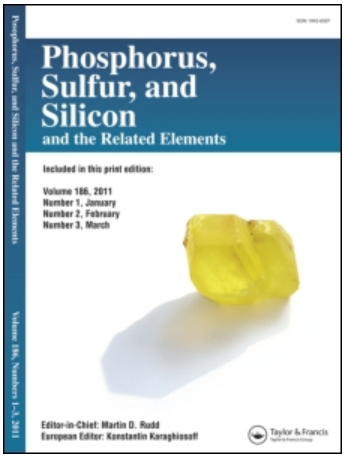

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Bone Scintigraphy and Tumor Markers in the Post-Operative Follow-Up of Breast, Colorectal, Prostate and Renal Cancer

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Between Jan 1986 and Dec 1997, 323 breast, 94 colorectal, 36 renal and 17 prostate cancer patients were serially followed-up with CEA-TPA-CA15.3, CEA-TPA-GICA-CA72.4, GICA-TPA-ferritin associations and PSA respectively. All patients presenting bone scintigraphy (BS) with equivocal interpretation and concomitant constant elevation (CE) or progressive increase (PI) in one or more of tumor markers (TM) were selected for computed tomography (CT), except those with equivocal BS of ribs, who were evaluated by skeletal x-ray. In non relapsed patients affected by the different cancer types, concomitant dynamic TM evaluation allowed to decrease by 13% up to 48% the equivocal BS subjects to be studied further with CT or x-ray. Moreover TM selected for radiological investigation 81% to 100% of those with skeletal metastases and equivocal BS. These data point out the relevant role of TM in improving BS specificity and in selecting those who need further radiological examinations.

Keywords: bone scintigraphy; skeletal metastases; tumor markers

INTRODUCTION

BS is routinely used by the oncologist to detect bone metastases "early". The commonest sites of bone metastases are sites of persistent red marrow, especially the axial skeleton (spine, pelvis, ribs and skull). Carcinoma of the breast and prostate account for most of the bone metastases, with cancers of the kidney, thyroid and lung following in descending frequency (1), while colorectal cancer rarely metastasizes to bone. Bone scan findings are however non-specific because virtually all disease processes result in an alteration in osteoblastic activity and blood flow (2). Low specificity accounts for the high percentage of BS with equivocal interpretation that occur during the follow-up of patients with cancer submitted to this imaging technique. To improve BS specificity, we started using tumor markers (TM) in 1986. This study assessed the efficacy of a protocol based on serial determinations of a

suitable tumor marker panel in selecting breast, prostate, renal and colorectal cancer patients to undergo computed tomography (CT) or skeletal x-ray aimed at hot spots of BS with equivocal interpretation. Moreover, it evaluated the accuracy of the radiological examinations aimed at hot spots of BS with equivocal interpretation in diagnosing the skeletal metastases.

MATERIALS AND METHODS

Patients

Between January 1986 and December 1997, 323 breast, 17 prostate, 94 colorectal and 36 renal cancer patients were serially followed-up. Two hundred seventy breast, 13 prostate, 74 colorectal and 32 renal cancer patients did not show secondary bone involvement, and the mean follow-up was 89 (range 12-120), 32 (range 12-57), 84 (range 14-126), 48 (range 7-82) months respectively. Skeletal metastases were ascertained by prolonged clinical and instrumental follow-up in 53 (16%) breast, 4 (23%) prostate, 9 (11%) colorectal and 2 (6%) renal cancer patients. The mean follow-up was 57 (range 8-120), 15 (range 2-31), 76 (range 14-126), 28 (range 10-47) months respectively.

Tumor markers and bone scintigraphy

In breast, colorectal and renal cancer patients CEA-TPA-CA15.3, CEA-TPA-GICA-CA72.4, GICA-TPA-ferritin associations respectively were serially measured. In prostate cancer patients, due to the high accuracy, only PSA was serially determined. Three kinds of increases were considered: isolated elevated value (IEV), constant elevation (CE) and progressive increase (PI). Only patients with CE or PI in one or more tumor markers, unexplained by concomitant benign pathology and by history, were considered to be suspected of tumor relapse (3). In order to interpret the BS findings better, the history and benign lesions (osteoarthritis, osteoporosis, trauma, etc.) detected with baseline skeletal x-ray were taken into account. The principal criteria for interpretation of the BS and the principal types of BS patterns were as follows. Bone metastases (pathological BS): multiple obvious hot spots in sites usual for breast cancer metastases not involved by benign lesions. Not due to bone metastases (negative BS): no hot spot; one or more hot spots with diffuse irregular uptake; one or more hot spots in sites unusual for breast cancer metastases and involved by benign lesions. Equivocal for bone metastases (equivocal BS): slight asymmetry of tracer uptake; one or more hot spots in sites unusual for breast cancer metastases (skull, arms) but not involved by benign lesions; one or more hot spots in sites usual for breast cancer metastases and also involved by benign lesions; a single hot spot in a site usual for breast cancer metastases and not involved by benign lesions. Patients with equivocal BS and concomitant CE or PI in one or more tumor markers were selected for radiological examinations. All hot spots on the BS with an equivocal interpretation and selected for radiological examination were examined by CT except those in the ribs that were evaluated by skeletal x-ray.

RESULTS

BS with equivocal interpretation occurred in 141(52%) of the 270 breast, in 6 (46%) of the 13 prostate, in 29 (39%) of the 74 colorectal, in 12 (38%) of the 32 renal cancer patients without sign of relapse. CT

aimed at the BS areas with equivocal interpretation was carried out in 6 breast and in 2 renal cancer patients because of the concomitant CE or PI in TM. In all but one of these 8 patients falsely suspected with TM, CT was negative. In the last patient operated for renal cancer, CT gave an uncertain result. In another non relapsed renal cancer patient with concomitant CE of TM, skeletal x-ray aimed at equivocal BS area of ribs was negative. BS with equivocal interpretation occurred in 26 (49%) of the 53 breast, in 1 (25%) of the 4 prostate, in 2 (22%) of the 9 colorectal and in 1 (50%) of the 2 renal cancer patients with skeletal metastases. A CE or PI in one or more TM concomitant with equivocal BS was found in 21 (81%), 1 (100%), 2 (100%) and 1 (100%) of these patients respectively. CT aimed at the BS areas with equivocal interpretation was carried out in 17 breast, 1 prostate, 1 colorectal and 1 renal cancer patient suspected of skeletal metastases because of the concomitant CE or PI in one or more TM. In 10 of the 17 breast and in the single prostate and colorectal cancer patients with equivocal BS selected for CT with TM, CT confirmed the skeletal metastases. In the 8 remaining (7 with breast and 1 with renal cancer) even CT gave an equivocal result. Skeletal x-ray was performed in 4 breast and in 1 colorectal cancer patients showing BS area of ribs with equivocal interpretation and concomitant CE or PI in TM. In all 4 breast cancer patients x-ray was negative and in the last patient it confirmed rib metastasis.

TABLE 1 Negative (NPV) and positive (PPV) predictive values of TM panel increase in predicting skeletal metastases in patients with equivocal BS.

		Equivocal BS			
		without	with	TM panel increase (CE or PI)	
Cancer type	TM Panel	skeletal metastases	skeletal metastases	NPV	PPV
		n	n	%	%
Breast	CEA-TPA-CA15.3	141	26	96	78
Prostate	PSA	6	1	100	100
Colorectal	CEA-TPA-GICA CA72.4	29	2	100	100
Renal	TPA-GICA-ferritin	12	1	100	25

TABLE 2 Accuracy of CT and x-ray in diagnosing skeletal metastases in patients with equivocal BS selected with TM panel.

Cancer type	Pts submitted to CT	Overall CT accuracy	Pts submitted to x-ray	Overall x-ray accuracy
	n	%	n	%
Breast	23		4	
Prostate	1		0	
Colorectal	2		1	
Renal	3		1	
Total	29	68	6	33

Table 1 shows NPV and PPV of TM increase in predicting skeletal metastases. NPV was 96% in breast and 100% in the other types of cancer patients . PPV was 25% and 78% in renal and breast cancer patients respectively, while in prostate and colorectal cancer subjects it was 100%. Table 2 shows the overall accuracy of CT and x-ray in diagnosing skeletal metastases in patients with equivocal BS selected with TM panel. CT showed 68% overall accuracy and that of x-ray was 33%.

DISCUSSION

BS with equivocal interpretation occurred in 38% of renal to 52% of breast cancer patients without skeletal metastases. Equivocal BS was found in 22% of colorectal to 49% of breast cancer patients with skeletal metastases. These data confirm the low specificity of BS. In patients without skeletal metastases the concomitant "dynamic" evaluation of TM decreased the percentage of equivocal BS to be studied with further radiological examinations by 13% in renal and by 48% in breast cancer. In patients with skeletal metastases, the selection with TM of those to be investigated further with radiological examinations ranged from 81% of breast cancer to 100% of other types of cancer. Therefore TM showed PPV and NPV of 80% or higher in all the studied patients except those operated for renal cancer. In this type of cancer an unexpected 25% PPV occurred likely due to the small sample size and the low specificity of the TM combination. The 68% overall accuracy of CT in diagnosing skeletal metastases confirms the relevant role that CT can play in breast, colorectal, prostate and renal cancer patients with equivocal BS selected with TM. Unlike that, the low overall accuracy of skeletal x-ray aimed at equivocal BS of ribs reflects the well known low sensitivity of routine skeletal x-rays in general. In conclusion, data from this study point out that CEA-TPA-CA15.3 and CEA-TPA-GICA-CA72.4 associations in breast and colorectal cancer respectively and PSA in prostate cancer can improve BS specificity with selection of those with equivocal BS who need further radiological investigation. In renal cancer patients a TM combination with higher specificity than TPA-GICA-ferritin should be investigated to improve the accuracy of BS findings.

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