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RESEARCH ARTICLE

EVALUATION OF TUMOR BURDEN RESPONSE TO SINGLE-CYCLE OF Lu-177 PSMA TREATMENT WITH WHOLE BODY SCINTIGRAPHIC PLANAR IMAGES IN PROSTATE CANCER PATIENTS

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ABSTRACT

Purpose: The aim of this study was to evaluate treatment response and survival with post-therapy images in patients who received one cycle of Lu-177 PSMA I&T treatment.
Material and Methods: After Lu-177 PSMA I&T treatment was administered to 54 patients, maximum count, pixel count (tumor extent) and sum (total tumor burden) values were calculated with a semiautomatic program. The images after the first treatment were evaluated as basal disease images. Images obtained after the second treatment were considered the response to the first cycle treatment.
Results: It was determined that the number of maximum counts (p: 0.015) and tumor extent (p: 0.014) were significantly reduced after one cycle of Lu177 PSMA treatment. No significant change in total tumor burden (p:0.206) was detected. After one treatment cycle the maximum count in 46% of the patients and the total tumor burden in 63% of the patients. The number of pixels (tumor prevalence) in 41% of the patients decreased by ≥25%. Based on the Naïve-Bayes method, one-year survival accuracy was 71.6%.
Conclusion: With the texture analysis and machine learning of the Lu-177 PSMA post-therapy images, treatment response and survival were determined with high accuracy.

Keywords: prostate cancer, Lu-177 PSMA, radioligand therapy, scintigraphy

INTRODUCTION

Prostate cancer is the second most common type of cancer in men worldwide, among the incidence and causes of death. Mortality is high in advanced prostate cancer patients, and treatment options are limited (1). Survival is lower in patients with visceral metastases compared to patients with bone metastases alone (2).

While prostate-specific membrane antigen (PSMA) is also expressed in normal prostate cells, it is a

transmembrane glycoprotein that is expressed much more intensely by prostate cancer cells (3). It has extracellular and intracellular domains. This glycoprotein is an excellent agent for targeted therapy. Lutetium-177 (Lu-177) attaches to the extracellular portion of the glycoprotein and then internalizes into the cell (4). PSMA expression has been shown to be positively correlated with tumor aggressiveness, Gleason grade, tumor stage, biochemical recurrence, and castration resistance (5). PSMA is an ideal marker for tumor imaging and treatment. Various PSMA peptides and anti-PSMA bodies can be labeled with Lu-177.

In the phase 3 VISION-trial, Lu-177 PSMA treatment was proven to prolong survival in castration-resistant prostate cancer patients (6). Routinely, pre-treatment disease status is assessed with Gallium-68 (Ga-68) PSMA Positron Emission Tomography/Computed Tomography (PET/CT). In patients who are suitable for treatment, 3-4 cycles of treatment are administer at 6 to 12 week intervals after which treatment responses are evaluated using Ga-68 PSMA PET/CT. It has been stated in the literature that up to 13 cycles of treatment can be given and it is safe (7). In some studies, it has been reported that the cumulative activity of 30-50 GBq Lu-177 PSMA is safe (8). Personalized medicine is gaining more and more importance day by day.

The aim of this study was to evaluate treatment response and survival with post-therapy images in patients who received one cycle of Lu-177 PSMA I&T treatment.

MATERIAL AND METHODS

Patient selection

The study was approved Izmir Katip Celebi University (Date: 28.08.2019, No: 347). Despite primary and secondary lines of treatment (docetaxel, cabazitaxel, abiraterone, enzalutamide, sipuleucel T, Ra-223), which are known to prolong survival, patients who showed progression based on Ga-68 prostate-spesific membrane antigen Positron Emission Tomography / Computed Tomography (PSMA PET/CT) were given Lu-177 PSMA I&T treatment. The treatment decision was approved by the tumor council which included an urologist, oncologist, radiologist, radiation oncologist and nuclear medicine physician.

The treatment process was explained to all patients by a nuclear medicine physician before the treatment, and informed consent forms were signed.

Patient preparation before treatment

All patients were evaluated with Ga-68 PSMA PET/CT before treatment. Hemogram, kidney function tests, liver function tests, electrolyte, lactate dehidrogenase (LDH), alkaline phosphatase (ALP) and serum prostate specific antigen (PSA) values were checked. Renal functions of all patients were evaluated with Tc-99m MAG3 scintigraphy.

Lu-177 PSMA preparation and application

Lu-177 PSMA synthesis was performed in the synthesis unit. At least 30 min before the treatment, intravenous (IV) ondansetron was administered to the patients to prevent nausea and vomiting and IV hydration was initiated. Lu-177 PSMA (7.4 GBq) was prepared in 100 cc saline and given to the patients by IV infusion for 10 to 30 min. IV hydration was continued for at least 2 h after radioligand therapy. Patients were advised to drink plenty of water and empty their bladders. After one night in the hospital, the patients were discharged after planar images of the whole body were obtained at the 24th h. Patients were given a second treatment with the same method 8-10 weeks after treatment.

Evaluation of whole body images after treatment

After the first and second treatment, the whole body anterior and posterior images were processed using the LifeX software (9). Based on the anterior and posterior images, areas of activity uptake showing PSMA expression were drawn as “regions of interest (ROIs)”. ROI areas were created by drawing lines around the lesions in a one-dimensional plane. In the drawing results, the highest activity (maximum count) in the pixel, total pixel count and total tumor load (sum) were calculated. The geometric mean of the anterior and posterior counts was calculated. The images after the first treatment were considered as the baseline state of the disease. Response to the first cycle treatment was evaluated from the images after the second treatmentThe highest activity in pixels, total pixel count and >25% reduction in total tumor burden were considered as treatment response. An increase of >25% in these values was considered as progression, and ±25% as stable disease.

Prostate spesific antigen (PSA) values obtained before both treatments were compared. The PSA value obtained before the second treatment was evaluated as a response to one cycle of treatment.

Statistics

Data were evaluated using the IBM SPSS 22 (Armonk, NY) program. The mean, median values and range of values for various variables were used. The Kaplan Meier method was used for survival analysis. Nonparametric test methods were used for survival analysis statistics. A p value ≤0.05 was considered significant.

Diagnostic performance tests were calculated with Naïve-Bayes and IBk model by repeating cross-validation 10 times using the Weka software (10-fold cross validation test), and the best parameters determining 1 and 2-year survivals were determined (10). According to the cross validation results; accuracy, sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively) data were obtained.

RESULTS

Patient characteristics

The data of 54 patients with a mean age of 68 (50-88) years who received Lu-177 PSMA I&T treatment were retrospectively reviewed. The median Gleason score was 8 (6-10). The median PSA value of the patients was 58.7 (1.4-1722) ng/ml. All patients received hormone therapy before treatment. It was determined that the maximum count number and tumor extent (pixel) were significantly reduced after one cycle of Lu177 PSMA therapy (Table 1). There was no significant change in the total tumor burden (sum) was found (Table 1).

PSA response to therapy is given in Table 2. While the PSA value of the cases was 302 (0.5-1722) ng/ml before treatment, it decreased to 248 (0.4-2059) ng/ml after treatment (p: 0.035).

Maximum count, sum and pixel percentage changes are given in Tables 3, 4 and 5, respectively.

Patient-based treatment response to maximum count, sum, pixel and PSA values are given in Figures 1, 2, 3 and 4, respectively.

Fifty-three of 54 patients died at a mean of 82 (3-218) weeks, with a median of 61 weeks. One patient is still alive.

While the mean survival of patients whose maximum count value decreased by more than 50% was 94±6 weeks, the survival of patients whose maximum count

Table 1. Maximum count, sum and pixel mean values pre and post treatment

	After first treatment	After second treatment	P value
Maximum count	134 ± 104	108 ± 80	**0.015**
Sum	340999 ± 537171	275775 ± 423176	0.209
pixel	9544 ± 11045	8487 ± 10465	**0.014**

Table 2. PSA value changes after treatment

Missing patient number	PSA decrease			Stable PSA	PSA increase
3 (6%)	≥25%	≥50%	≥75%	±25%	≥25%
	21 (39%)	14 (26%)	10 (18.5%)	19 (35%)	11 (20%)

Table 3. Response percentage of maximum count value to one cycle treatment

Maximum count decrease			Stable maximum count	Maximum count increase
≥25%	≥50%	≥75%	±25%	≥25%
25 (46%)	14 (26%)	2 (3.7%)	20 (37%)	9 (17%)

Table 4. Response percentage of Sum value to one cycle treatment

Sum decrease			Stable Sum	Sum increase
≥25%	≥50%	≥75%	±25%	≥25%
29 (53%)	18 (33%)	6 (11%)	15 (28%)	10 (19%)

Table 5. Response percentage of pixel value to one cycle treatment

Pixel decrease			Stable pixel	Pixel increase
≥25%	≥50%	≥75%	±25%	≥25%
19 (35%)	11 (20%)	3 (6%)	29 (54%)	6 (11%)

Table 6. Comparison of maximum count, sum and pixel response percentages to 1 cycle treatment

		Sum ≥25% increase	Sum stable+regression
Pixel ≥25% increase	Count ≥25% increase	1 (2%)	0 (0%)
		2 (4%)	3 (5%)
Pixel stable+regression	Count stable+regression	5 (9%)	4 (8%)
		2 (4%)	37 (68%)

Table 7. Comparison of sum and PSA response percentages to one cycle treatment

	PSA stable+regression	PSA decrease
Sum stable+regression	4 (7%)	6 (11%)
Sum decrease	7 (13%)	34 (63%)

value increased or decreased by ≤ 50% was 47±6 weeks (p:0.063) as shown in Figure 5.

The mean survival of patients whose sum value decreased by > 50% was 94±7 weeks, while the survival of patients whose sum value increased or decreased by ≤50% was 47±7 weeks (p:0.090) as shown in Figure 6.

The mean survival of patients whose pixel value decreased by more than 50% was 128±47 weeks, while the survival of patients whose pixel value increased or decreased by less than 50% was 49±9 weeks (p:0.002) as shown in Figure 7.

After one cycle of treatment, the maximum count number in 46% of the patients was determined and, the total tumor burden in 63%. The number of pixels in 41% decreased by more than 25%. (Tables 3, 4, 5). The maximum count was determined in 83% of the patients and the sum in 91%. The pixel values in 87% remained stable or decreased.

Maximum count, sum and pixel changes are compared in Table 6.

As showmn in Table 7, the total tumor burden and PSA response to one cycle of treatment were compared.

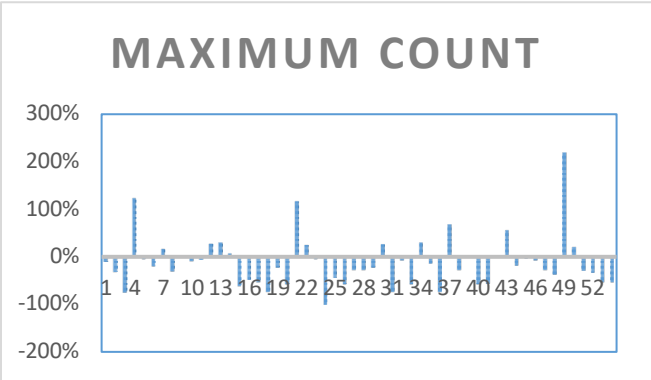

Figure 1. Patient-based maximum count change

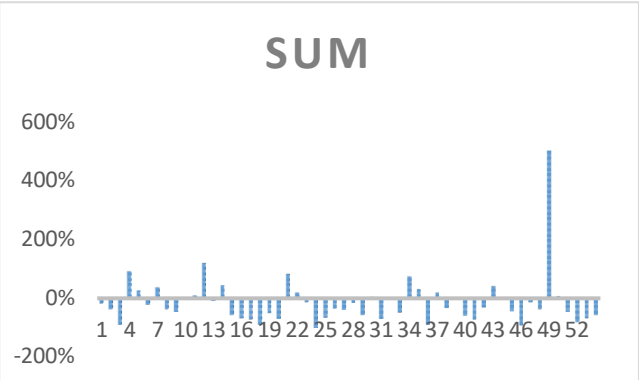

Figure 2. Patient-based sum change

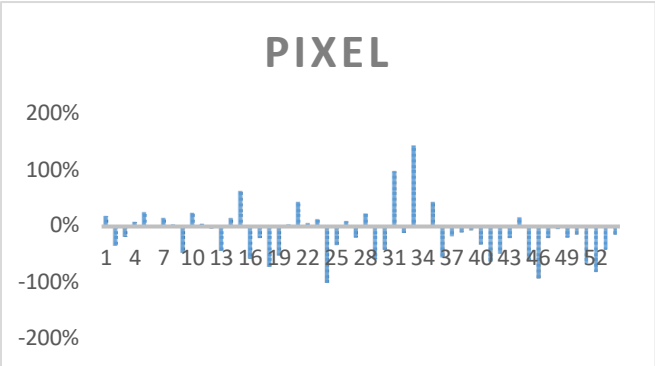

Figure 3. Patient-based pixel change

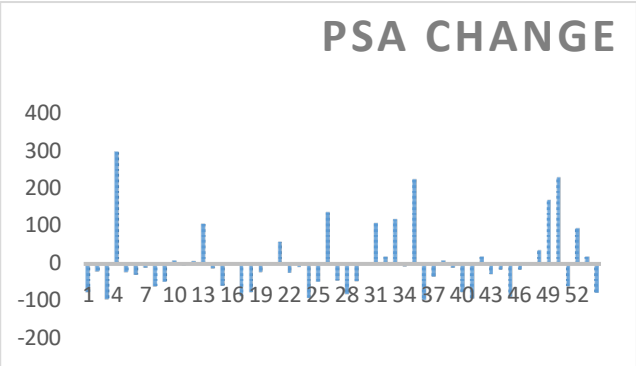

Figure 4. Patient-based PSA change

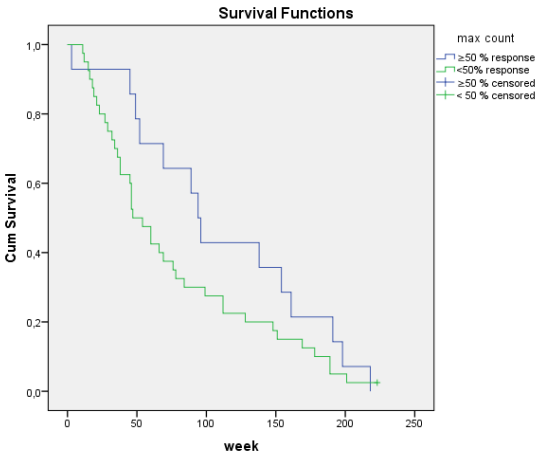

Figure 5. Graph of survival for patients with a maximum count value ≥50% and <50% decreased after one cycle of treatment

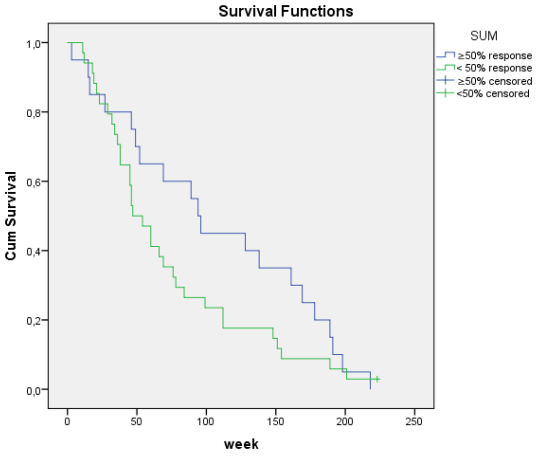

Figure 6. Graph of survival in patients whose Sum value ≥50% and <50% decreased after one cycle of treatment

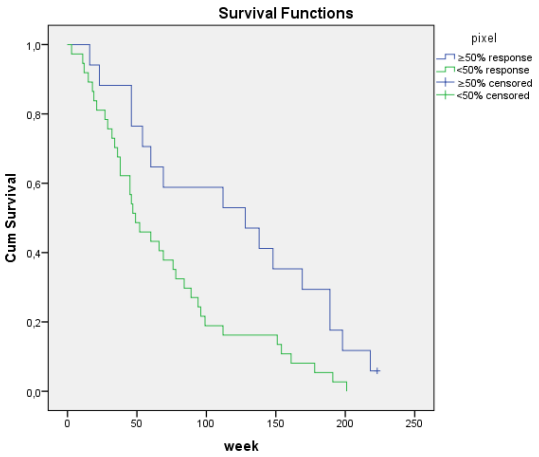

Figure 7. Graph of survival in patients whose pixel value ≥50% and <50% decreased after one cycle of treatment

Machine learning algorithms were performed with all parameters, PSA and age values. With the Naïve-Bayes method, one-year survival accuracy was calculated as 71.6%, true positive rate as 72%, false positive rate as 35%, precision (positive predictive value) as 72%, and recall as 72%.

With the Naïve-Bayes method, two-year survival accuracy was calculated as 67.9%, true positive rate as 68%, false positive rate as 21%, precision as 79%, and recall as 68%. With the IBk method, two-year survival accuracy was calculated as 75.4%, true positive rate as 76%, false positive rate as 39%, precision as 74%, and recall as 76%.

DISCUSSION

In our study, we evaluated the single-cycle treatment response to Lu-177 PSMA treatment on planar images. A significant decrease was observed in the PSA and maximum count response, and tumor extent after one cycle of treatment. A significant increase in survival was noted in cases in which the pixel value decreased by more than 50%. One-year and 2-year survival could be predicted with high accuracy using machine learning. This study describes a potential method that can be used to determine survival with 1 cycle of Lu-177 PSMA treatment.

Ga-68 PSMA PET/CT is extensively used to evaluate treatment response to Lu-177 PSMA treatment (11, 12). Ga-68 and Lu-177 are different radionuclides. Ga-68 PSMA and Lu-177 PSMA cannot replace each other with 100% compatibility. For this reason, we designed a study in which scintigraphic images obtained after treatment were used to evaluate the treatment response of Lu-177 PSMA.

Calculating tumor burden with Ga-68 PSMA PET/CT is a good treatment response evaluation method. (13, 14). Similarly, in our study, we calculated the tumor burden from the post-treatment images and evaluated the next post-treatment imaging as a response to the first treatment. Thus, we were able to determine the status of the disease after one treatment, without waiting for 3 to 4 cycles of treatment routinely used to evaluate the treatment response and a response time of about six weeks to the last treatment. Treatment response evaluation methods using PSMA PET/CT, biochemical response and clinical parameters have also been reported in the literature. (15).

Studies reporting that the use of interim PSMA PET/CT is a good predictor of survival after two courses of Lu-177 PSMA treatment are available

(16). Some centers administer Lu-177 PSMA treatment every four weeks. (17). The method of our study is also used in the interim treatment process. Significant regression or progression of the patients can be detected without delay, and personalized treatment methods can be adminestered to the patients. Routine 8-12 week treatment regimens can be continued in patients who present regression and stabilization. In progressive patients, according to the condition of the disease; The time between treatments may be shortened, the treatment dose increased, or the Lu-177 PSMA treatment discontinued, and other treatment options, such as alpha treatments, may be considered (18).

It has been reported in the literature that Lu-177 PSMA treatment between 4 to 9.3 GBq.can be used (19). We prefer 7.4 GBq in our routine practice. Patients receiving the same dose of treatment ensured that the study was homogeneous.

We use the PSA response extensively in the Lu-177 PSMA treatment response. Although 12 weeks after treatment is usually recommended for PSA measurement, there are studies showing that PSA response can be seen after a few days. (1). In our study, we evaluated the PSA response to the first cycle of LU-177 PSMA treatment after 8-10 weeks.

It has been determined in previous studies that there may be a concordance between PSMA expression and PSA response. (20, 21). In our study, agreement was found in the percentage change of PSA and sum values in 13 (24%) patients. Similar to the study of Kind et al. (1) a PSA value of >25% was considered as progression in our study.

A ≥50% PSA reduction was concidered a biochemical response to treatment in several studies (21, 22). A systemic review and meta-analysis of Sadaghiani et al. (22) reported a PSA reduction of ≥50% after treatment in 52% of patients. In the systematic review of Sun et al. (23) this rate was reported as 57%. In our study, the PSA response to one cycle of treatment was 26%. It is thought that the low response rate is due to the incompleteness of the 3 to 4 cycle treatment process.

Post-treatment scintigraphic images are used extensively for dosimetry assessments (24). We routinely use these images only to visually assess treatment response. In the study of Maffey-Steffen et al. (25), post-treatment dosimetry data were used to determine survival. In their study, overall survival was reported as 12 months. In our study, these images were used to both evaluate the treatment response quantitatively and to predict survival. In addition, one- and two-year survival could be predicted by using machine learning. The mean survival in our study was 61 weeks (approximately 15 months). In another study, survival was reported as 7.5 to 15 months. (26). In the study of Rasul et al. (17) who applied treatment every four weeks, survival was reported as 52 weeks. According to the results of the phase 3 study published very recently in which applied treatment was administered every 6 weeks, the survival was reported as five months, a result that is similar to our study (6).

It has been reported that different lesions can give a mixed response to Lu-177 PSMA treatment. (27). In our study, it was found in Table 6 that 30% of the patients had concordance in various combinations. This may be related to the fact that some lesions respond to treatment while others do not. In addition, while old lesions respond to treatment due to radioligand involvement, the emergence of new metastases due to circulating tumor cells also agreed with our results.

It has been reported in the literature that 30% of patients did not respond to treatment (28, 29). In our study, an increase in maximum count, sum and pixel numbers were detected in 37% of patients. The reason for this higher rate in our study is that the response to only 1 cycle of treatment was evaluated. No publication in the literature that evaluates responses to one cycle of treatment.

Machine learning and artificial intelligence have been used frequently in imaging, diagnosis, evaluation of treatment response, and survival (30). In our study, one-year survival was determined with an accuracy of up to 71% using machine learning.

To our knowledge, our study is the first in the literature to determine treatment response and survival of Lu-177 PSMA based on machine learning and planar imaging texture analyses.

Our study has some limitations. The most important of limitation is its retrospective design and the small patient group. Our study was done with planar images. It is thought that performing the study with single photon emission computed tomography (SPECT) or single photon emission computed tomography / computed tomography (SPECT/CT) images can increase the accuracy of diagnosis. Large and prospective studies are needed for the method to be routinely applied in the clinic.

CONCLUSION

Using texture analysis, Lu-177 PSMA post-treatment appearances in prostate cancer, treatment response and survivals were determined with high accuracy using machine learning. It is thought that detecting treatment response and survival the day after the second cycle of treatment will make a unique contribution to patient treatment and disease management.

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Conflict of interests: There is no conflict of interest.
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