CORRELATION OF NEOPLASMS WITH INCIDENCE AND LOCALIZATION OF SKELETAL METASTASES: AN ANALYSIS OF 1,355 DIPHOSPHONATE BONE SCANS

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A total of 1,355 patients from clinical trials with the ^{99m}Tc-labeled bone agent, Osteoscan® (^{99m}Tc-Sn·EHDP), has shown a higher incidence of skeletal abnormalities than previously reported. Overall in this study, 60% of bone scans were abnormal in patients with nonosseous neoplasms. Carcinoma of breast, lung, and prostate yielded 67%, 64%, and 62% skeletal involvement, respectively. Over 50% of all the skeletal abnormalities for the neoplastic indications were detected in the thorax and vertebra while the skull, pelvis, and extremities accounted for 22%, 38%, and 34%, respectively.

Detection of metastatic disease by bone scintigraphy is presently experiencing a rapid growth in nuclear medicine. Initially bone scintigraphy was limited to ^{85}Sr and it was soon followed by a rapid succession of isotopes, of which ^{87m}Sr and ^{18}F were most prominent until the introduction of ^{99m}Tc-polyphosphate by Subramanian in 1971 (*1*). The increased utilization of the bone scan for the management of patients with malignant metastatic neoplasms and osseous disorders can be credited to the widespread availability of the ^{99m}Tc phosphorus-based skeletal-imaging agents.

Each successive radionuclide bone agent not only had a higher sensitivity for the detection of skeletal metastases than roentgenography (*2,3*) but also enabled the procedure to be completed more rapidly and yielded higher quality scintigrams. In this report, the incidence and location of metastatic skeletal involvement, as derived from clinical trials with ^{99m}Tc-labeled distannous ethane-1-hydroxy-1,1-diphosphonate (^{99m}Tc-Sn·EHDP) bone agent, are presented and compared to previous studies of osseous metastatic disease detection for the most common forms of neoplasms.

MATERIALS AND METHODS

A group of 1,891 patients from 16 medical institutions was scanned during the clinical trials of the ^{99m}Tc-Sn·EHDP skeletal-imaging agent, Osteoscan®. Since the clinical study was not limited to a specific stage of the patient's disease, this study can be considered a cross section of patients referred for a bone scan in nuclear medicine departments participating in the trial and not selected patients.

Following preparation of the bone agent according to the package insert, each patient was administered 10–15 mCi of ^{99m}Tc-Sn·EHDP. All patients were scanned at an average of 3.5 hr after administration of the bone agent. The clinical protocol included information on the patient's age and sex, informed consent, clinical indication, dose, clinical usefulness, and whether or not the scintigram was normal or abnormal. If the scan was interpreted as abnormal, the physician was requested to indicate areas of increased uptake on a skeletal model and to document any known reason for increased uptake other than skeletal abnormalities, for example, urine bags, injection site, etc. Areas denoted as equivocal by the clinicians were recorded as normal for all tabulations. For purposes of tabulation, skeletal uptake was differentiated as to skull, vertebra, thorax (ribs, sternum, scapula, shoulders), limbs, and pelvic area. The limbs are defined as one or more extremities. In tabulating the distribution of skeletal involvement to specific areas, the reported values represent uptake irrespective of the number of abnormal sites in that area. In many of the scintigrams, arthritic patterns of increased joint uptake were visualized but were not included in the tabulation. All

Received March 7, 1975; revision accepted June 1, 1975.

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TABLE 1. INCIDENCE OF SKELETAL ABNORMALITIES DETECTED WITH ^{99m}Tc-Sn·EHDP IN NONOSSEOUS NEOPLASMS

	Number of patients	Percentage
Total indications	1,355	
Abnormal	817	60
Normal	538	40

TABLE 2. PERCENT ABNORMAL SCINTIGRAMS DETECTED WITH ^{99m}Tc-Sn·EHDP FOR NONOSSEOUS MALIGNANT NEOPLASMS

Bone scan indication	Total	Abnormal	Percent
Breast	368	247	67
Lung	230	147	64
Prostate	191	119	62
Hodgkin's	58	29	50
Lymphoma	42	16	38
Cervix	41	23	56
Rhabdomyosarcoma	39	22	56
Colon	37	21	57
Kidney	35	21	60
Bladder	35	15	43
Melanoma	30	17	57
Rectum	23	14	61
Thyroid	14	6	43
Total	1,143	697	61
All others	212	120	57

data are based on the findings of the clinical investigators.

The case report forms completed by the investigators were designed to maximize use of our computer data-processing facilities. Data from the case reports were coded for storage and retrieval. An information retrieval program was used to tabulate and correlate the coded data with our IBM 376/168 computer.

RESULTS

Of the total 1,891 patients in the clinical trial, 1,355 patients were scanned for evaluation of metastatic involvement from nonosseous primary malignant neoplasm. The remaining indications (536/1,891) for bone scan were associated with both primary bone neoplasms and nonmalignant diseases and were excluded from this paper. The percentage of abnormal scans for all 1,355 patients with nonosseous primary malignant neoplasms, irrespective of the indication, was 60% (Table 1).

In order to obtain a more meaningful correlation of the incidence of skeletal metastases with the primary site, only reported primary neoplasms in 20 or more patients, with the exception of thyroid, are included under the primary indication in Table 2. Other types of primary neoplasms are tabulated under the classification "all others." Carcinoma of the breast, lung, and prostate accounted for 58% (789/1,355) of all patients in the clinical trials. As expected, these three primary malignancies constitute the major source of all metastatic neoplasms to bone.

TABLE 3. DISTRIBUTION OF ABNORMAL SKELETAL AREAS FOR NONOSSEOUS MALIGNANT NEOPLASMS*

Bone scan indication	Abnormal	Skeletal area: Skull	Vertebra	Thorax	Extremity	Pelvic
Breast	247	70 (28%)	147 (60%)	146 (59%)	80 (32%)†	94 (38%)
Lung	147	23 (16%)	63 (43%)	95 (65%)	40 (27%)	37 (25%)
Prostate	119	17 (14%)	71 (60%)	60 (50%)	45 (38%)	68 (57%)
Hodgkin's	29	5 (17%)	12 (41%)	17 (59%)	11 (38%)	13 (45%)
Lymphoma	16	5 (31%)	8 (50%)	9 (56%)	5 (31%)	7 (44%)
Cervix	23	6 (26%)	6 (26%)	5 (22%)	10 (43%)	10 (43%)
Rhabdomysocarcoma	22	3 (14%)	9 (41%)	8 (36%)	9 (41%)	3 (14%)
Colon	21	7 (33%)	13 (62%)	8 (38%)	8 (38%)	6 (29%)
Kidney	21	7 (33%)	10 (48%)	11 (52%)	10 (48%)	7 (33%)
Bladder	15	2 (13%)	7 (47%)	8 (53%)	1 (7%)	7 (47%)
Melanoma	17	6 (35%)	6 (35%)	5 (29%)	8 (47%)	2 (12%)
Rectum	14	3 (21%)	5 (36%)	4 (29%)	6 (43%)	6 (43%)
Thyroid	6	0 (0%)	4 (67%)	2 (33%)	3 (50%)	2 (33%)
Total	697	154 (22%)	361 (52%)	378 (54%)	236 (34%)	262 (38%)
All others	120	29 (24%)	38 (32%)	48 (40%)	48 (40%)	30 (25%)

* Percentages represent number of patients having abnormal uptake in each skeletal area.

† In one institution in which only whole-body scintiscans were taken an incidence of 50% to extremities was obtained (91 of 183 abnormal scans).

Except for lymphoma, bladder, and thyroid carcinomas, all the primary indications had 50% or greater incidence of metastatic skeletal involvement. An average incidence of 64% of skeletal involvement was found for breast, lung, and prostate carcinomas.

The distribution of skeletal metastatic involvement is tabulated in Table 3. The data as percent of abnormal scans having involvement in either skull, vertebra, thorax, pelvis, or extremities are correlated with each primary neoplastic indication. Overall tabulated metastatic involvement and the percent distribution for skull, extremities, pelvis, vertebra, and thorax were 22%, 34%, 38%, 52%, and 54%, respectively, for the reported neoplastic indications.

DISCUSSION

The skeleton is one of the most common sites for metastases, and numerous studies on the extent of skeletal metastases have been reported in the literature. These clinical results with the ^{99m}Tc-Sn·EHDP bone-scanning agent clearly support the extensive skeletal involvement for the more common malignant neoplasms. However, we find the incidence of skeletal metastases from patients with carcinoma of breast, prostate, and lung are higher than previously believed for all pooled stages of the disease.

Interestingly, our values approach early autopsy studies that detected high levels of skeletal involvement. In an extensive autopsy study by Abrams, et al (*4*) metastatic involvement to bone was detected in 73% of 167 consecutive autopsy cases of carcinoma of the breast. Taking all stages of breast carcinoma in our study, it is significant that the 67% level of skeletal involvement approaches the 73% values obtained by Abrams. These comparative data support the high sensitivity of the ^{99m}Tc-Sn·EHDP bone agent. This high sensitivity of the ^{99m}Tc-diphosphonate bone agent is also evident when compared to ^{18}F in the recent review of ^{18}F bone scanning by Shirazi, et al (*3*). They reported that in unspecified stages of breast carcinoma from 490 patients referred for the ^{18}F bone scan the abnormal scintiscan level is 43%. The higher level of skeletal detection with the diphosphonate is in agreement with a comparative study of ^{99m}Tc-Sn·EHDP and ^{18}F by Silberstein, et al (*5*) and Wellman, et al (*6*) in which ^{18}F revealed only 56% and 54% of the bone metastases, respectively, visualized with ^{99m}Tc-Sn·EHDP. The difference may relate to the more lytic nature of breast carcinoma metastases, which are not picked up by the less-sensitive ^{18}F agent (*7*).

Contrary to the incidence of skeletal metastases, only limited published data are available on the distribution of metastases within the skeleton for the reported indications in Table 3. The metastatic distribution from breast carcinoma indicates approximately 60% of patients had metastases to vertebra and thorax, 38% to the pelvic area, and 32% to the extremities. The value for extremity involvement is probably low since not all institutions imaged the complete skeleton. In one major institution, which routinely images the extremities, an incidence of 50% was obtained (Table 3). The greater frequency of skull metastases (28%) than previously reported (*8*) supports the high incidence of skull metastases more recently observed in patients by Hopkins and Kristensen (*9*) and is in agreement with the 25% diphosphonate value reported by Coleman, et al (*10*).

A high incidence of skeletal metastases is common with prostatic carcinoma patients and values from 53% to 60% have been reported with ^{18}F (*3,11*). The ^{99m}Tc-Sn·EHDP detected 62% abnormal scans for prostatic carcinoma patients which is in agreement with the ^{18}F studies. This agreement with ^{18}F scan percentages is in line with prostatic carcinoma metastases consistently having osteosclerotic reaction and hence would expect to be readily detected with ^{18}F (*7*). Skeletal distribution from prostatic cancer was again high in the vertebra and thorax with the pelvic involvement highest of all the other reported nonosseous indications. The 64% skeletal metastases from primary lung carcinoma is greater than the 46% value reported for ^{18}F from 114 preoperative patients scanned with all stages of bronchogenic carcinoma (*12*), again probably a result of the less osteosclerotic and more lytic nature of lung carcinoma metastases. Somewhat surprising is the high incidence of skeletal abnormalities reported with carcinomas of cervix, colon, kidney, bladder, and rectum.

The distribution is highest for the region of the thorax and lowest for the pelvic region of the most common carcinomas. The incidence of metastatic skeletal involvement with malignant lymphoma was lowest with 38% of abnormal scans. The other primary indications (Table 2) all yielded a high incidence of skeletal involvement and indicated an extension (Table 3) to all skeletal areas with the exception of the limited series of thyroid carcinoma that revealed no case of metastases to the skull.

It is evident from the 60% abnormal scan level and the widespread dissemination throughout the skeleton that whole-body bone scans (including extremities) should be used in staging all forms of malignant carcinomas that are known to metastasize to bone, as well as in followup management of carcinoma patients.

ACKNOWLEDGMENTS

We thank the staff and technologists from the nuclear medicine departments of Billings Hospital (Chicago, Ill.); Columbia-Presbyterian (New York, N.Y.); Denver, Colo., VA; Gainesville, Fla., VA; Indiana University Medical Center (Indianapolis, Ind.); Mount Auburn Hospital (Cambridge, Mass.); Mount Sinai (Miami Beach, Fla.); New England Deaconess (Boston, Mass.); Peter Bent-Brigham (Boston, Mass.); Roswell Park Memorial (Buffalo, N.Y.); Memorial-Sloan Kettering (New York, N.Y.); Stanford Medical Center (Palo Alto, Calif.); St. Josephs (Reading, Pa.); St. Lukes-Rush Presbyterian (Chicago, Ill.); University of Cincinnati Medical Center (Cincinnati, Ohio); and University of Tennessee College of Medicine (Memphis, Tenn.) for their participation in the clinical trials and for completing the clinical case report forms. Special appreciation is expressed to Kathleen Murphy and the Data Processing Group at Miami Valley Laboratories for their assistance with the tabulation of the clinical data.

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