Diagnostic Utility Of Lutetium-177 (Lu 177) Prostate-Specific Membrane Antigen (PSMA) Scintigraphy In Prostate Cancer Patients With PSA Rise And Negative Conventional Imaging

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Purpose: Prostate cancer is a major worldwide health concern with up to 60% of patients experiencing biochemical relapse after radical treatment. Introduction of prostate-specific membrane antigen (PSMA)-based radiotracers for imaging and therapy had gained increasing attention in recent years. Positron emission tomography (PET) imaging with Ga68 PSMA is the most promising technique, but PSMA-based radiotracers SPECT imaging with low dose of 177Lu-PSMA when PET imaging is not available may also be considered. The goal of the study is to evaluate the sensitivity of 177Lu_psma for detection of metastatic sites in patients with biochemical relapse and negative conventional (MRI, MRS, CT scan and bone scintigraphy) imaging.

Materials & methods: 26 patients with biochemical recurrence after curative (surgery and/or radiotherapy) therapy, which had previous negative imaging as pelvic CT scan, pelvic MRI, MRS and bone scan, were enrolled in this clinical imaging approach between 2015 and 2017.After injection of 5 mCi (185MBq)177Lu-PSMA-617, diagnostic planar whole body scan and SPECT study was obtained after 3 hours, 24 hours and 72 hours. The images were analyzed visually by an expert nuclear medicine physician for the presence of active regional or distant lesions. Results were then prospectively checked by new CT scan images as a control.

Result: A total of 26 patients, with a mean age of 70 years (range: 46 to 89 years) were included in this study. The overall detection rates were 38.5% (10 out of 26 patients). Most common site of detected lesions was lung in 6 patients, abdominal lymph nodes in 2 and mediastinum in another 2 patients.

Conclusion: 177Lu-PSMA SPECT scan can help detecting metastatic lesions in more than one third of patients with biochemical recurrence and negative conventional investigations, when 68Ga- PSMA PET is not available.

Keywords: 177Lutetium; PSMA; Scintigraphy; prostate cancer; PSA

INTRODUCTION

Prostate cancer is universally the most common malignant tumor in male gender [(1)],causing 19% of all diagnosed cancer cases in American men and estimated number of 26,730 deaths in the United States alone in 2017[(2)]. In spite of the fact that more than 80% of cases are diagnosed in a form of localized disease and are usually treated by radical prostatectomy , postoperative recurrence happens in about 15% of patients within 5 years and up to 40% within 10 years[(3)]. Once biochemical recurrence is detected, it is vital to find whether this signifies local recurrence or metastatic disease, or both and follow best treatment strategies[(4)].Different modalities like CT scan, MRI and choline PET have been introduced to detect possible sites of recurrence but each of them comes with special shortcomings[(5)]. Prostate-specific membrane antigen PSMA, is a type II transmembrane glycoprotein belonging to the M28 peptidase family. The protein acts as a glutamate carboxypeptidase on various substrates, including the nutrient folate and the neuropeptide N-acetyl-L-aspartyl-L-glutamate. PSMA is considered to be the best-established target antigen in prostate cancer as it is highly and specifically expressed on the surface of prostate tumor cells at all tumor, making PSMA an excellent target for both imaging and therapy. Previous studies have shown that [68Ga]-PSMA PET T imaging can detect lesions that were not previously recognized in MRI images and at lower median PSA levels[(1,6)].Various therapeutic trials using beta emitters bound to PSMA have also confirmed that treatments- like -177Lu-PSMA- are safe and effective options for patients with metastatic or local recurrence of prostate cancer and has a low toxicity profile as positive response to therapy in terms of decline in PSA occurs in about 70% of patients[(7-10)].
SPECT imaging after injection of 177Lu-PSMA for therapeutic purposes clearly shows sites of local recurrences or distant metastases[(11)]. This opportunity, while Lack of PET scanners in some centers has made the diagnostic use of [68Ga]-PSMA PET impossible, brings to mind that low doses of 177Lu-PSMA may also help physicians to find unidentified locations of disease re-

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Table1. characteristics of patients investigated in the study.

Patient No	Age	Gleason score	PSA level(ng/dl)	Positive finding	Location of Metastasis
1	63	8	15	no	-
2	78	7	4.34	yes	mediastinum
3	61	6	2.50	no	_
4	62	9	1.53	no	-
5	59	7	2.38	no	-
6	78	8	2.17	no	-
7	72	9	1.53	no	-
8	78	8	1.27	no	-
9	78	7	12.60	yes	Abdominal lymph nodes
10	82	8	9	Yes	Lung
11	71	7	4.02	Yes	Lung
12	61	9	3.03	Yes	Abdominal lymph node
13	59	8	2.72	Yes	lung
14	62	9	5.33	No	-
15	73	7	1.54	No	-
16	89	7	2.12	No	-
17	46	8	2.60	No	-
18	82	7	2.67	No	-
19	86	7	200	Yes	Mediastinum
20	77	8	3.7	yes	Lung
21	68	7	2.04	No	-
22	72	8	2.34	No	-
23	66	6	3.24	No	-
24	73	8	1.70	No	-
25	57	8	2.35	No	lung
26	61	9	3.2	yes	lung

currence or metastases which were not shown in traditional imaging (MRI, Bone scintigraphy, etc..).
In this study we investigated the benefit of using low doses of 177Lu-PSMA in prostate cancer patients with biochemical recurrence (PSA rise), whom all other imaging was negative, to find places of recurrence or distant metastases.

MATERIALS AND METHODS

We studied 26 prostate cancer patients between August 2015 and September 2016 with biochemical recurrence (PSA rise). All patients had undetectable PSA level after initial curative therapy (surgery and/or radiotherapy) and later in different intervals during the follow up showed PSA elevation. Initial assessments including pelvic MRI and MRS as well as bone scan, were all negative.
After injection of 5-mCi (185MBq)177Lu-PSMA-617 diagnostic planar whole-body scan (with bed speed of 10 mm/min) and SPECT(64 30 second views over 360 degree((Siemens Symbia Evo Excel dual head variable angle gamma camera, LEHR collimator) study was obtained after 3 hours, 24 hours and 72 hours. The images were inspected visually by an expert nuclear medicine physician for the presence of active regional or distant lesions and abnormal findings were confirmed by CT scan. Then the results were gathered and analyzed using SPSS software versions 23.
The study was approved by ethics committee of Shahid Beheshti University of medical sciences. The procedure was fully discussed with patients and a written consent was obtained. In addition,

RESULTS

A total of 26 patients, with a mean age of 70 years

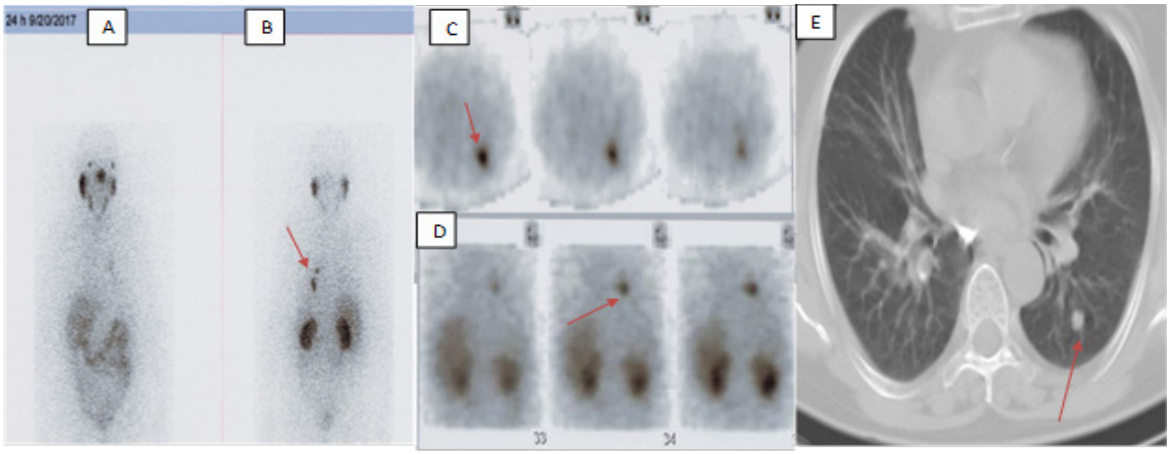

Figure 1. A anterior planar, B posterior planar, C transaxial SPECT, D coronal SPECT and E computed tomography images of the patient No 8. Images A-D are obtained 24 hours after IV injection Lu177-PSMA. The abnormal focus is shown with red arrow in each image. Abnormal activity in the base of the left lung indicates lung metastasis which was confirmed in CT scan images.

MA PET/CT with high sensitivity can show places of local recurrence or distant metastases which were not unidentified in previous imaging[15]. It is clear that PET imaging is superior to SPECT in resolution and may delineate more lesions than that of SPECT, however PET is more expensive and is less in hand than SPECT.

To our knowledge this is the first study to evaluate low doses of Lu-PSMA SPECT in detecting recurrence in prostate cancer patients and was performed in the time that 68Ga-PSMA or 99mTC-PSMA were not available for imaging. Our study showed that more than one third of patients with biochemical evidence of disease recurrence and negative initial imaging may benefit from SPECT imaging using 177-Lu PSMA. It is very important to note that this technique can find lesion in less expected regions like lung and mediastinum which are not routinely checked by MRI or bone scintigraphy. One may claim that using 177-Lu PSMA harbors risk of beta radiation; but with low dose administration, this risk is ignorable[16]. Among 19,316 routine autopsies performed from 1967 to 1995 on men older than 40 years of age, the reports from those 1,589 (8.2%) with prostate cancer were analyzed. Hematogenous metastases were present in 35% of 1,589 patients with prostate cancer, with most frequent involvement being bone (90%), lung (46%), liver (25%), pleura (21%), and adrenals (13%)

Among 26 patients we studied, 10 patients were diagnosed with distant metastasis and lung was the most common site. Although lung is not generally supposed to be involved in the process of prostate cancer but our study and other studies as well contradict the belief , for example in a recent study, lung metastases was proved pathologically in a patient with prostate cancer[17]. Therefore, using PSMA ligand imaging may increase the frequency of detection of unusual metastatic sites. The main disadvantage of 177Lu-PSMA imaging is low spacial resolution of this imaging technique, however it can be used in patients who cannot afford 68Ga-PET/CT, and sometimes in pre-radioligand therapy to assess PSMA avidity of metastatic lesions. Our study gives an estimation of sensitivity of 177Lu-PSMA SPECT, in these patients.

Limitations: It was optimal to prove positive findings of the imaging with biopsy, however obtaining biopsy in most cases was very difficult and in some cases was impossible, so regarding few false positive reports, we employed CT scan to confirm positive findings which is however to some degrees suboptimal.

CONCLUSIONS

Although PET imaging using Ga68-PSMA with its high sensitivity and positive predictive value is the most promising imaging method in patients with prostate cancer recurrence[18-21] when is not available can be replaced with SPECT imaging using 177-Lu PSMA as a great asset in cases of biochemical recurrence and negative traditional imaging (MRI, CT, Bone scintigraphy) which is able to demonstrate sites of malignant involvement in more than one third of patients.

CONFLICT ON INTEREST

No conflict of interest was declared by the authors.

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