

Non-invasive Quantitative Characterization of Skeletal Metastasis in Carcinoma Prostate by Tc99m MDP Bone Scans Using Dr. V. Siva's Retention Ratio in Correlation with Serum PSA Levels

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Abstract

Background: In patients suffering from carcinoma prostate the incidence of skeletal metastases had been found to be very high. The presence of skeletal metastasis could be inferred by the multiple focal hotspots in the skeletal tissue. The metastatic nature of the hotspots could be inferred by multiple lesions, asymmetric distribution with increased tracer concentration. In the case of Solitary focal spot in the bone scan metastatic nature could not be attributed to it. The invasive biopsy procedure could only confirm or discard the metastatic involvement. A new non-invasive Scintimetric characterization and evaluation of skeletal hot spots in bone scans of carcinoma prostate patients was proposed and tested.

Materials and methods: The bone scan was done 4 and 24 hours after intravenous injection of 15 to 25 mCi of Tc99m Methylene Di-Phosponate with adequate hydration using the e-cam Siemens dual head gamma camera with e-cam whole body acquisition protocol in 75 patients with biopsy proven carcinoma prostate. Metastatic involvement was seen in 53 patients and was negative in 22. The Serum PSA levels were obtained from the Patient medical records were tabulated. The 185 focal hotspots in various sites in 34 patients were characterized using the temporal scintimetric method. Both 4 and 24hr bone scan images were selected using the general display protocol. Then with the help of the region ratio processing protocol the 4 and 24hr anterior and posterior images were selected separately. Maximum counts in the selected regions were then tabulated. Then the 4/24hr Dr. V. Siva's retention ratio was derived by dividing the 4hr counts of the focal hotspots with 24hr counts along with the Israel's 24/4hr ratio as well. Similarly 4/24hr Dr.V.Siva's retention ratio of whole body scan total counts at 4 and 24hr scans was also calculated. The results were compared and analysed.

Results: The mean of 4/24hr Dr. V. Siva's retention ratio was found to be 12.32 ± 3.3 and that of 24/4hr Israel's ratio to be 0.08 ± 0.02 for Focal hot spot evaluation. The 4/24hr Dr. V. Siva's retention ratio was derived by dividing the total whole body counts at 4 and 24hr whole body bone scan was 12.21 ± 2.78 which was closer to the Focal hot spot retention ratio. The Total PSA, Free PSA and the %PSA Values were 61.8, 19.2 and 26.8 in the Metastatic positive group and 34.5, 6.8 and 12.8 in the negative group respectively.

Conclusion: Scintimetric characterization of the skeletal hot spots provided a non-invasive means for identifying the underlying pathology to enable proper management decisions. The 4/24hr Dr. V. Siva's retention ratio was useful clinically because of its whole integer value, unlike the Israel's 24/4hr ratio which was in decimal value. The utility of the scintimetric characterization in inferring the metastatic nature of the lesion was confirmed through biopsy of the site afflicted followed by histopathological examination.

Keywords: Non-invasive characterization; Skeletal metastasis; Ca. prostate; Tc 99m MDP bone scans; Dr.V.Siva's retention ratio; Serum total PSA; Free PSA; %PSA

Introduction

The Carcinoma Prostate had been found to involve the skeletal tissues as their preferred metastatic sites during the course of the disease. The metastatic lesions predominantly appear as focal hot spots. In some rare cases they might appear as a Photopenic lesion as well. The focal hot spots showed multiplicity, asymmetrical distribution on both sides of the body in the metastatic involvement. The single Focal hot spot when seen in a bone scan cannot be attributed to the metastatic origin only as it could have been caused by other benign causes as well. The role of imaging in the evaluation of metastatic involvement in Carcinoma Prostate had been described by Langsteger et al. [1]. Hence various methods were resorted to quantify and characterize them. Soloway et al. [2] have classified them by visual inspection method based on the presence and number of focal hotspots as follows. No lesion -0, less than 6 – stage 1, 6 to 20 stage - 2, more than 20 without super scan stage - 3 and Super Scan – Stage 4. The staging by Amico similar but it had not taken the Super Scan appearance into account there by resulting in three stages only. Chylowski [3] proposed a simpler classification into negative, positive and intermediate stages. Dann et al. [4] had measured

the 24hr whole body retention as an objective method. Erdi et al. [5] have established a computer analysis based Bone Scan Index using Image segmentation. Noguchi et al. [6] have devised a quantitative evaluation by measuring the percentage area of positive bone scan combining both visual and computer analysis. Elizabeth R Dennis et al. [7] have documented the utility of Bone Scan index as an effective measure of treatment response assessment in Castration resistant Ca. Prostate cases along with the bio-markers. However all these methods could not differentiate between the malignant and benign causes of the focal hot spots in a bone scan. The Temporal scintimetric method of

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Received March 08, 2016; Accepted May 27, 2016; Published June 05, 2016

Citation: Sivasubramaniyan V, Venkataramaniah K (2016) Non-invasive Quantitative Characterization of Skeletal Metastasis in Carcinoma Prostate by Tc99m MDP Bone Scans Using Dr. V. Siva's Retention Ratio in Correlation with Serum PSA Levels. Med Surg Urol 5: 164. doi:10.4172/2168-9857.1000164

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characterizing the Skeletal Hotspots in a bone scan was first reported by Israel et al. [8]. The maximum counts in the focal hotspot in the 24hr Bone scan was divided by the maximum counts in the 4hr bone scan image. He had proved that clear cut differentiation could be established between the degenerative lesions, metastases and the treated metastatic group of patients. However the resultant ratio was in decimal fraction values and no useful cut off values could be derived. Hence it was not accepted for wide clinical usage.

Dr. V. Siva's retention ratio

In our method the procedure was reversed to get the whole number values. The maximum counts in the Focal hotspot region were obtained by using the region ratio protocol in both the 4hr and 24hr whole body bone scans. The retention ratio was calculated by dividing the 4hr counts by the 24hr counts for the focal hot spot sites. The method of calculating the Dr.V.Siva's retention ratio is depicted in Figure 1. The whole body total counts in the 4hr and 24hr also were tabulated and the retention ratio was calculated as mentioned above. This scintimetric characterization of the skeletal hotspots had been proved to have different values for the malignant and benign origin by us [9].

Materials and Method

The bone scan was done 4 and 24 hours after intravenous injection of 15 to 25 mCi of Tc99m Methylene Di-Phosponate with adequate hydration using the e-cam Siemens dual head gamma camera with e-cam whole body acquisition protocol in 75 patients with biopsy proven carcinoma prostate. Metastatic involvement was seen in 53 patients and was negative in 22. The Serum PSA levels were obtained from the Patient medical records was tabulated. The 185 focal hotspots in various sites in 34 patients were characterized using the temporal

scintimetric method as the 24hr images were not available in the 12 patients of the positive group. Both 4 and 24hr bone scan images were selected using the general display protocol. Then with the help of the region ratio processing protocol the 4 and 24hr anterior and posterior images were selected separately. Maximum counts in the selected regions were then tabulated. Then the 4/ 24hr of Dr. V. Siva's retention ratio was derived by dividing the 4hr counts with 24hr counts along with the Israel's 24/ 4hr ratio as well. Then 4/ 24hr Dr. V. Siva's retention ratio derived by dividing the whole body counts of 4 and 24hr whole body bone scan. The results were compared and analysed.

Results

The details of the Focal hot spot sites, 4hr and 24hr counts, derived 24/ 4hr Israel's ratio and 4/24hr Dr.V.Siva's retention ratio values were tabulated and shown in the Table 1.

The mean of 4/24 hr Dr. V. Siva's retention ratio was found to be 12.32 +/- 3.3 and that of 24/4hr Israel's ratio to be 0.08 +/- 0.02 in the focal hot spot evaluation. The retention ratios of the focal hotspots and the whole body bone scan total counts obtained were shown in Table 2.

The 4/24 hr Dr. V. Siva's retention ratio derived by dividing the whole body counts of 4 and 24hr whole body bone scan was 12.21 +/- 2.78 which was identical to that of the Focal hot spot retention ratio. The serum Total PSA, Free PSA and the %PSA levels in the Bone scan metastasis positive and negative groups were shown in Tables 3 and 4.

The Total PSA, Free PSA and the %PSA Values are 61.8, 19.2 and 26.8 in the Metastatic positive group and 34.5, 6.8 and 12.8 in the negative group respectively.

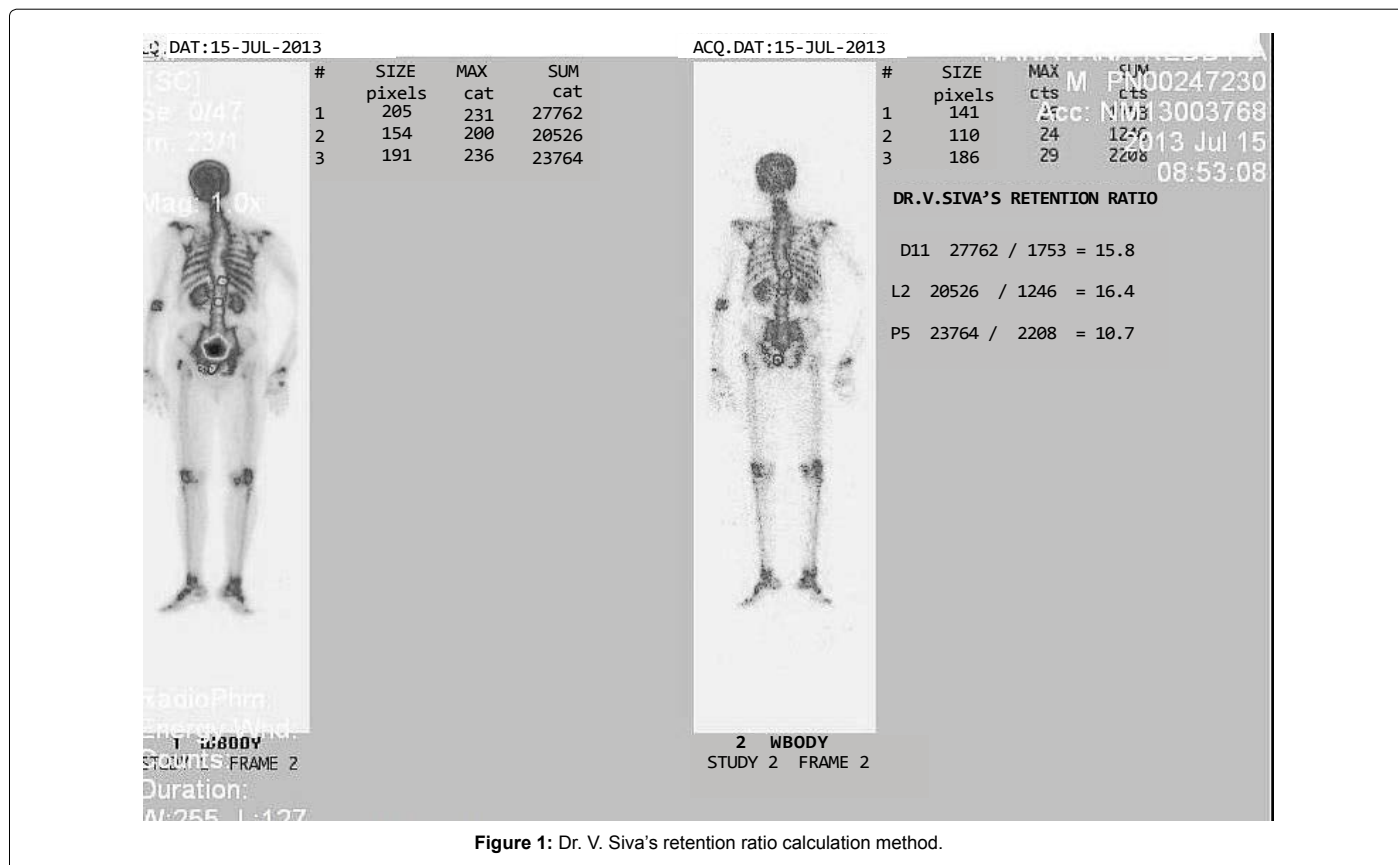


Figure 1: Dr. V. Siva's retention ratio calculation method.

Site	4 Hr Counts	24 Hr Counts	Israel's 24/ 4 Hr	Dr. V. Siva's 4 / 24 Hr
Pubic symphysis	46947	4356	0.09	10.7
D11	27762	1753	0.06	15.8
L2	20526	1246	0.06	16.4
PS	23764	2208	0.09	10.7
Rt. rib	21920	1629	0.07	13.4
L 5	37105	2619	0.07	14.1
Lt rib	14839	1124	0.07	13.2
RT12	18141	1093	0.06	16.5
RT 5	14826	1289	0.08	11.5
RT Rib	6939	614	0.08	11.3
L3	23488	2811	0.11	8.3
R SIJ	31138	3009	0.09	10.3
RT Rib	18853	1816	0.09	10.3
L4	17642	1831	0.1	9.6
RT Rib	23790	1661	0.06	14.3
RT Frontal	145552	10598	0.07	13.7
LT Foot	63036	5315	0.08	11.8
LT Pari	15157	1307	0.08	11.5
D5	21945	1561	0.07	13.9
RT Frontal	61375	4967	0.08	12.3
LT Foot	38417	1900	0.04	20.2
RT Rib	20810	1990	0.09	10.4
RT5Rib	37597	3765	0.1	9.9
Rt rib	75984	7242	0.09	10.4
Lt rib	61015	6486	0.15	9.4
L4	25655	2538	0.09	10.1
D1	56045	4049	0.07	13.8
D7	82119	6260	0.07	13.1
RT SIJ	114114	9839	0.08	11.5
RT ISCH	49097	5884	0.11	10
Rt rib	40830	2576	0.06	14
Stern	188301	13654	0.07	13.7
Rt foot	33202	3051	0.09	10.8
Lt rib	141923	12909	0.09	10.9
D4	50374	3615	0.07	13.7
Rt fem	16615	1128	0.06	14.7
Rt rib	10087	902	0.08	11.1
Lt rib	9814	772	0.07	12.7
scrot	6527	511	0.07	12.7
Lt gt	10427	707	0.06	14.7
Rt rib	11138	777	0.06	14.3
D12	9011	1259	0.13	7.1
RT knee	5941	554	0.09	10.7
LT GT	7525	654	0.08	11.5
L3	89624	14065	0.15	6.3
L4	97733	11548	0.11	8.4
LT IC	158441	20594	0.12	7.6
RT IC	304334	29736	0.09	10.2
L1	50118	5568	0.11	9
L3	121252	15169	0.12	7.9
LT sij	76088	7134	0.09	10.6
LT isc	56785	6137	0.1	9.2
cal	17232	1286	0.07	14.2
Lt shoul	13952	1187	0.08	11.7
Lt rib	21298	2178	0.1	9.7
Rt spg	61808	7469	0.12	8.2
Lt occi	5376	396	0.07	13.5
Lt shoul	8671	621	0.07	13.9
Lt rib	20672	2578	0.12	8

lips	9588	878	0.09	10.9
Stern	40265	3423	0.08	11.7
Rt knee	10183	739	0.07	13.7
L5	29209	1902	0.06	15.3
Lt rib	23286	2321	0.09	10
Rt rib	32810	2002	0.06	16.3
Stern	21174	2044	0.09	10.3
Lt fem	16931	1383	0.09	10.6
Rt rib	11538	1016	0.08	11.3
Lt foot	7440	666	0.08	11
Lt rib	16931	1076	0.06	15.7
L3	21257	1004	0.04	21.1
L3	15304	1462	0.09	10.4
LPS	15688	1257	0.08	12.4
RT frontal	68905	6210	0.09	11
Lt parei	17337	2095	0.12	8.2
C7	40764	3922	0.09	10.3
RT clav	23189	1871	0.08	12.3
Rt rib	17829	1959	0.1	9.1
Stern	90704	7813	0.08	11.6
D12	81694	7033	0.08	11.6
LT rib	16182	1620	0.1	9.9
L2	44670	2542	0.05	17.5
SAC	29937	3743	0.12	7.9
RT ic	27544	3085	0.11	8.9
LT ps	33425	4194	0.12	7.9
LT front	19667	3291	0.16	5.9
RT Front	31028	2457	0.07	12.6
IC	7189	955	0.13	7.5
RT Occi	13941	957	0.06	14.5
C3	22692	2441	0.1	9.2
RT clav	12266	1350	0.11	9
LT rib	21919	2198	0.1	9.9
RT rib	26034	2611	0.1	9.9
L3	40277	4132	0.1	9.7
SAC	35916	4299	0.11	8.3
RIC	17560	2049	0.11	8.5
LT isc	29557	3080	0.1	9.5
PS	46947	4356	0.09	10.7
D11	27762	1753	0.06	15.8
L2	20526	1246	0.06	16.4
PS	23764	2208	0.09	10.7
rib	38048	2908	0.07	13
Lt foot	51883	3109	0.05	26.6
Lt rib	18896	1544	0.08	12.2
Rt rib	35695	2902	0.08	12.3
Lgt	17885	1751	0.09	10.1
Lgt	19980	828	0.09	10.9
Rib	6471	304	0.04	21.2
Rib	11084	1019	0.09	10.8
L1	6369	594	0.09	10.7
I4	26869	1821	0.06	14.7
I2	6185	610	0.09	10.1
Rt ic	12476	2559	0.2	4.8
Rt act	6701	599	0.08	11.1
Lt foot	10448	1161	0.11	16.6
L2	15982	1321	0.08	12
S1	30572	2346	0.07	13
RT ic	20573	1595	0.07	12.8
Lt foot	36629	3374	0.09	10.8
Stern	35740	3309	0.09	10.8

D12	20728	1451	0.07	14.2
L4	30169	2181	0.07	13.8
C7	91093	10047	0.11	9
L4	13851	817	0.05	16.9
C7	57805	4290	0.07	13.4
D2	56757	6130	0.1	9.2
D4	39575	3105	0.07	12.7
L5	35391	2122	0.05	16.6
LS ij	39123	3224	0.08	12.1
RT ps	92641	7388	0.07	12.5
LS ij	75121	7886	0.1	9.5
RT ps	25139	1754	0.06	14.3
RT rib	9486	725	0.07	13
RT fem	19643	1667	0.08	11.7
LT rib	8676	856	0.09	10.1
LT rib	9446	864	0.09	10.9
LT max	12184	956	0.07	12.7
LT rib	9265	688	0.07	13.4
Stern	19928	1141	0.05	17.4
LT leg	14676	1084	0.07	13.5
D6	25500	1569	0.06	16.2
RT rib	4818	156	0.03	30.8
LT leg	15682	838	0.05	18.7
RT rib	9021	572	0.06	15.7
LT rib	8941	490	0.05	18.2
LT rib	3812	512	0.13	7.4
LIC	4855	653	0.13	7.4
L5	10930	620	0.05	17.6
RT sho	64574	5248	0.08	12.3
LIC	126050	12001	0.09	10.5
RT fem	42374	4158	0.09	10.1
RT rib	61007	5044	0.08	12
LT fem	21778	1803	0.08	12
L5	24929	1431	0.05	17.4
RT sc	9134	890	0.09	10.2
RT ank	56009	4269	0.07	13.1
Lt shoul	10930	604	0.05	18
LT rib	13158	986	0.07	13.3
RT ank	48427	4044	0.08	11.9
D6	25068	1817	0.07	13.7
LT sc	15258	1146	0.07	13.3
RT rib	13170	1284	0.07	10.2
RT tib	14759	1185	0.08	12.4
RT rib	23790	1661	0.06	14.3
RT pat	145552	10598	0.07	13.7
LT foot	63056	5316	0.08	11.8
LT pari	15157	1309	0.08	11.5
D5	21945	1569	0.07	13.9
LT foot	38417	1900	0.05	20.2
RT pari	61375	4967	0.08	12.3
D1	10379	822	0.07	12.6
RT sca	17362	1227	0.07	14.1
RT rib	24939	2099	0.08	12.6
RT max	35474	2802	0.07	12.6
L1	44987	3283	0.07	13.7
RT fem	25504	2351	0.09	10.8
CAL	17232	1206	0.07	14.2
LT skul	13952	1187	0.08	11.7
LT occi	5376	396	0.07	13.5
Lt shoul	8671	621	0.07	13.9
LT pr	9586	878	0.09	10.9

RT rib	22291	1932	0.08	11.9
RT ank	57414	4525	0.07	12.6
LT sij	102150	6546	0.06	15.6
RT ank	76341	6536	0.08	11.9
		Mean	0.08	12.316
		STD	0.02	3.35

Table 1: Dr.V.Siva's retention ratio values.

RRFHS	RRWBS	RRFHS	RRWBS
13.5	13.2	11.6	10.5
9.96	9.3	13.4	10.3
13.9	16.1	15	13.4
10.1	10.4	21.9	13.5
11.1	9.9	15.7	10.1
12.9	12.9	12.8	9.7
11.8	9.7	7.4	8.8
8.6	11.4	17.6	8.6
11.2	12.5	12.7	12.1
13.5	10	10.9	11
13.1	24.1	14.5	11.3
10.8	11	13.6	11.4
14.9	18	11.6	11.4
9.3	8.5	12.4	11.4
13.4	14	14	16.1
16	15.7	13.6	13.6
12.5	15.6	13	11.6
11.3	14.8	10.8	11.3
12.1	14.3	14.2	11.3
12.5	9.9	13.9	11.3
12.8	10.2	11.9	11.7
13.8	13.3	12.6	10.9
11.4	13.06	15.6	10.5
14	14.1	11.9	14.4
11.8	14.1		
	Mean	12.32	12.21
	Std Dev	3.3	2.78

Table 2: Dr. V. Siva'S retention ratio in focal hot spots - Rrfhs & whole body bone scans -Rrws.

Result	Total PSA	Free PSA	% PSA	Result	Total PSA	Free PSA	% PSA
Positive	100	12.38		Positive	0.98		
Positive	58.05	16.24	27.9	Positive	19.62	4.27	46.4
Positive	0.55			Positive	65.98	11.33	17.17
Positive	7.8	3.57	45.7	Positive	80.02	10.17	12.7
Positive	18.7	6.45	34.49	Positive	17.08	2.91	17.03
Positive	100	50		Positive	67.15	14.36	21.38
Positive	0.01			Positive			
Positive	65.59	10.8	16.4	Positive	29.64	1.29	4.35
Positive	100	10.58		Positive	65.08	2.79	4.29
Positive	100	16.84		Positive			
Positive	38.59	11.46	29.69	Positive	67.89	9.04	13.31
Positive	100	22.69		Positive	5.91	2.34	39.5
Positive	100	50		Positive	26.86	9.26	34.47
Positive	20.95	3.13	14.94	Positive	100	50	
Positive	94.02	9.15	9.73	Positive	100	50	
Positive	100	6.54		Positive	100	24.77	
Positive	30.68	2.77	9.02	Positive	100	5.59	
Positive	100	39.41		Positive	23.04	6.24	27.03
Positive	100	50		Positive	100	34.84	
Positive	100	37.39		Positive	23.53	15.55	66.08
Positive	66.67	29.12	43.67	Positive	11.45	3.12	27.24

Positive	72.53	22.58	31.13	Positive	2.7		
Positive	34.94	21.57	61.7	Positive	50.24	5.39	10.7
Positive	100	50	50	Positive			
Positive	100	22.54		Positive	100	50	
Positive	100	50		Positive	99.77	11.6	11.62
Positive	28	6.7	23.42	Mean	61.8804	19.2776087	26.82357143

Table 3: Serum PSA levels in bone metastasis positive group.

Result	Total PSA	Free PSA	% PSA
Negative	26.81	5.68	21.18
Negative	96.97	4.92	5.07
Negative	69.12	4.64	6.71
Negative	0.54		
Negative	31.66	10.19	32.1
Negative	80.49	21.61	26.84
Negative			
Negative	33.17	2.22	6.69
Negative	0.58		
Negative	100	24.81	
Negative	11.1	1.82	16.39
Negative	22.25	3.47	15.59
Negative	60.15	11.83	19.66
Negative	0.01		
Negative	32.28	2.16	6.69
Negative	26.21	1.13	4.31
Negative	15.21	1.74	11.43
Negative	69.48	5.52	7.94
Negative	9.06	0.97	10.7
Negative	0.32		
Negative	21.4	1.58	7.3
Negative	18.01	1.31	7.27
Negative			
Mean	34.5152381	6.211764706	12.866875

Table 4: PSA level is in bone metastasis negative group.

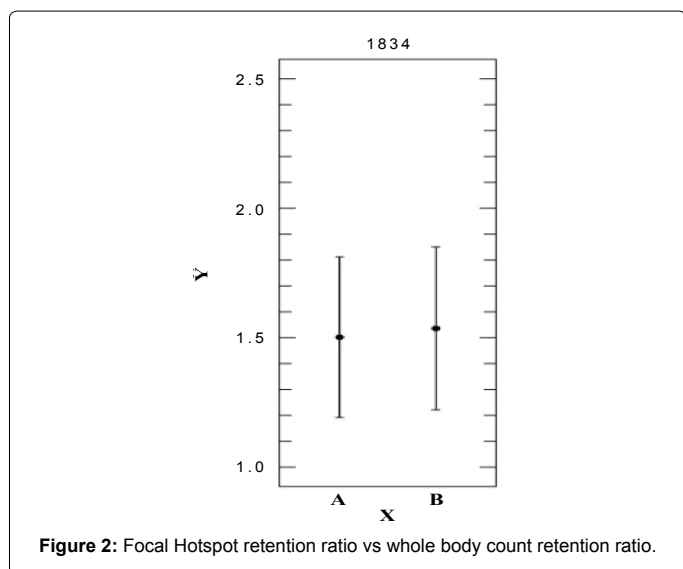


Figure 2: Focal Hotspot retention ratio vs whole body count retention ratio.

Discussion

The counts in the focal hotspots represent the osteoblastic activity occurring at that site. The basic mechanism of localization of the radiotracer Tc99m MDP is termed as Chemisorption.

The ionic radius of the Tc99m MDP complex is equal to that of

the Calcium -hydroxy appetite crystals. Hence they are adsorbed to the basic building blocks of the skeletal tissue. The retention ratio of benign lesions has been shown to be between 1 to 5 numerical value as the metabolic bone turnover of the skeletal tissue is minimal and constant. Whereas the metastatic and malignant lesion which have increased and rapid metabolic bone turnover due to the underlying disease process always have the numerical value of 10 and above. The fact that the focal hotspot retention ratio and the whole body count retention ratios are identical values confirms the fact that the retention ratio is the true representative of skeletal tissue turnover. The student t test evaluation of the focal retention ratio values and the whole body count retention ratio values confirms that there is no significant difference between them as shown in Figure 2.

The roles of modern techniques in the detection of Prostate Cancer's Bone Metastasis have been well narrated and the question about the end of era of bone scan is discussed [10]. The role of serum PSA concentration in determining the need for bone scan was reported by John et al. [11]. The cut of level of serum PSA >8 ng/ ml was mentioned.

The good correlation between the serum PSA levels of >10 ng/ml and the presence of bone metastasis had been documented by Wojcieh Sztot [12]. In a study of 1116 it had been proved that the chance of detecting bone metastasis was greater when the serum PSA level was >20 ng/ml by Lojanapiwat et al. [13]. In a study of 48 patients of Ca. Prostate the mean serum PSA level was >109.9 ng/ml in the positive bone metastasis group and it was >54.7 ng/ml in the negative group as documented by Oommen et al. [14]. The serum PSA level in the bone scan positive group was almost TWICE the serum PSA value in the negative bone scan group in this study too as shown by our reported values. Recently the elevated levels of serum miR-141 was shown to be well correlated with bone metastasis in Ca. Prostate patients than the serum PSA levels by Hai-Liang Zhang [15]. This clearly depicts the current situation of lack of implementation of quantitative measurements in the regular practice of bone scan studies.

Conclusion

The current study proves that the skeletal metastatic lesions could be characterised correctly by the non-invasive quantitative Dr.V.Siva's retention ratio as they show the value to above 10. This will help in the characterization of solitary hotspots as metastatic lesion or not, so that appropriate correct treatment could be decided without resorting to invasive bone biopsy. Similarly the benign degenerative lesion that might be interspersed along with metastatic lesions in a proven case of Carcinoma Prostate could be identified and treated accordingly. However the method is dependent on the correct method of procedure in both 4 and 24hr scans, identical and exact drawing of the region of focal hot spots in both the images for the best results. Any error in these will hamper the outcome of the results. More over this single institutional study must be put to test in more institutions for assessing its universal applicability. It can be concluded that the non-invasive quantitative scintimetric characterization of skeletal metastasis in Carcinoma Prostate patients deserves a place in the proper management protocol.

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