of regions of interest over metastatic hot spot of ^{99m}Tc -MIBI uptake in left iliac bone (1) and contralateral normal region (2).

MIN: 0 MAX: 659 TOTAL: 508538

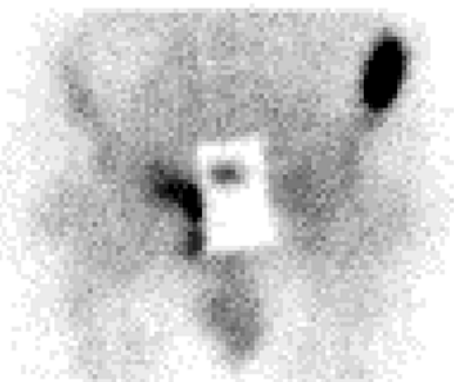


Figure 1B. ^{99m}Tc -MDP scan of pelvic bones in the same patient. On the upper margin of the scans the minimum and maximum counts per pixel and also the total count per scan are shown. Bladder activity is partially covered with lead shield.

The local Medical Ethics committee approved the study and after presentation of an extensive information leaflet about the peculiarities of the $^{89}\text{SrCl}_2$ treatment as well as about the research techniques employed in the study a written informed consent was obtained from every one of the patients referred for the study.

Results

In all the patients of the group referred for the study multiple bone metastases (in average 9, s.d. 6, metastases) were revealed in first study, performed before injection of $^{89}\text{SrCl}_2$. The metastases were detected by ^{99m}Tc -MDP whole body scanning with efficiency equal to MRI and only one metastatic lesion (in the spine, located in Th12) was not revealed by this modality. Before $^{89}\text{SrCl}_2$ injection the bone metastases were seen as typical isolated sin-

gle or multiple confluent spots of increased ^{99m}Tc -MDP uptake on bone scans with simultaneous shape as low T1-signal area in the corresponding MRI-scan. Multiple metastatic invasion of pelvic bones was imaged as relatively even, prominent increase of ^{99m}Tc -MDP uptake close to superscan picture (Figure 2a), whereas MRI scan gave evidence of the multiple character of pathological hotbeds in the bones (Figure 2c).

Three months after injection of $^{89}\text{SrCl}_2$ in 8 patients with multiple bone metastases a prominent reduction of the number of hot spots in bone was obvious on ^{99m}Tc -MDP scans, down to an average of 5, s.d. 3. In 6 patients with an initially small number of metastatic "hot spots" (< 5), after 3 months we observed prominent regression approaching entire disappearance (Figure 3a, b), and that pattern remained unchanged in the 6-month post- $^{89}\text{SrCl}_2$ injection scan. In 2 patients in whom the ^{99m}Tc -MDP bone scan before $^{89}\text{SrCl}_2$ injection demonstrated superscan-like confluence of multiple pelvic metastases into a continuum of increased ^{99m}Tc -MDP bone uptake, 3 months later a tendency to form separate hot spots instead of "superscan" was obvious (Figure 2b). In total, 6 months after injection of $^{89}\text{SrCl}_2$ in 6 patients a near to full regression of bone metastases was achieved, whereas in eight it was partial and in two the metastatic process was only stabilised.

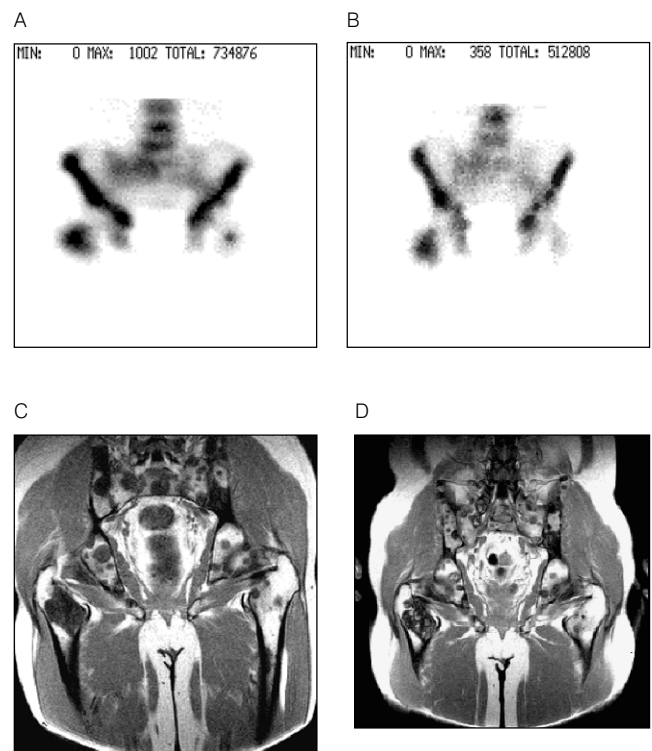


Figure 2. (A, B) ^{99m}Tc -MDP bone scans in a patient with massive multiple metastatic invasion of pelvic bones before (A) and 3 months after (B) $^{89}\text{SrCl}_2$ injection. Decrease of ^{99m}Tc -MDP uptake can be seen. On the upper margin of the scans the minimum and maximum counts per pixel and the total count per scan are shown. (C, D) T1-weighted MRI scans in the same patient before (C) and after (D) the treatment. Multiple areas of replacement of metastatic tissue with T1-intense "islands" — compare C and D.

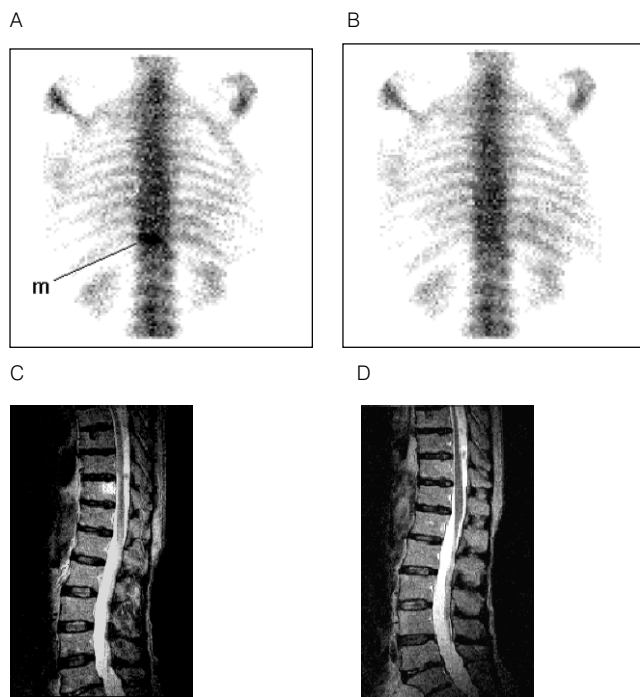


Figure 3. ^{99m}Tc-MDP in a patient with a painful single spinal metastasis (Th11) before (A) and 3 months after (B) ⁸⁹SrCl₂ treatment. T2-weighted MRI scans before (C) and 3 months after ⁸⁹SrCl₂ treatment (D) demonstrate disappearance of viable metastasis.

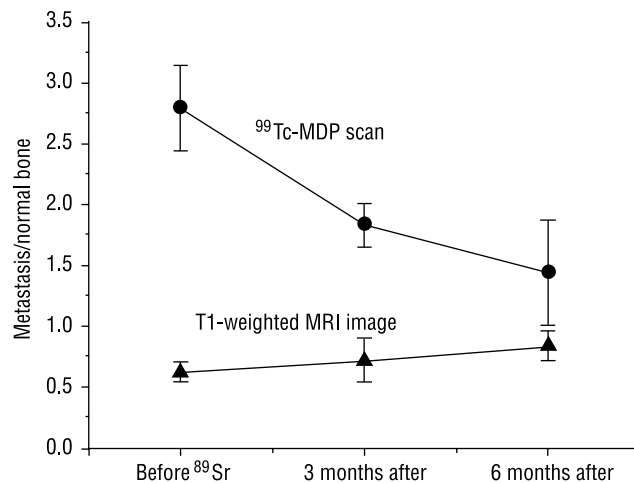


Figure 4. Dynamics of (metastasis/normal bone) indices in patients with disseminated prostate cancer treated with ⁸⁹SrCl₂. Systemic intravenous radiotherapy in the course of follow-up. For ^{99m}Tc-MDP and T1-weighted MRI scans the (metastasis/normal bone) indices were calculated as a ratio of mean signals over relative regions of interest.

Both 3 and 6 months after injection of ⁸⁹SrCl₂ in remaining pathological foci a tendency of progressive decrease of ^{99m}Tc-MDP uptake and growing intensity of T1-signal was demonstrated (Figure 4). MRI images showed this as the appearance of small foci with T1-signal close to normal in central and peripheral areas of metastases because of neoosteogenesis in sites of irreversibly damaged tumour tissue (Figure 2d). T2 images demonstrated this regression of metastases as the disappearance of T2-intensive

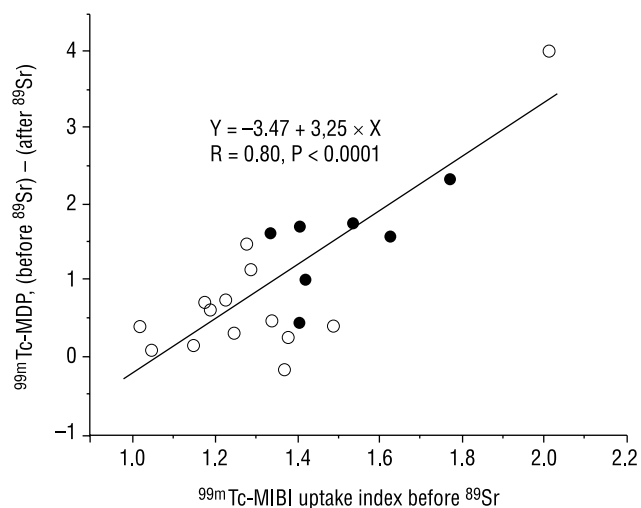


Figure 5. Correlation between pre-treatment value of ^{99m}Tc-MIBI (metastasis/normal bone) accumulation index and decrease in ^{99m}Tc-MDP metastatic uptake index induced by ⁸⁹SrCl₂ therapy in 3 months after injection. Metastases with full anatomic regression observed on T1-weighted spin-echo MRI scans are represented by solid points. All these metastases with full regression were smaller than 20 mm in cross-dimension.

intraosseous pathological foci (Figure 3c, d). Nevertheless in the 6th post-injection month we did not observe any case of disappearance of any metastasis that was seen 3 months after injection of ⁸⁹SrCl₂.

A significant correlation was observed between the pre-treatment ^{99m}Tc-MIBI (metastasis/intact bone) ratio and the decrease in the ^{99m}Tc-MDP metastatic uptake (Figure 5). Metastases with ^{99m}Tc-MIBI pre-treatment (metastasis/intact bone) index over 1.5 and anatomic cross-dimensions below 19 mm demonstrated near-full regression when studied using ^{99m}Tc-MDP and MRI 3 and 6 months after injection of ⁸⁹SrCl₂ (Figure 5).

Evaluation of quantitative changes in the clinical details of disease, in particular of pain syndrome, in our patients in the course of ⁸⁹SrCl₂ treatment and their relations to personal scintigraphic and MRI characteristics were not the particular aim of the study. Moreover, a correct evaluation of pain syndrome before the treatment in terms of the Karnofsky scale or the use of any quantitative pain scale was not always possible as the patients had been sent for the treatment to the Institute of Oncology from various hospitals of West Siberia, with non-uniform type of evaluation of patient's condition at admittance. Nevertheless, we can state that in all patients the drastic decrease in pain syndrome over 3 weeks after injection of ⁸⁹SrCl₂ was obvious, with full withdrawal of morphine analgesics in all. In 14 out of 18 patients the pain syndrome disappeared almost entirely, whereas 4 remained on low-dose diclofenac treatment. A detailed study of relationships between the effectiveness of suppression of pain syndrome and the imaging characteristics of the metastases in ⁸⁹SrCl₂ systemic radiotherapy is now in progress.

Discussion

⁸⁹Sr is a pure β -emitter (10), and also a close metabolic analogue of Ca⁺⁺ (11). This determines its unique ability for high accumulation in peripheral areas of osteoblastic bone metastases, with suppression of osteoblastic reaction of surrounding bone, reducing

involvement of periosteum and, therefore, curing the pain (5, 6, 12). This effect is of the greatest importance for the provision of acceptable quality of life in patients with disseminated prostate cancer, as it is the bone pain syndrome that creates main daily social problems for these patients. Because of this feature the $^{89}\text{SrCl}_2$ therapy has been widely accepted as the treatment of choice in the control of pain syndrome in cases of multiple disseminated bone metastases (13). Nevertheless, the metastatic disease has not been studied regularly using facilities of nuclear medicine and MRI.

Data presented in this study give evidence for significant changes which occur not only in peripheral, but also in central regions of metastases when using a single injection of 4 mCi of $^{89}\text{SrCl}_2$ (Figure 2, 3). Even distribution of $^{89}\text{SrCl}_2$ around the metastasis provides delivery of radiation doses mainly inside the range of the 4–5 mm wide osteoblastic region encompassing the metastatic focus (8). Due to the operation of this mechanism more than half of the volume of osteoblastic bone metastasis, smaller than 15–17 mm turns out to be inside the zone of irradiation action of ^{89}Sr . 1.4 MeV β -particles. Some small bone metastases, 8–9 mm in cross-diameter, have demonstrated full regression and disappeared, being substituted by normal bone tissue (Figure 3). In other words, $^{89}\text{SrCl}_2$ causes damage and cell death deep inside the bone metastases, with later substitution of neurotic foci with normal bone tissue. Bearing this fact in mind, the use of doses of $^{89}\text{SrCl}_2$ higher than presently invariably employed 4 mCi could be thought of in terms of increasing the radiotherapeutic effect of $^{89}\text{SrCl}_2$ in patients with multiple metastases.

Blood supply to metastasis entirely depends on the vascularity of the surrounding osteoblastic zone (14). Earlier it was shown that extraction and long-term retention of $^{89}\text{SrCl}_2$ in highly perfused regions of osteoblastic metastases is significantly higher than in normal bone (11, 12). Our data show that decrease of metastatic uptake of $^{99\text{m}}\text{Tc-MDP}$ correlates with pre-treatment $^{99\text{m}}\text{Tc-MIBI}$ uptake (Figure 5). This fact could possibly be explained by a suggestion that $^{99\text{m}}\text{Tc-MIBI}$ uptake in metastases reflects the blood supply to metastases.

It has been shown widely, that $^{99\text{m}}\text{Tc-MIBI}$ behaviour in myocardium (15), breast cancer, (16, 17), lung tumors (18), bone and soft tissue tumors (19) demonstrates a high initial extraction and no significant redistribution. This sort of uptake kinetics, designated as "chemical microspheres", is typical for blood flow markers (20). Myocardial uptake of $^{99\text{m}}\text{Tc-MIBI}$ depends almost entirely on blood flow (21). Data of $^{99\text{m}}\text{Tc-MIBI}$ kinetics in bone tumors, typically demonstrating high initial uptake to neoplastic tissue and rapid blood clearance, can be employed for quantification of tumor blood flow, both in animal experiments (22) and in clinics (23). The high uptake of $^{99\text{m}}\text{Tc-MIBI}$ to tumors is based on several pathophysiological mechanisms, comprising high vascularity (24), increased permeability of blood-tissue barrier in tumor (25), and also intracellular mitochondrial retention (26) of the agent. All these components of tumoral retention of $^{99\text{m}}\text{Tc-MIBI}$ entail high first-pass extraction and persistent retention of the radiopharmaceutical, behaving like "chemical microspheres", i.e. reflecting local blood supply. Bearing this in mind, we can suggest that the uptake of $^{99\text{m}}\text{Tc-MIBI}$ to bone metastases probably represents the blood flow delivery to the viable tumor tissue there. The correlation between pre-treatment value of $^{99\text{m}}\text{Tc-MIBI}$ uptake index and decrease in $^{99\text{m}}\text{Tc-MDP}$ uptake, induced by $^{89}\text{SrCl}_2$ can be interpreted as a se-

quel of better delivery of $^{89}\text{SrCl}_2$ radioactivity to better-perfused metastases. Metastases with significant decrease in $^{99\text{m}}\text{Tc-MDP}$ also demonstrated beneficial changes in MRI image of the pathology (Figure 2). Thus, it is probable that perfusion-dependent accumulation of $^{89}\text{SrCl}_2$ in the area induces damage to the microvascular net, followed by a decrease in the blood supply below the range ensuring viability of the tumour cells and by irreversible lesion of the metastasis, in its entire volume, or partially. This could be proved directly in a positron-emission tomography study of the volume of viable neoplastic tissue in the metastases in the course of $^{89}\text{SrCl}_2$ treatment with ^{18}F -fluorodeoxyglucose, as this agent is highly sensitive in detection of viable tumor tissue, both in primary neoplasm and metastases (27). Also PET could provide a quantification of blood flow supply to metastases and validate the perfusion-dependent pattern of accumulation of $^{99\text{m}}\text{Tc-MIBI}$ in osteoblastic metastases.

Nevertheless the data obtained in our study give evidence that the effect of $^{89}\text{SrCl}_2$ treatment in metastatic bone disease is not limited to symptomatic suppression of pain syndrome. $^{89}\text{SrCl}_2$ as a radiopharmaceutical with local β -radiation effect on metastases delivers a certain therapeutic effect, up to full regression of metastases smaller than 20 mm. Further, this therapeutic effect is more prominent in osteoblastic metastases with preserved increased blood supply.

Thus, it looks rational to suggest the use of $^{89}\text{SrCl}_2$ in every prostate cancer patient with metastatic bone involvement, even when still pain-free, not as a substitute for, but rather as an addition to, total androgen blockade and other methods. Obviously, $^{89}\text{SrCl}_2$ therapy can not act upon biologic features of primary prostatic tumor and is effective only in metastatic bone disease. Now we are performing a prospective study in order to determine to which degree the early use of $^{89}\text{SrCl}_2$ as an addition to convenient therapy improves the prognosis in pain-free prostate cancer patients with distant bone metastases.

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