Original Article

Determination of the optimal cut-off value of serum prostate-specific antigen in the prediction of skeletal metastases on technetium-99m whole-body bone scan by receiver operating characteristic curve analysis

ABSTRACT

Radionuclide whole-body bone scan is a useful investigation of choice to detect the skeletal metastases in prostate cancer. It is indicated in patients having elevated serum prostate-specific antigen (Sr. PSA) or patients with bone pain. Elevated Sr. PSA levels have high predictive value for skeletal metastases; however, there is no consensus regarding cut-off value of Sr. PSA above which bone scan is indicated. This study was performed to find out the accuracy of Sr. PSA test and to know the optimal cut-off value of Sr. PSA with high sensitivity and specificity in the prediction of skeletal metastases on bone scan in prostate cancer patients. A retrospective analysis of medical records of 307 prostate cancer patients referred to the department of nuclear medicine for bone scan between June 2009 and June 2014 was done. Of 307 patients, 15 cases were excluded due to nonavailability of Sr. PSA. Bone scan was performed 3 h after administration of 20 mCi Tc-99m methylene diphosphonate intravenously. Whole-body sweep imaging was performed and spot views were taken wherever required. Of 292 cases, 174 (59.58%) patients had positive bone scan for metastases and 118 (40.41%) patients had negative bone scan for metastases. Maximum and minimum Sr. PSA levels in positive and negative bone scan patients were 1260 and 0.02 ng/ml and 198.34 ng/ml and 0.01 ng/ml, respectively. On comparison of the mean Sr. PSA levels between positive and negative groups, we found significant Sr. PSA levels ($P < 0.05$). We used receiver operating characteristic (ROC) curve analyses to find out the accuracy of Sr. PSA test and to know the optimal cut-off value of Sr. PSA with maximum sensitivity and specificity in the prediction of skeletal metastases on bone scan. Area under ROC curve was 0.878 (87%). This indicates that the accuracy of Sr. PSA test in the prediction of skeletal metastases on bone scan was good. The optimal cut-off value of Sr. PSA in the prediction of positive bone scan for skeletal metastases in the management of prostate cancer was 29.16 ng/ml, with sensitivity and specificity of 89.0% and 74.6%, respectively. In this study, we conclude that the accuracy of Sr. PSA test in the prediction of skeletal metastases is good. ROC-derived optimal cut-off value of Sr. PSA for positive skeletal metastases on bone scan is >29.16 ng/ml; thus, the chances of getting positive bone scan for skeletal metastasis are less in prostate cancer patients with Sr. PSA <29.16 ng/ml. ROC-derived sensitivity and specificity of different possible cut-off points of Sr. PSA help reduce the false positive results and increase the diagnostic accuracy of bone scan in the detection of skeletal metastases in prostate cancer patients.

Keywords: Prostate cancer, prostate-specific antigen, receiver operating characteristic curve analyses, technetium-99m

INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide.[1] The incidence of prostate cancer has been increasing in the Asian population due to change in lifestyle and implementation of screening programs.[2] Serum prostate-specific antigen (Sr. PSA) is most sensitive test with high negative predictive value to detect prostate cancer and as well as local and distant metastases.[3] Distant metastasis

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is common in prostate cancer involving almost all major organs, among them bone is the most common site of distant metastases followed by lung and liver.[4] At early stage of the disease, nearly 30% of the patients present with skeletal metastases, and this is increased by 90% at later stage of the disease;[5] because of high incidence of skeletal metastases in prostate cancer, it is important to detect the bone metastases to plan the treatment and assess the prognosis. Whole-body bone scan is sensitive to detect the sclerotic metastases of prostate cancer.[6] Clinicians advise the bone scan in prostate cancer patients to know the stage of the disease and to assess the response to chemotherapy in a known metastatic skeletal disease.

They are various predictors such as Sr. PSA, Gleason score, and tumor size to predict skeletal metastases on bone scan, among them Sr. PSA is a good predictor for the detection of skeletal metastases on bone scan.[7] According to the European Association of Urology guidelines, a staging bone scan is not indicated in asymptomatic prostate cancer patients who have Sr. PSA <20 ng/ml with well and moderately differentiated tumor.[8] However, this criterion may not be applicable for all patients belonged to different regions of the world. There are fewer studies in literature to suggest the optimal cut-off value of Sr. PSA with best predictive value for skeletal metastases on technetium-99m (Tc-99m) whole-body bone scan.

This study was conducted to find out the accuracy of Sr. PSA test and to know the optimal cut-off value of Sr. PSA in the prediction of skeletal metastases on Tc-99m whole-body bone scan.

MATERIALS AND METHODS

This study was conducted in the Department of Nuclear Medicine of Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu and Kashmir, after approval from the institutional ethics committee with reference letter number SIMS 1 31/IEC-SKIMS/2012. A retrospective analysis of medical records of diagnosed prostate cancer patients referred to the department of nuclear medicine for bone scan between June 2009 and June 2014 was done. All bone scans were advised for staging purpose before surgery, radiotherapy, and androgen deprivation therapy. The PSA tests were performed within 30 days of bone scan. Bone scan was performed 3 h after administration of 20 mCi Tc-99m methylene diphosphonate intravenously. Whole-body sweep imaging was performed and spot views were taken wherever required. All bone scans were reported by two experienced nuclear medicine physicians. Exclusion criteria included patients with abnormal renal function test (elevated blood urea and serum creatinine), and patients with unknown pathology and

nonavailability of Sr. PSA. Positive bone scan is defined as focal increased tracer uptake or multiple asymmetrical foci of increased tracer uptake in skeleton system excluding tracer uptake in relation to previous trauma and degenerative sites.

Statistical methods

The standard statistical test such as Student's *t*-test has been used to compare the different groups. The receiver operating characteristic (ROC) curve analyses were used to find out the accuracy of Sr. PSA test in the prediction of the skeletal metastases on Tc-99m whole-body bone scan and to conclude the optimal cut-off value of Sr. PSA in the prediction of skeletal metastases on bone scan. The data were analyzed with the help of SPSS 20 statistical package from Windows SPSS (Inc., Chicago, IL, USA). All the results were discussed on 5% level of significance, i.e., $P < 0.05$ was considered statistically significant.

RESULTS

Total 307 diagnosed prostate cancer patients were referred to the department of nuclear medicine in a 5-year study period. Fifteen patients were excluded from the study due to nonavailability of Sr. PSA and the remaining 292 patients were included in the study population. Among 292 cases, 174 (59.58%) patients had positive bone scan for metastases and 118 (40.41%) patients had negative scan for metastases. Maximum and minimum Sr. PSA levels in positive and negative bone scan patients were 1260 and 0.02 ng/ml and 198.34 ng/ml and 0.01 ng/ml, respectively [Table 1]. When we compared the mean Sr. PSA levels between these two group patients, we found significant difference of Sr. PSA levels ($P < 0.05$), indicating that high levels of Sr. PSA are associated with increased incidence of bony metastases. ROC curve was derived by comparing the Sr. PSA levels of patients with positive and negative bone scan results to know the sensitivity and specificity of Sr. PSA levels at different possible cut-off points and to find out the optimal cut-off point of Sr. PSA which have high sensitivity + specificity value and also to know the accuracy of Sr. PSA test in the prediction of the skeletal metastases [Figure 1]. Area under ROC curve was 0.878 (87%) with a standard error of 0.020 ($P < 0.05$) [Table 2]. This indicates that the accuracy of Sr. PSA test in the prediction of skeletal metastases on bone scan was good. The statistical results for sensitivity, specificity, likelihood ratio for a positive test, and likelihood ratio for a negative test of the different possible PSA cut-off values are shown in Table 3. The optimal cut-off value of Sr. PSA in the prediction of skeletal metastases on bone scan in prostate cancer patients was 29.16 ng/ml, with sensitivity and specificity of 89.0% and 74.6%, respectively.

Group	Number of patients	Mean (ng/ml)	Minimum Sr. PSA levels (ng/ml)	Maximum Sr. PSA levels (ng/ml)
A	118	130.07	0.01	198.34
B	174	147.46	0.02	1260.00
Total	292	92.75	0.01	1260.00

Group A: Patients with negative bone scan; Group B: Patients with positive bone scan; Sr. PSA: Serum prostate-specific antigen

Table 2: Receiver operating characteristic curve-derived results.

Area	SE	P	95% CI Lower bound
0.878	0.20	<0.001 (significant)	0.838

Test result variables: PSA. SE: Standard error; CI: Confidence interval; PSA: Prostate-specific antigen
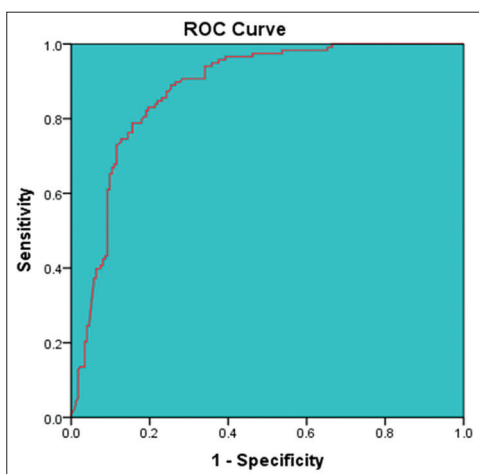

Figure 1: The receiver operating characteristic curve for predicting skeletal metastasis on bone scan in prostate cancer patients

DISCUSSION

Radionuclide whole-body bone scan is a sensitive investigation of choice to detect the skeletal metastases in prostate cancer. Because of low specificity of bone scan, false positive results are common.[9] Because of less availability, high cost, and radiation exposure, it is not always possible to use the bone scan in all patients of prostate cancer. Studies from different regions of the world suggest different cut-off values of Sr. PSA levels in the prediction of skeletal metastases on bone scan. These cut-off values vary with different regions of the world. it is crucial to establish the optimal cut-off value of Sr. PSA with optimal sensitivity and specificity to reduce the false positive results and increase the diagnostic accuracy. Ling-Huei *et al*.[10] conducted a study with 101 patients; depending on the ROC analyses, they reported optimal Sr. PSA cut-off value of 13 ng/ml in the prediction of skeletal metastases. Lin *et al*.[11] reviewed the medical records of 703 prostate cancer patients; according to their results, a bone scan is not necessary when Sr. PSA is <20 ng/ml or Gleason grade is less than or equal to 7. Ritenour *et al*. [12]

reported in thier study that the combination of Gleason score and PSA increases predictability of bone scans in prostate cancer patients. They suggested that a staging bone scan should be adjusted according to Gleason score. For patients with Gleason scores < / = 7, they recommended a bone scan if PSA is > 30 ng/ml. For patients with Gleason scores between 8 -10, they suggested bone scan if PSA > 10 ng/ml. A retrospective study by Rhoden *et al*.[13] concluded that a staging bone scan is not required in asymptomatic patients with Sr. PSA less than or equal to 20 ng/ml. Kosuda *et al*.[14] did a retrospective assessment of 1294 patients from different hospitals in Japan to know the usefulness of Sr. PSA in the elimination of a bone scan and they found that bone scan can be avoided in prostate cancer patients with Sr. PSA <10 ng/ml. However, this result varies from different regions of world and with study population. A study from India by Sharma *et al*.[15] with 89 newly diagnosed prostate cancer patients found that the incidence of skeletal metastases in their study group is 48.3%, they suggested that bone scan should be the part of initial evaluation in all patients irrespective of Sr. PSA levels. Kamaleshwaran *et al*[16] conducted a retrospective study with 270 newly diagnosed prostate cancer patients. The incidence of skeletal metastases in their study was 56% and according to them a staging bone scan can be avoided if Sr. PSA < 20 ng/ml.

Published data from different regions of the world show a significant difference in the incidence of skeletal metastases in prostate cancer patients [Table 4]. As the incidence of the skeletal metastases vary with study population,it is necessary to derive the optimal cut-off value of Sr.PSA suitable for local population in prediction of skeletal metastases on bone scan. In this study, we included 292 newly diagnosed prostate cancer patients and we used ROC analysis to know the accuracy of Sr. PSA test in the prediction of skeletal metastases and to derive sensitivity and specificity at different possible cut-off values of Sr. PSA and to know the optimal cut-off value of Sr. PSA with maximum sensitivity + specificity value. In our study population, we found that the incidence of skeletal metastases is 59.5%, which is almost near to the incidence that was found in studies conducted on Indian patients.[15,16] Based on the ROC analyses, we found that the accuracy of Sr. PSA test in the prediction of skeletal metastases was good (area under the curve was 0.878), which agrees well with other studies,[10,11]

Table 3: Receiver operating characteristic curve derived sensitivity, specificity, likelihood ratio for a positive test, and likelihood ratio for a negative test of serum prostate-specific antigen at different cut-off levels

Criterion	Sensitivity (95% CI)	Specificity (95% CI)	LRP	LRN
≦1.0	21.2 (14.2-29.7)	96.0 (91.8-98.4)	5.24	0.82
≦2.0	38.1 (29.4-47.5)	93.6 (88.9-96.8)	6.00	0.66
≦3.0	39.8 (30.9-49.3)	93.1 (88.2-96.4)	5.74	0.65
≦4.0	42.4 (33.3-51.8)	91.9 (86.8-95.5)	5.24	0.63
≦5.0	43.2 (34.1-52.7)	90.8 (85.4-94.6)	4.67	0.63
≦6.0	47.5 (38.2-56.9)	90.8 (85.4-94.6)	5.13	0.58
≦7.0	50.0 (40.7-59.3)	90.8 (85.4-94.6)	5.41	0.55
≦8.0	54.2 (44.8-63.4)	90.8 (85.4-94.6)	5.86	0.50
≦9.0	61.0 (51.6-69.9)	90.2 (84.7-94.2)	6.21	0.43
≦10	64.4 (55.1-73.0)	90.2 (84.7-94.2)	6.55	0.39
≦11	65.3 (55.9-73.8)	89.6 (84.1-93.7)	6.27	0.39
≦12	66.9 (57.7-75.3)	89.6 (84.1-93.7)	6.43	0.37
≦13	67.8 (58.6-76.1)	88.4 (82.7-92.8)	5.86	0.36
≦14	70.3 (61.2-78.4)	88.4 (82.7-92.8)	6.08	0.34
≦15	73.7 (64.8-81.4)	87.3 (81.4-91.9)	5.80	0.30
≦16	74.6 (65.7-82.1)	85.5 (79.4-90.4)	5.16	0.30
≦17	76.3 (67.6-83.6)	84.4 (78.1-89.5)	4.89	0.28
≦18	78.0 (69.4-85.1)	84.4 (78.1-89.5)	5.00	0.26
≦19	78.8 (70.3-85.8)	83.8 (77.5-89.0)	4.87	0.25
≦20	78.8 (70.3-85.8)	82.7 (76.2-88.0)	4.54	0.26
≦21	78.8 (70.3-85.8)	82.1 (75.5-87.5)	4.40	0.26
≦22	80.5 (72.2-87.2)	81.5 (74.9-87.0)	4.35	0.24
≦23	81.4 (73.1-87.9)	80.9 (74.3-86.5)	4.27	0.23
≦24	82.2 (74.1-88.6)	80.9 (74.3-86.5)	4.31	0.22
≦25	83.1 (75.0-89.3)	79.8 (73.0-85.5)	4.11	0.21
≦26	83.9 (76.0-90.0)	78.6 (71.7-84.5)	3.92	0.20
≦27	84.7 (77.0-90.7)	77.5 (70.5-83.5)	3.76	0.20
≦28	86.4 (78.9-92.0)	75.7 (68.6-81.9)	3.56	0.18
≦29.16*	89.0 (81.9-94.0)	74.6 (67.4-80.9)	3.50	0.15
≦30	89.0 (81.9-94.0)	74.0 (66.8-80.4)	3.42	0.15
≦31	89.0 (81.9-94.0)	73.4 (66.2-79.8)	3.35	0.15

*Optimal cut off value; -: the value giving highest sensitivity; +: specificity
LRP: Likelihood ratio for a positive test; LRN: Likelihood ratio for a negative test;
CI: Confidence interval

and the optimal cut-off value of Sr. PSA in the prediction of positive bone scan for skeletal metastases was <29.16 ng/ml, with sensitivity and specificity of 89.0% and 74.6%, respectively. To the best of our knowledge, very few studies used ROC analysis to derive sensitivity and specificity at different possible cut-off values of Sr. PSA in the prediction of skeletal metastases. Due to different statistical analyses, the optimal cut-off value of Sr. PSA in our study is different from the cut-off value of other Indian studies.[15,16] However, there are some limitations in this study, which may explain the high cut-off value of Sr. PSA in our study. First, it is a retrospective study. Second, other predictors for skeletal metastases such as Gleason grade and size of the tumor are not considered. A properly designed local patient population-based interinstitutional prospective study should be conducted to avoid these limitations and to derive the optimal cut-off value of Sr. PSA in the prediction of skeletal metastases.

CONCLUSION

In this study, we conclude that the accuracy of Sr. PSA test in the prediction of skeletal metastases is good. ROC curve derived optimal cut-off value of Sr. PSA for positive skeletal metastases is >29.16 ng/ml; thus, the chances of getting positive bone scan for skeletal metastasis are less in prostate cancer patients with Sr. PSA <29.16 ng/ml. ROC-derived sensitivity and specificity of different possible cut-off points of Sr. PSA help reduce the false positive results and increase the diagnostic accuracy of bone scan in the detection of skeletal metastases in prostate cancer patients.

Conflicts of interest
There are no conflicts of interest.

Table 4: Comparing incidence of skeletal metastases in prostate cancer and recommended cut-off levels of serum prostate-specific antigen in the prediction of metastases on bone scan in different studies

Author(s)	Type of study	Study place	Study population (*n*)	Incidence of bone metastasis (%)	Cut-off value of Sr. PSA (ng/ml)
Lin *et al*.[11]	Retrospective	China	703	15.08	<20
Ritenour *et al*.[12]	Retrospective	Georgia	800	4	>30
Rhoden *et al*.[13]	Retrospective	Brazil	214	16.3	>20
Sharma *et al*.[15]	Prospective observational	India	89	48.3	No threshold limit of Sr. PSA
Kamaleshwaran *et al*.[16]	Retrospective	India	270	56	<20
Zaman *et al*.[17]	Retrospective	Pakistan	204	33	<10
Present study	Retrospective	India	292	59.58	29

Sr. PSA: Serum prostate-specific antigen

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