EFFECTS OF RADIATION THERAPY ON BONE LESIONS AS MEASURED BY ^{47}Ca AND ^{85}Sr LOCAL KINETICS

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The presence of osseous metastases may be detected by the use of bone scan as a result of the increased deposition of bone-seeking radionuclides in those areas (*1,2*). Little is known, however, about the local kinetics of these nuclides in the diseased portions of the skeleton following radiation therapy of these bone metastases.

Several investigators have described changes in the uptake of ^{85}Sr or ^{47}Ca by bone metastases after therapy. Both increased and decreased uptake have been reported (*3–6*). However, most of the reported findings were not based on multiple serial observations obtained at short intervals but were rather limited to single sets of measurements taken before and again at long intervals after treatment.

The purpose of this study is to investigate by means of sequential quantitative measurements the patterns of deposition and loss of ^{47}Ca and ^{85}Sr resulting from irradiation of tumor-involved bone. The HEG quantitative computerized scanning system was employed for these studies (*7*). It is also its purpose to explore the feasibility of using these measurements as a method to evaluate the radiation response of tumors in bone.

MATERIALS AND METHODS

Our study was carried out on eight females with metastatic breast cancer and one with primary reticulum cell sarcoma of bone. Their ages ranged from 45 to 73 years.

Of the eight breast cancer patients, six had destructive lesions in the spine with partial collapse of vertebral bodies, one had an osteolytic lesion in the ischium, and one had mixed osteolytic and osteoblastic metastases in the upper femur. The patient with reticulum cell sarcoma presented with diffuse mottled areas of radiolucency involving the lower femur associated with slight periosteal reaction and marked soft tissue swelling. All patients had pain in the involved areas requiring radiation therapy. None of the patients were receiving hormonal or nonhormonal chemotherapy when selected for this study.* The study was terminated if and when the patient was placed on systemic treatment for her cancer since such treatment might affect the interpretation of the results of radiation therapy.

Before irradiation, baseline radiographic studies of the bones were obtained. A single dose of ^{85}Sr of approximately 100 μCi was given intravenously for the purpose of labeling the skeleton usually 14 days before the onset of radiation therapy. Approximately 1 week later, the first 50 μCi tracer dose of ^{47}Ca was given. This schedule could not always be followed because clinical problems sometimes required an early initiation of treatment. Daily determinations of the total body retention and of the uptake measured over diseased and normal bones were carried out for both these radionuclides for at least 1 week before the onset of treatment. The techniques of these measurements have been described in detail previously (*7,8*). Patients with metastatic bone lesions from mammary carcinoma received a tumor dose of 2,500–3,000 rads, delivered in 2–3 weeks, with the majority receiving 2,500 rads to the metastatic lesion in 2 weeks. Either ^{60}Co gamma rays (telecobalt) or 6-MeV x-rays produced by a linear accelerator were used for treatment. The spine was usually treated through a single posterior field, averaging 15 × 8 cm in size. The femur (upper third) was treated through anterior and posterior opposing fields measuring 19 × 13 cm and the ischium was treated with anterior and posterior opposing fields measuring 15 × 15 cm. The patient with primary reticulum

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* Three patients who had undergone hypophysectomy several months previously were on maintenance replacement of cortisone and thyroid preparations in physiologic doses.

cell sarcoma involving the left femur was given 4,000 rads in 4 weeks using ^{60}Co and anterior and posterior opposing fields measuring 38 × 11 cm.

Strontium-85 total body retention, as well as uptake over the diseased bone and a number of normal bony landmarks, were followed at weekly, monthly, and up to 2-month intervals after completion of the radiation therapy. Calcium-47 tracer doses were administered repeatedly at intervals of 1–4 months after completion of radiation therapy, with occasional earlier times. Each time both the total body retention and local uptake measurements were carried out daily for 7–14 days. Local uptake measurements were expressed as percent of the administered dose. The latter was calculated on the basis of an aliquot of the injected solution counted in a standardized geometry.

The total body retention was also expressed as percent of the total administered dose. The latter however was measured by total body counting 1 hr after injection of the radionuclide and before any excretion had taken place.

The percent standard deviation on all data points on graphs labeled percent of injected dose is no greater than 4%. Most are less than 3% with the exception of the last two ^{85}Sr measurements on patient SW. For the normal bone at 316 days post-injection, it is 6%, whereas at 373 days it rose to 11% and for the lesion it was 5%. Similarly, the percent standard deviation for data points on the retained dose graphs are no greater than 4% for both ^{47}Ca and ^{85}Sr except for the last two ^{85}Sr values on SW. They are in the range of 7–13%. These last values were determined using the fractional variance of a quotient, i.e., the square of the standard deviation of the numerator divided by the numerator squared plus the square of the standard deviation of the denominator divided by the denominator squared.

Radiographic studies of bones were usually obtained at 1–2-month intervals to determine changes following radiation therapy. Clinical symptoms such as pain and incapacitation were also followed closely.

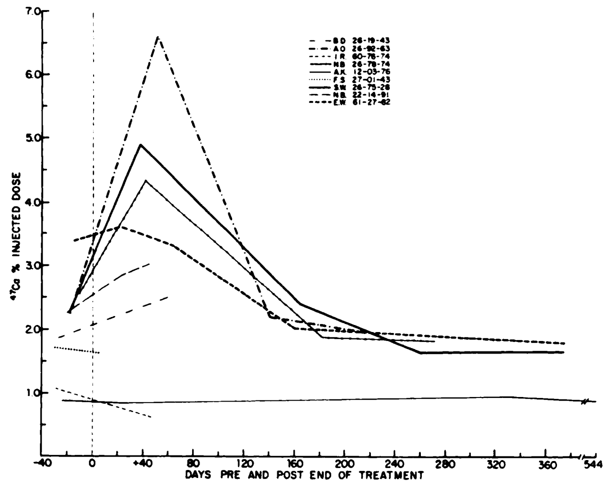

FIG. 1. Serial maximum uptakes relative to administered dose of ^{47}Ca measured over bone lesions before radiation therapy and at intervals thereafter.

RESULTS

Clinical course. Seven patients with metastatic breast cancer had reduction in pain and improvement of mobilization shortly following radiation therapy. The relief of pain continued and lasted either to the time of death, 1–6 months after treatment or for those with longer followup periods lasted about 9 months when pain recurred and a second course of radiation therapy was required. One did not experience much symptomatic improvement and she subsequently developed other metastases and died about 3 months later.

The patient with reticulum cell sarcoma involving the femur experienced a decrease in pain and the soft tissue swelling improved but she died of dissemination of her disease 4 months later after completion of radiation therapy to the involved femur.

Radiographic findings. All the patients who received radiation therapy for metastatic mammary carcinoma showed signs of recalcification of the lytic lesions about 3–6 weeks after completion of the treatment. Recalcification reached its maximum about 2 months later and then no further change in the appearance of the bone was observed for several months.

The patient with reticulum cell sarcoma showed only minimal evidence of radiographic improvement in bone after receiving 4,000 rads in 4 weeks, although there was marked reduction of soft tissue swelling and considerable relief of pain.

Uptake and retention of ^{47}Ca. Figure 1 summarizes the general trend in ^{47}Ca uptake over the bone lesions in relation to radiation therapy. Excluding one patient who became too ill to undergo bone uptake measurements shortly after the onset of treatment and another whose ischial lesion was technically difficult to scan, all patients with breast carcinoma metastatic in bone showed a rise in the uptake of this radionuclide within 30 to 60 days following completion of therapy. The magnitude of this rise was variable and in one patient a three-fold rise was noted. The patient with reticulum cell sarcoma, however, showed a decrease in uptake in spite of the previously noted clinical improvement.

The local ^{47}Ca kinetics in cancer-involved bone and in normal bone were compared by daily counting after each of the serial injections. The comparison in one patient is shown in Fig. 2. It is clear that the dynamics are different in these two bony areas. Prior to radiation therapy the diseased bone showed high ^{47}Ca uptake with sometimes rising values on successive days. Serial injections of ^{47}Ca after radiation therapy showed a sharp overall and daily rise in uptake in the lesion areas 1–2 months following therapy. The uptake then fell toward its original value or in some instances below it in 4–9 months after therapy but never reached the baseline value of the normal bone.

Uptake and retention of ^{85}Sr. Bones prelabeled with ^{85}Sr were measured periodically and the results of a representative case are illustrated in Fig. 3. The

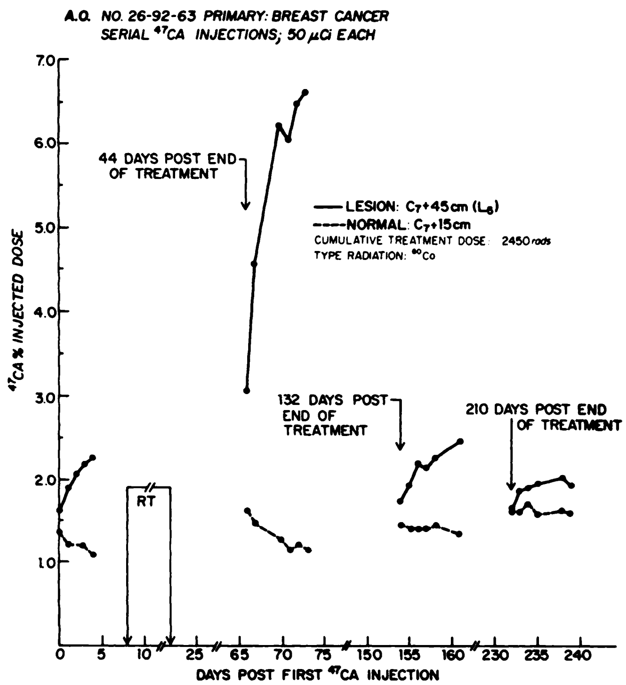

FIG. 2. Calcium-47 uptakes over bone lesions and comparable normal bone (patient AO) measured serially for 1-week periods before and at intervals after radiation therapy.

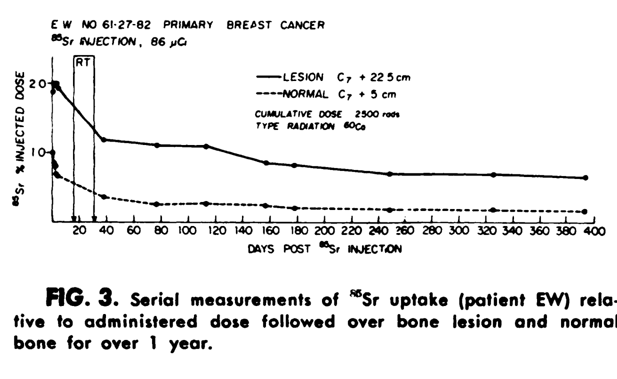

FIG. 3. Serial measurements of ^{85}Sr uptake (patient EW) relative to administered dose followed over bone lesion and normal bone for over 1 year.

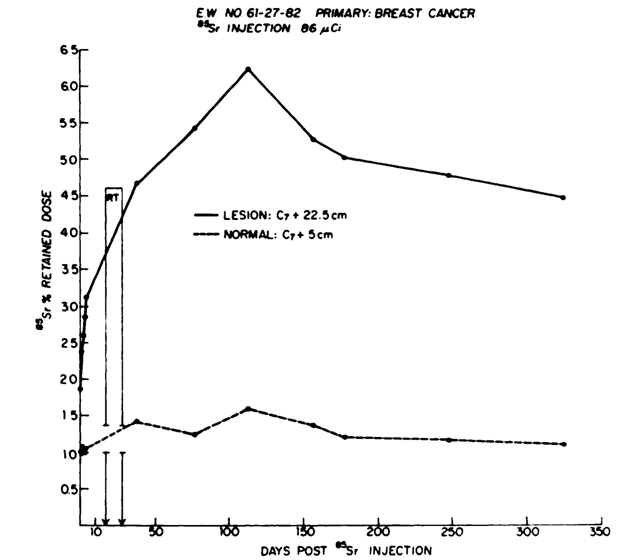

FIG. 4. Serial determination of ^{85}Sr uptake relative to total body retention over bone lesion and normal bone (patient EW).

procedure was similar to that employed in a study of the effect of radiation on bone metabolism in dogs (9). The metastatic lesions showed an abnormally high uptake. The initial rapid loss is interpreted as deriving from a readily exchangeable portion of bone mineral from where it moves into the extracellular fluid and is excreted. Both the normal and metastatic lesions lost ^{85}Sr gradually after this initial rapid fall, but the irradiated metastases maintained a higher level of this radionuclide than the normal bones throughout the followup period of up to 1 year.

The distribution of ^{85}Sr in the bone relative to the total body retention was determined by measuring the latter and plotting the bone uptake as percent of dose retained in the body (Fig. 4). It appears that the dose retained in normal bone relative to the whole body is about constant. This is consistent with the fact that the skeleton is the major reservoir of strontium in the body. On the other hand, the rising retention in the lesion indicates that the net amount of ^{85}Sr deposited there is removed at a much slower rate than from the normal bone and, therefore, relatively to a diminishing total body (or skeletal) retention, the retention in these lesions increases. This net amount is deposited either initially or both initially and through recirculation of ^{85}Sr previously deposited in other bones. This rapidly rising relative retention peaks at 82 days and then falls steadily to the last measurement at 294 days after the end of treatment.

In another patient it was observed that there was a relative rise in lesion retention during and following radiotherapy, followed by a fall during three consecutive measurements from 21 to 92 days

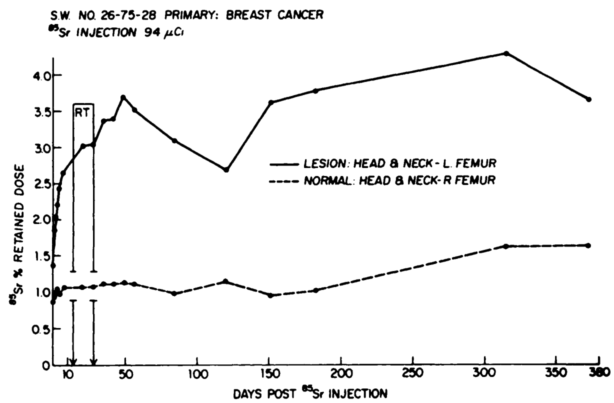

FIG. 5. Serial determinations of ^{85}Sr uptake relative to total body retention over bone lesion and normal bone (patient SW).

postradiotherapy and then a rise again (Fig. 5). If this is an effect of radiotherapy, it may mean that during this period of relatively decreasing retention the ^{85}Sr was mobilized from the lesion and excreted at a greater rate than from the rest of the skeleton. Then the retention stabilized and while the gradual loss from the rest of the skeleton continued, the relative retention in the irradiated metastatic bone increased again. Two hundred eighty-eight days after the end of therapy the lesion curve started on its second fall. The interpretation of such changes in a single case is unclear although they follow some of the patterns of the previous ones.

An interesting observation in this same patient was the relative rise in ^{85}Sr retention in the contralateral control bone for the last two measurements. At about that time pain had developed in that area. Subsequent radiographic study revealed the presence of a metastatic lesion and radiotherapy was given for palliation.

DISCUSSION

Normal bones undergo constant and balanced remodeling in normal adults. When bone is involved by a malignant lesion there is an increased activity of osteoblasts in the proximity of the lesion in an attempt to deposit new bone and an increase in surface exchange of bone mineral. However, the malignant process causes more bone destruction than new bone formation resulting in an osteolytic lesion.

Our study with serial injections of ^{47}Ca showed a temporary increase in the already elevated deposition of this radionuclide in tumor-involved bone during the first 2 months following radiotherapy. A relative increase of ^{85}Sr retention reflecting an increased retention of bone mineral for up to 1 year after radiation therapy was also observed. These two processes lead to a recalcification of previously destructive bone lesions. The increased mineralization may be due in part to proliferation of bone tissue into the areas in which the invading tumor was destroyed by the treatment. As noted in the introduction, some reports in the literature have shown decreased uptakes of bone-seeking radionuclides several months after radiation therapy. These measurements may have missed the period of sharp increase in uptake 1–2 months after treatment.

Pain relief usually occurred fairly promptly after radiotherapy although the mechanism for this improvement is not fully understood. After 1–2 months pain relief was usually maximal and some recalcification of the osteolytic lesion was visible. At this time, the uptake and retention of ^{85}Sr and ^{47}Ca were at their highest levels.

The time of occurrence and the degree of these changes may depend on the type of tumor, the extent of the involvement, the radiation dose, and its fractionation and protraction. Through further studies, it may become possible to establish whether a return to normal local kinetic states of ^{47}Ca and ^{85}Sr in bone lesions is compatible with a longer and more effective control of the malignant process.

SUMMARY AND CONCLUSIONS

A study was carried out to investigate the sequential changes of uptake and retention of ^{47}Ca and ^{85}Sr after radiation therapy of malignant bone lesions and to correlate these changes with clinical symptoms and roentgenographic findings. Eight patients with bone metastases from breast carcinoma and one patient with primary reticulum cell sarcoma of the bone were studied. Calcium-47 given prior to radiotherapy and at intervals of 1–4 months afterward served to measure the changes in uptake of mineral by bone over a 1-year period. A single dose of ^{85}Sr given prior to therapy as a labeling dose to the skeleton was measured at similar intervals as an index of the rate of loss of mineral bone.

The majority of patients exhibited a rise in ^{47}Ca uptake by tumor-involved bone 1–2 months after radiation therapy, followed by a gradual fall. A relative increase of ^{85}Sr retention in the irradiated bone was observed and these two processes of increased uptake and higher retention of minerals lead to a recalcification of previously destructive lesions. Practically all the patients experienced a relief of pain and showed radiographic evidence of recalcification.

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