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TITLE: Diagnostic performance and clinical impact of ^{68}Ga-PSMA-11 PET/CT imaging in early relapsed prostate cancer after radical therapy: a prospective multicenter study (IAEA-PSMA study).

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RUNNING TITLE: PSMA-PET/CT IAEA Study

ABSTRACT

Biochemical recurrence (BCR) is a clinical challenge in prostate cancer (PCa) patients as recurrence localization guides subsequent therapies. The use of positron emission tomography (PET) with prostate-specific membrane antigen (PSMA) provides better accuracy than conventional imaging practice. This prospective, multicenter, international study evaluates the diagnostic performance and clinical impact of PSMA-PET/CT in evaluating BCR in Pca in a worldwide scenario.

Methods

Patients were recruited from 17 centers in 15 countries. Inclusion encompassed histopathology-proven prostate adenocarcinoma with previous primary treatment and clinically established BCR, with serum PSA < 4 ng/mL or < 10 ng/mL with negative MR and bone scintigraphy. All patients underwent PET/CT scanning with ^{68}Ga-PSMA-11. Images and data were centrally reviewed. Multivariate logistic regression analysis was applied to identify the independent predictors of PSMA-positive results. Variables were selected for this regression model based on significant associations in the univariate analysis and previous clinical knowledge: Gleason Score, PSA at PET time, PSA doubling time and primary treatment strategy. All patients were followed for a minimum of 6 months.

Results

From a total of 1004 patients, 77.7% were treated initially with radical prostatectomy and 22.3% with radiotherapy. Overall, 65.1% presented PSMA-PET/CT positive scans. PSMA-PET/CT positivity was correlated with Gleason, PSA at PET time, PSA doubling time and radiotherapy as primary treatment (p<0.001). Treatment was modified based on PSMA-PET/CT results in 56.8% of patients. PSMA-PET/CT positivity rates were consistent and not statistically different among different income countries.

Conclusion

This multicenter international prospective trial on PSMA-PET/CT confirms its capability in detecting local and metastatic recurrence in most prostate cancer patients in the setting of BCR. PSMA-PET/CT positivity was correlated with Gleason score, PSA at PET, PSA doubling time and radiotherapy as primary treatment. PSMA-PET/CT results led to changes in therapeutic management in more than half of the cohort. The study demonstrates the reliability of PSMA-PET/CT in the workup of PCa patients with BCR, and its worldwide feasibility.

Key Words*:* PSMA; PET/CT; prostate cancer; biochemical relapse.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men, accounting for 7.1% of all cancers in this population (*1*). Greater life expectancy worldwide and improved access to screening and diagnostic methods in developing nations are mainly responsible for a current trend of increment in incidence (*2*).

Initial treatment with curative intent is feasible, with radical prostatectomy or radiotherapy, nevertheless, early recurrence occurs in up to 50% of patients within 10 years (*3-5*)**.** Biochemical recurrence (BCR) is defined as increasing serum prostate specific antigen (PSA) levels following initial treatment, under specific criteria (*6-8*)*.*

The key question in BCR remains whether the rise of PSA is reflective of local, regional, or distant recurrence, for proper treatment planning. With increasing success rates of early salvage therapy, the diagnosis of local tumor recurrence at the earliest possible stage has become pertinent. Salvage radiotherapy after radical prostatectomy has been shown to be most effective, reaching a durable response, when postoperative PSA is preferably below 0.5 ng/mL, with better outcomes if the PSA level is still under 0.2 ng/mL (*4,9*).

Despite guidelines indicating PSMA-PET/CT as the imaging modality of choice in BCR (*10-17*), in some countries, especially those of lower income, conventional imaging with computed tomography (CT) and bone scintigraphy (BS) are still being used, even if the diagnostic yield of these techniques is low, especially for patients with low PSA levels (*11*).

The majority of PSMA PET/CT studies have been carried out at a single institution, or were retrospectively planned; furthermore, most reported studies were conducted in academic centers of highly developed countries, and thus no data exists on large prospective international trials. The International Atomic Energy Agency initiated a Coordinated Research Project to evaluate the feasibility and usefulness of PSMA-PET/CT to study PCa patients with BCR in 15 countries worldwide, to inform international practice.

The primary aim of this prospective study was to evaluate the diagnostic performance of PSMA-PET/CT in PCa patients with BCR worldwide, through an international multicenter effort, and the impact of PSMA-PET/CT on clinical management.

MATERIALS AND METHODS

Study Design

Two investigators' meetings were held: in 2017 and 2019. The first defined the study protocol, while in the second, an interim evaluation was carried out, together with image and data review. The study followed a prospective, multicenter, international design, encompassing 17 centers from 15 countries (Azerbaijan, Brazil, Colombia, India, Israel, Italy, Jordan, Lebanon, Malaysia, Mexico, Pakistan, Poland, South Africa, Turkey, and Uruguay). Standard forms for data registration were developed and agreed on between the investigators. Data were collected for PSMA-PET/CT positivity rate, localization of positive findings and impact on patient management (supplemental figure 1). All centers obtained local ethical clearance for prospective recruitment of patients and data collection, according to national regulations. All subjects signed an informed consent form.

Patients

Patients with histopathologically proven prostate adenocarcinoma who have undergone primary definitive treatment (radical prostatectomy or radiotherapy), with BCR, were recruited. All patients were followed for a minimum period of 6 months after PSMA-PET/CT.

Inclusion criteria were a) age >18yo; b) histopathology proven prostatic adenocarcinoma; c) previous primary treatment for PCa (radical prostatectomy or radiotherapy); d) BCR defined as after radical prostatectomy, a PSA level over 0.2 ng/mL confirmed by two subsequent consecutive measurements; after radiotherapy, an absolute increase in PSA level of 2 ng/mL above nadir; e) patients with PSA levels between 4-10 ng/mL were considered eligible only if presenting negative conventional imaging (CT + BS) and MRI; f) written informed consent.

Exclusion Criteria were a) history of any malignancy other than PCa; b) history of Paget's disease; c) patients with BCR and PSA levels ≥ 10 ng/mL.

PET/CT Imaging

All patients were submitted to PSMA-PET/CT using the same radiopharmaceutical ^{68}Ga-PSMA-11 (*18-21*), that was synthesized at the radiopharmaceutical laboratories of each participating center. PET studies were carried out on dedicated PET/CT scanners with image quality evaluated by board certified nuclear medicine physicians.

According to the methodology proposed in medical literature (*10*), patients were administered ^{68}Ga-PSMA-11 (2MBq per/Kg, minimum of 125 MBq) by slow intravenous injection. Sixty to 90 minutes after the injection, standard image acquisition was carried out. Low dose/diagnostic CT images were obtained from mid-thigh up to above the orbital-meatal line. 3D PET images were acquired for the same body extension, for at least 2 minutes/bed position. Real true body (images from head to toes), contrast enhanced CT, diuretic and late images were allowed.

PET/CT studies were assessed by two nuclear medicine board certified physicians with extensive experience in PSMA-PET/CT oncological imaging at each center and all scans were

later centrally reviewed. Discordant findings were addressed at consensus meetings and final results were used for analysis.

PET/CT Images Analysis

The studies were classified either positive or negative regarding identification of suspect findings for recurrence based on procedure guidelines for prostate cancer imaging (*10*) (Figure 1). The anatomical sites of the lesions were registered.

PSMA-PET/CT findings were compared with: a) Histology (when necessary, in the judgment of the clinician); b) Correlative imaging methods, such as: CT with contrast, MRI, whole body MRI and bone scan; and c) Clinical and laboratory data (PSA behavior). All data provided in the normal care pathway.

Given the composite nature of the standard of reference, we could not calculate sensitivity nor specificity; furthermore, a proper evaluation of negative findings was beyond the scope of the present study, which focused on accessing PSMA-PET/CT detection rate (positive rate), defined as proportion of patients with PSMA-PET/CT positive results.

Intent to Treat

Previously to the PSMA-PET/CT, an intent to treat questionnaire was filled by the assistant uro-oncology teams by the time of referral for evaluation, and was thus categorized: radiotherapy only, radiotherapy and anti-androgenic therapy (ADT), salvage lymphadenectomy, ADT only, active surveillance, bilateral orchiectomy, second-generation ADT (abiraterone or enzalutamide), radionuclide therapy and chemotherapy (taxane).

After the PSMA-PET/CT results were made available, the assistant uro-oncology team filled the same questionnaire based on the actual treatments were submitted.

Statistical Analysis

The demographic and clinical variables were tabulated using descriptive analysis. Continuous variables were assessed for the Gaussian distribution of the data and presented as mean ± standard deviation, if normally distributed, or median [percentile 25th, percentile 75th] if non-normally distributed. Comparison between patients with positive vs negative PSMA were performed using t-test or Wilcoxon-Mann-Whitney test, accordingly. Discrete variables were presented as proportions and compared between groups using the Chi-squared test. We then performed a multivariate logistic regression analysis to identify the independent predictors of positive PSMA results. Variables were selected for this regression model based on significant associations in the univariate analysis and previous clinical knowledge. Level of significance was set as a p value < 0.05. Analyses were performed using Stata version 15.1 (Stata Corp, College Station, Tx).

RESULTS

Patients' Characteristics

From the 1198 PCa patients referred for PSMA-PET/CT between November 2017 and December 2019 due to BCR were enrolled; 194 were subsequently excluded because of missing information and/or loss of follow-up data. Therefore, a cohort of 1004 patients could be analyzed, here divided by country: Azerbaijan (48), Brazil (165), Colombia (29), India (86), Israel (16), Italy (172), Jordan (26), Mexico (91), Malaysia (35), Pakistan (19), Poland (111), Turkey

(57), South Africa (42) and Uruguay (42). Two nations (India and Turkey) had 2 centers contributing, that were pooled together for the scope of the study (see list of participant centers and contributors on the supplemental material). Patients' distribution according to Gleason Score was: GS 7 = 613 patients (61.1%), GS 8 = 196 (19.5%), GS 9 9 = 180 (17.9%) anda GS 10 = 15 (1.5%); according to PSA at PET/CT: PSA <0.2 = 41 patients (4.1%), PSA ≥0.2 and <0.5 = 188 (18.7%), PSA ≥0.5 and <1 = 232 (23.1%), PSA ≥1 and <2 = 235 (23.4%), PSA ≥2 and <4 = 206 (20.5%); and PSA ≥4 and <10 = 102 (10.2%). Mean PSA doubling time was 11.18 months (±13.15) (Table 1). Overall, 780 (77.7%) patients were treated initially with radical prostatectomy while 224 (22.3%) with radiotherapy. The mean time from PCa diagnosis to BCR was 15.6 months (0.6 - 43.7) at the time of PET, 248 (24.7%) patients were ongoing ADT; 630 (62.7%) presented PSA doubling time ≤10 months.

The mean age of patients was 67.3 years-old (range 45-87); 908 (90.4%) men fulfilled eligibility based on having PSA < 4ng/mL, while 96 (9.6%) presented PSA concentration between 4-10 ng/mL with negative MR, CT and BS. Mean PSA at PSMA was 1.55 ng/mL. Regarding the stage at presentation, 443 men (44.1%) had clinical stages T1–2 and 341 (34.0%) clinical stages T3–4; in 220 (21.9%), T Stage was unknown. The mean duration of follow-up after PSMA-PET/CT was 16.8 months (standard deviation 9.3 months).

Regarding income, there were 105, 509, and 390 patients in the lower middle, upper middle- and high-income groups, respectively. PSA differences were not significant among them ($p = 0.94$). Of notice, there were statistically significant differences regarding PSA doubling time, ongoing ADT and radiotherapy as primary treatment between the different income groups. Respectively, mean PSA doubling time was 9.14, 9.98 and 13.3 months ($p < 0.001$); ongoing ADT patients totaled 40(38.1%), 131 (25.7%) and 77 (19.7%) ($p < 0.001$); and radiotherapy as primary treatment was observed in 42 (40.0%), 129 (25.3%) and 53 (13.6%) patients ($p < 0.001$).

PSMA-PET/CT

At least one malignant lesion was found in 65.1% (654/1004) of the patients, while 34.9% (350/1004) had a negative PSMA-PET/CT scan with no detectable disease. Summary results of PSMA-PET/CT are reported in Table 1.

There was a correlation between PSMA-PET/CT and Gleason Score (GS) ($p<0.001$): detection rate was 60.5% (371/613) for patients with GS 7, 66.3% (130/196) for GS 8, 77.8% (140/180) for GS 9 and 86.7% (13/15) for GS 10 (Figure 2).

We also found a significant correlation between PSMA-PET/CT positivity and PSA values ($p<0.001$): detection rate was 51.2% (21/41) for PSA <0.2, 44.7% (84/188) for PSA ≥0.2 and <0.5, 53.4% (124/232) for PSA ≥0.5 and< 1, 67.2% (158/235) for PSA ≥1 and <2; 83.0% (171/206) for PSA ≥2 and <4; and 94,1% (96/102) for PSA ≥4 and <10 (Figure 3).

PSMA-PET/CT was positive in 69.4% (437/630) of the patients whose PSA doubling time was ≤ 10 months versus 58.0% (217/374) whose PSA doubling time was above 10 months ($p = 0.003$) (Figure 4).

The positivity rates of PSMA-PET/CT per anatomical sites were prostate or prostatic bed only in 13.7% (138/1004); at prostate or prostatic bed and pelvic lymph nodes in 3.9% (39/1004); pelvic lymph nodes only in 20.5% (206/1004); metastasis at any site in 27.0% (271/1004), being bone only in 10.0% (100/1004) (Table 2). At univariate analysis, factors associated with a positive PSMA-PET/CT results were age, PSA at time of PET scan (PSA at PSMA), PSA doubling time (PSAdt), initial PSA before therapy, TNM, Gleason score, ongoing ADT and radiotherapy as first treatment. Logistic regression showed that positivity of PSMA-PET/CT scan was associated with Gleason Score, PSA at PSMA, decreasing PSA doubling time, and radiotherapy as primary treatment (Table 3).

From the 1004 cases included, 12.4% (124 patients) presented doubtful PET findings (as reported by local readers); among these, 90 patients had other positive findings, regardless

of the indeterminate one(s), thus, were already defined as PSMA-PET/CT positive scans. In the remaining 34 patients (3.3%) in which the indeterminate lesion at PSMA-PET/CT was the sole finding, 3 were confirmed to be true positive on basis of follow-up data, while 31 (3.1%) were regarded as false positives (encompassing reactive lymph nodes, bone fractures, trauma, and benign pulmonary lesions).

Impact of PSMA-PET/CT on Clinical Management

Patients' disease management changed in 56.8% (570/1004) of our cohort after PSMA-PET/CT information. The following changes occurred as a result of PSMA-PET/CT: 77 patients were submitted to active surveillance, 35 to radiotherapy only, 55 to radiotherapy and ADT, 152 to ADT only, 48 to salvage lymphadenectomy, 5 patients to bilateral orchiectomy, 140 underwent a second-generation ADT (abiraterone or enzalutamide), 10 were submitted to radionuclide therapy and 48 polymetastatic patients were started on taxane chemotherapy.

In 43.2% (434/1004) of the patients for which there was no management change motivated by PSMA-PET/CT results: 118 patients remained under active surveillance, 57 were submitted to radiotherapy only, 48 to radiotherapy and ADT, 5 to salvage lymphadenectomy, 155 to ADT, 2 to bilateral orchiectomy, 32 underwent a second-generation ADT (abiraterone or enzalutamide) and 17 polymetastatic patients were submitted to taxane chemotherapy (Figure 5).

PSMA-PET/CT Worldwide

The centers were grouped in two distinct ways: by country income (high income: Israel, Italy, Poland and Uruguay; upper middle income: Azerbaijan, Brazil, Colombia, Jordan, Mexico,

Malaysia, Turkey, South Africa; lower middle income: India and Pakistan) and by continent (Africa, America, Asia, Europe). There were no significant differences between positivity of PSMA-PET/CT in lower middle, upper middle and high income (61%, 69% and 62%) and by continent (Africa: 57%, Asia 65%, Europe 66% and Latin America 65%), p =0.07 and p = 0.73, respectively; (Table 1).

DISCUSSION

Our findings resonate with the available literature on the use of PSMA-PET/CT in the evaluation of PCa patients in the scenario of BCR (*3-8,10,20-44*). We analyzed four main aspects of PSMA-PET/CT in this setting: positivity rate, clinical factors associated with PSMA-positivity, differences of performance regarding continents and income reality and impact on clinical management. The positivity rate of PSMA-PET/CT was 65.1%, similar to the positivity rates reported in other studies, overall ranging from 63-75% (*10,14,16,21,22*). Also, increasing PSA levels at the time of scan were associated with higher PSMA-PET/CT positivity, with similar rates as previously reported (supplemental table 1), except for a higher PSMA-PET/CT positivity in the PSA <0.2 group when compared to the mean of previously available literature: 51.2% vs 36.8% (*3-8,10,20-44*). This might be explained by the small number of patients in this group in our cohort (41) but also the small number of patients evaluated in the sum of the cohort of all patients reported (316). Nevertheless, 51.2% falls into the range observed in the literature (11.3 - 58.3%). In the other scenarios (PSA < 0.5, < 1.0 and < 2.0) the positivity rates were quite similar (44.7% vs 43.3%; 53.4% vs 52.2% and 67.2% vs 58.9% respectively).

The observed location of malignant lesions is in agreement with previous reports, with lymph nodes being the principal site of recurrence (24.4%), followed by local recurrence on prostate bed (17.6%), and with any metastatic disease in 27.0% (*9,45*).

Furthermore, higher positivity rates were also associated with features of advanced and/or aggressive disease other than increasing PSA levels: shorter PSA doubling time (≤ 10 months) and higher Gleason Score. These findings are also in tune with the current available literature (*42,46*) and are likely due to neoplastic lesions to be present to a greater extension, and with higher tumoral cells turnover, thus, providing more available sites for PSMA ligand binding, which leads to positive PET/CT results.

One interesting finding was the association of radiotherapy as primary radical treatment with PSMA-PET/CT positivity in the BCR setting. Although patients submitted to radiotherapy represented only 22.3% of all patients, they comprised 28.9% of all positive PSMA-PET/CT results (p<0.001). It is already known that, in comparison to radical prostatectomy, radiotherapy is associated with higher biochemical recurrence rates (*46*). Our results suggest that in addition to more frequent residual/recurrent disease, these patients are also more likely to present a positive PSMA-PET/CT scan in the BCR setting.

The most relevant finding in our understanding is that there were no statistically significant differences in PSMA-PET/CT performance among continents, nor among the different income categories in which the participants were distributed. This is important as it highlights that even though great heterogeneities exist among nations, this does not seem to interfere with each country's capacity of providing high quality PSMA-PET/CT studies in the appropriate medical centers.

PSMA-PET/CT impacted clinical management in more than half of our cohort, as the therapeutic strategy was altered by PSMA-PET/CT results in 56.8% of the time, similar to previous reports in different studies (*13,16,21*).

Regarding the limitations of the present study, a major one is that histopathology as a gold standard was only available in a minority of cases. It is well known that histopathologic confirmation in all patients is not feasible because of practical and ethical issues. Hence, in most patients, a composite standard of reference (histopathology, clinical and laboratory

evaluation) was used. Another important limitation are the relatively small percentages of patients included in low-income countries and in Africa. Furthermore, South Africa's income reality and PSMA PET/CT availability do not paint a representative picture of the continent. Moreover, regarding the impact of PSMA-PET/CT impact on clinical management, the available data unfortunately do not permit evaluation of its effects on survival rates.

The endeavor of performing this multicenter international study, enrolling more than a thousand patients from around the globe, was only made possible by the conjunct effort of several different researchers, with the support of the International Atomic Energy Agency, a non-profit agency, which enabled gathering this large and diverse cohort.

CONCLUSION

This multicenter international prospective trial on PSMA-PET/CT confirms its capability in detecting local and metastatic recurrence in most prostate cancer patients in the setting of biochemical recurrence. PSMA-PET/CT positivity was correlated with Gleason score, PSA at PET, PSA doubling time and radiotherapy as primary treatment. PSMA-PET/CT results led to changes in therapeutic management in more than half of the cohort. The study demonstrates the reliability of PSMA-PET/CT in the workup of PCa patients with BCR, and its worldwide feasibility.

DISCLOSURES

There were no personal grants, consulting fees, or honoraria involved in the present paper. No potential conflicts of interest relevant to this article exist.

KEY POINTS

Question

In a large international cohort of prostate cancer patients in the setting of biochemical recurrence, how similar are PSMA-PET/CT positivity rates and impact on clinical management among countries from different continents and incomes?

Pertinent Findings

PSMA-PET/CT positivity has shown correlation with Gleason Score, serum PSA levels and radiotherapy as primary treatment. Impact on clinical management following PSMA-PET/CT results was observed in the majority of cases. All findings were similarly consistent regardless of the country.

Implications for Patient Care

Our results confirm the worldwide feasibility and usefulness of PSMA-PET/CT in the setting of prostate cancer biochemical recurrence.

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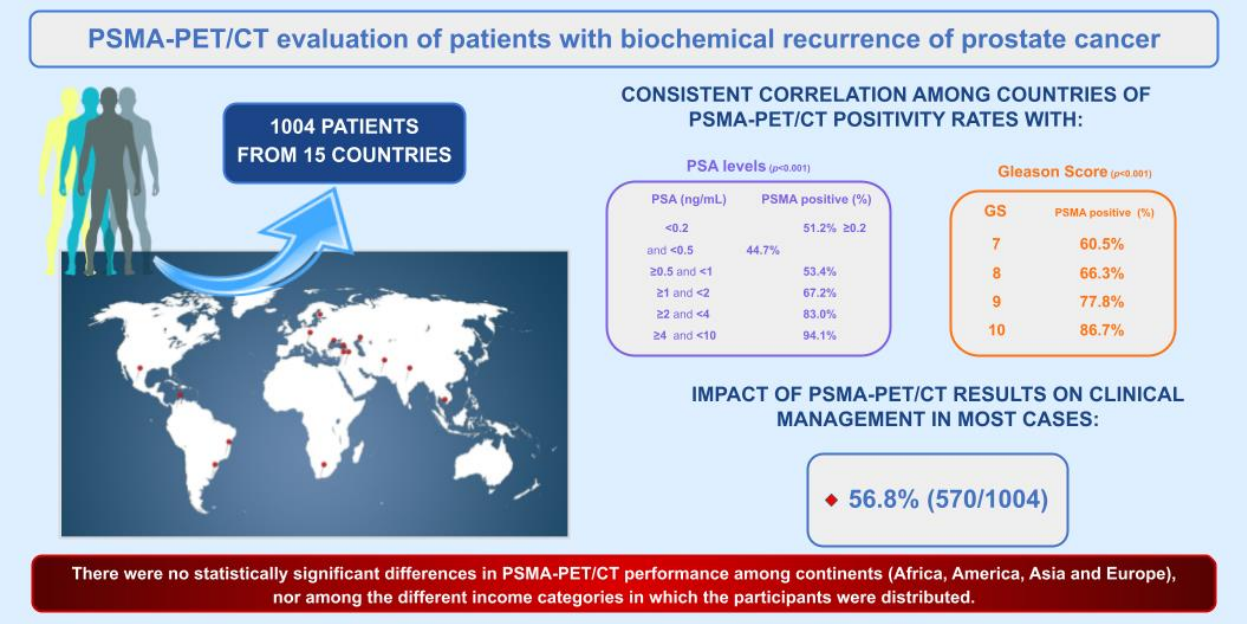
GRAPHICAL ABSTRACT



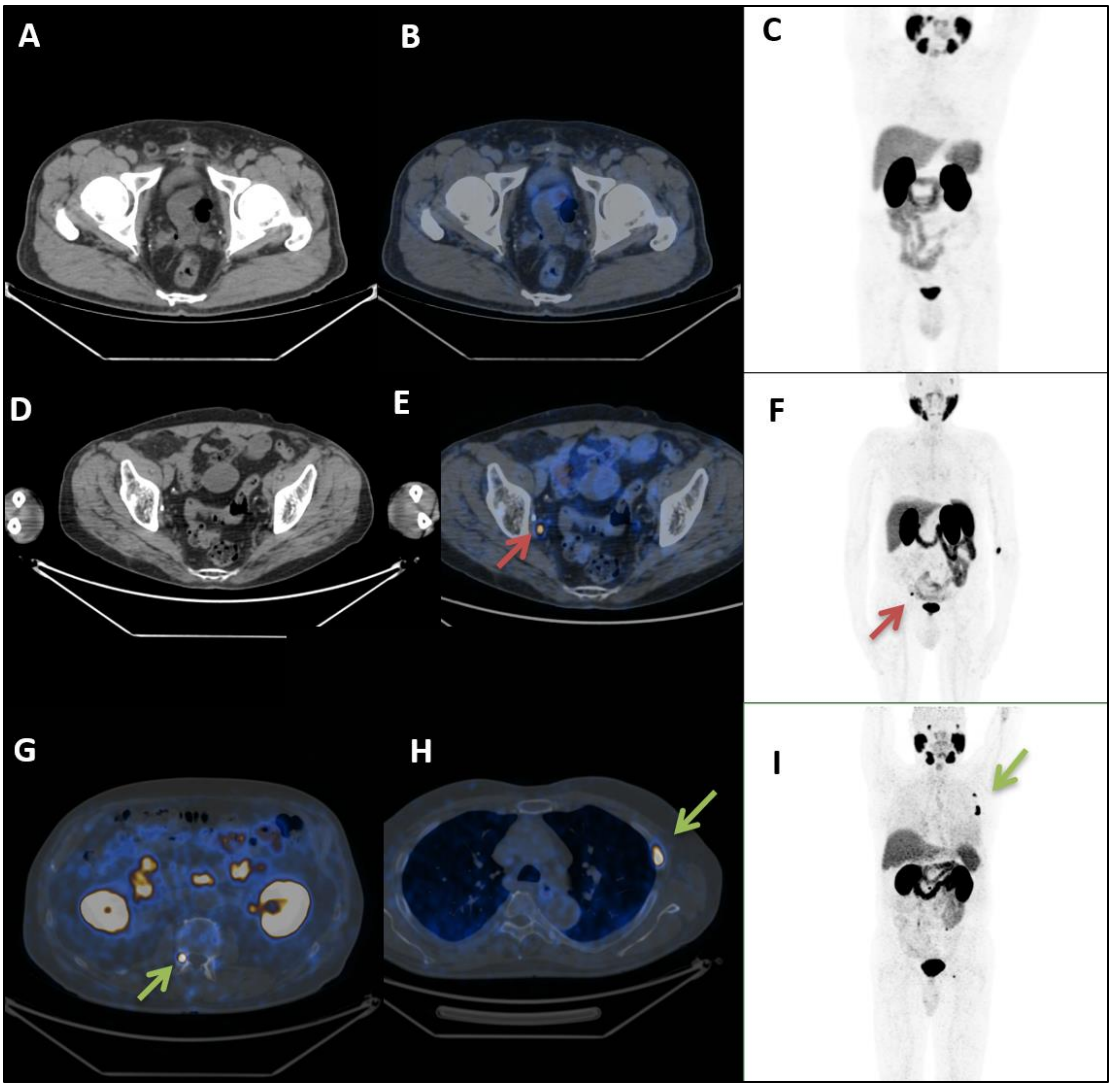


Figure 1: Panels **A-C** show a 65yo patient, T3bN0, submitted to radical prostatectomy + PNLD, with BCR (PSA 0.55 ng/mL) showing a PSMA-PET/CT-negative scan. Treatment plan was not altered by PSMA-PET/CT results (radiotherapy) (**A:** axial CT; **B:** axial fusion and **C:** MIP). Panels **D-F** show a 67yo patient, T2aN1, submitted to radical prostatectomy + PNLD, with BCR and PSA 0.4 showing a PSMA-PET/CT-positive scan. Treatment plan was modified from radiotherapy to ADT (**D:** axial CT, **E:** axial fusion and **F:** MIP) with 0,4cm lymph nodes commitment (red arrows). Panels **G-I** show a 65yo patient, T3aN0, submitted to radical prostatectomy + PNLD, with BCR and PSA 0.2 showing a PSMA-PET/CT-positive scan. Treatment plan was modified from radiotherapy to chemotherapy (**G:** axial CT, **H:** axial fusion and **I:** MIP) with metastatic bone lesions (green arrows).

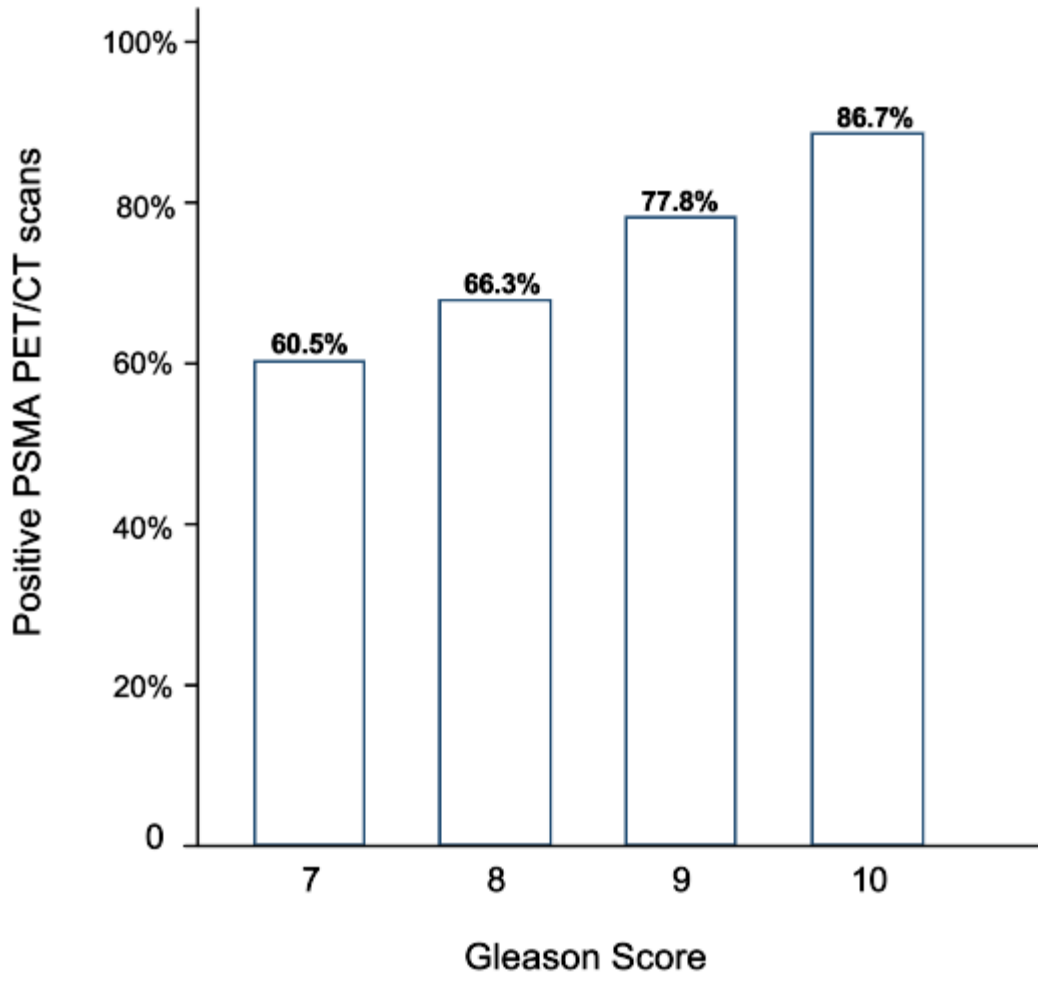


Figure 2: Correlation between PSMA-PET/CT positivity and Gleason Score.

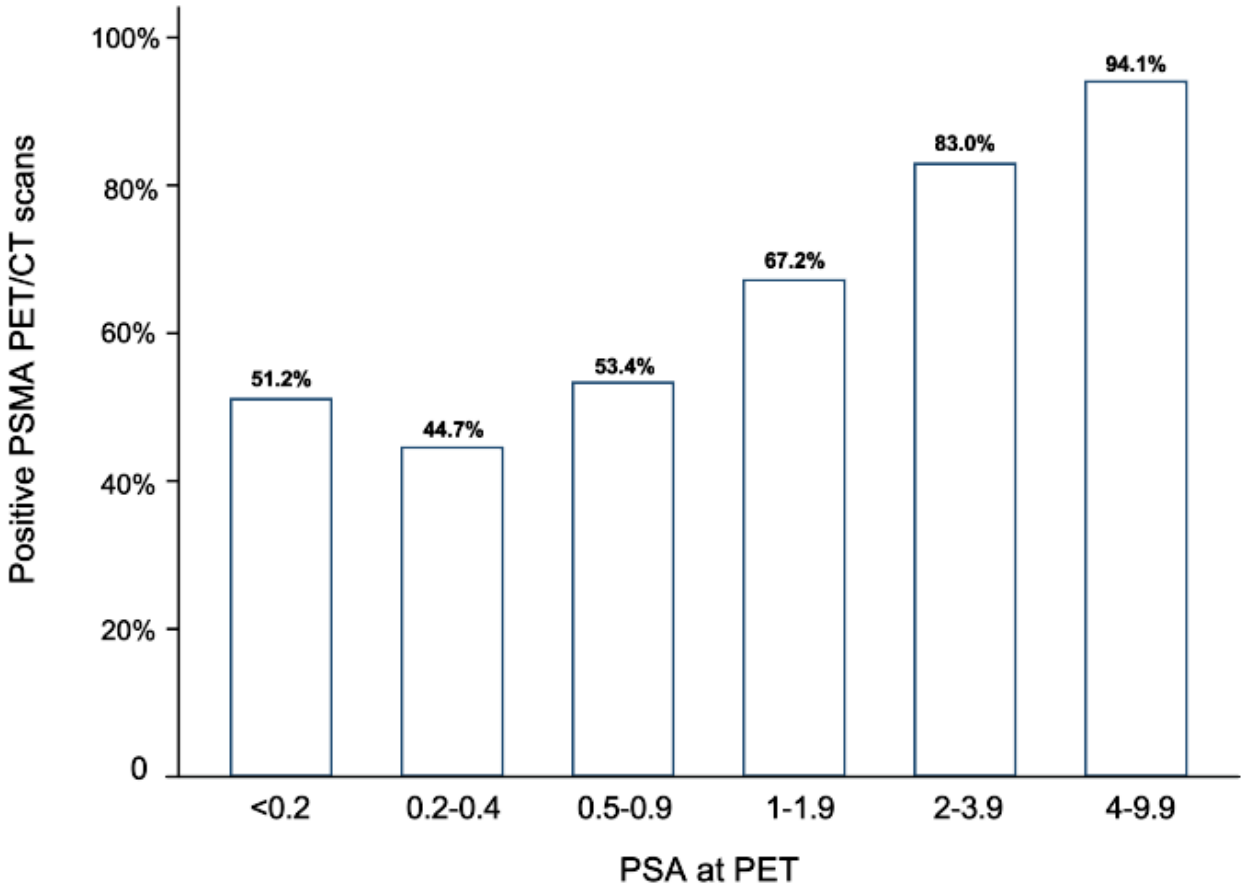


Figure 3: Correlation between PSMA-PET/CT positivity and PSA values.

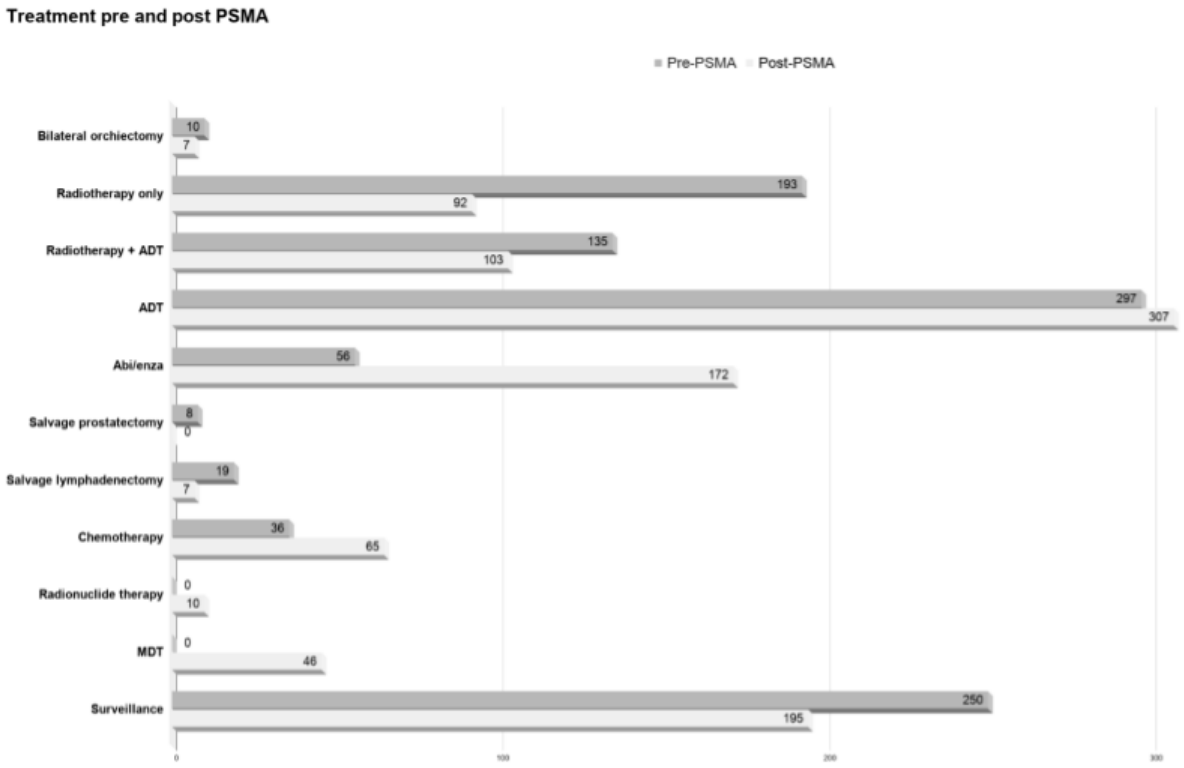


Figure 4: Impact of PSMA-PET/CT on Clinical Management.

Number of patients	All patients n=1004	PSMA-PET/CT negative n=350	PSMA-PET/CT positive n=654	*p*
Age	67.29 ± 7.48	66.37 ± 7.36	67.77 ± 7.51	0.005
PSA at PSMA				<0.001
<0.2	41 (4.1%)	20 (5.7%)	21 (3.2%)	
0.2-0.5	188 (18.7%)	104 (29.7%)	84 (12.8%)	
0.5-1.0	232 (23.1%)	108 (30.9%)	124 (19.0%)	
1-2	235 (23.4%)	77 (22.0%)	158 (24.2%)	
2-4	206 (20.5%)	35 (10.0%)	171 (26.1%)	
>4	102 (10.2%)	6 (1.7%)	96 (14.7%)	
PSA Doubling Time	11.18 ± 13.15	12.97 ± 14.04	10.22 ± 12.56	0.002
Initial PSA Before Therapy	17.27 ± 22.10	14.63 ± 17.69	18.69 ± 24.02	0.006
TNM				<0.001
T1	4 (0.5%)	2 (0.6%)	2 (0.4%)	
T2	439 (56.0%)	208 (65.8%)	231 (49.4%)	
T3	333 (42.5%)	103 (32.6%)	230 (49.1%)	
T4	8 (1.0%)	3 (0.9%)	5 (1.1%)	
On going ADT	248 (24.7%)	62 (17.7%)	186 (28.4%)	<0.001
Radiotherapy as first treatment	224 (22.3%)	35 (10.0%)	189 (28.9%)	<0.001
Time to Relapse	23.0 [8.0, 49.0]	22.5 [8.0, 48.0]	24.0 [9.0, 51.0]	0.57
Gleason				<0.001
7	613 (61.1%)	242 (69.1%)	371 (56.7%)	
8	196 (19.5%)	66 (18.9%)	130 (19.9%)	
9	180 (17.9%)	40 (11.4%)	140 (21.4%)	
10	15 (1.5%)	2 (0.6%)	13 (2.0%)	
Country Income				0.07
High income	390 (38.8%)	149 (42.6%)	241 (36.9%)	
Upper middle income	509 (50.7%)	160 (45.7%)	349 (53.4%)	
Lower middle income	105 (10.5%)	41 (11.7%)	64 (9.8%)	
Continent				0.73
Africa	42 (4.2%)	18 (5.1%)	24 (3.7%)	
Asia	182 (18.1%)	64 (18.3%)	118 (18.0%)	
Europe	388 (38.6%)	132 (37.7%)	256 (39.1%)	
Latin America	392 (39.0%)	136 (38.9%)	256 (39.1%)	

Table 1: Patients' characteristics based on PSMA PET results.

	PSMA-PET/CT positive studies
Anatomical site	
Prostate or prostatic bed only	138 (13.7%)
Prostate or prostatic bed + lymph nodes	39 (3.9%)
Lymph nodes only	206 (20.5%)
Metastasis at any site	271 (27.0%)
Bone only	100 (10.0%)

Table 2: PSMA-PET/CT positive studies per anatomical sites.

	Odds Ratio	Z	P	[95% Conf. Interval]	
Age	1.01	1.69	0.091	0.99	1.03
PSA at PCa diagnosis	0.99	-0.05	0.958	0.99	1.01
Gleason Score	1.37	3.30	0.001	1.25	1.65
PSA at PSMA-PET/CT	1.72	7.57	0.001	1.47	1.97
PSA Doubling Time	0.98	-3.30	0.001	0.97	0.99
On going ADT	1.23	1.14	0.255	0.93	1.76
Radiotherapy First	2.17	3.56	0.001	1.42	3.34

Table 3: Association of clinical covariates with likelihood of detection by PSMA-PET/CT.

SUPPLEMENTAL MATERIAL

List of participant centers and contributors:

Austria: Division of Human Health, International Atomic Energy Agency

Azerbaijan: National Centre of Oncology, Azerbaijan

Brazil: Quanta Diagnostics and Therapy

Colombia: Instituto Nacional de Cancerologia

India: All India Institute of Medical Sciences; Tata Memorial Centre

Israel Rambam Medical Centre

Italy: Azienda Ospedaliero-Universitaria di Bologna

Jordan: King Hussein Cancer Center

Lebanon: American University of Beirut; Medical Center

Malaysia: Institute Kanser Negara

Mexico: Instituto Nacional de Cancerologia

Pakistan: Pakistan Atomic Energy Commission (PAEC)

Poland: Medical University of Warsaw

South Africa: University of Pretoria

Turkey: Ankara University, Turkey; University of Gaziantep

Uruguay: Centro Uruguayo de Imagenología Molecular

Supplemental Figure 1: Final Form Report

IAEA International Atomic Energy Agency

Final Form Report

IAEA CRP "Use of PET–CT with Gallium-68 Labelled Prostrate Specific Membrane Antigen in the Diagnosis and Follow-up of Patients with Prostate Cancer"

(To be completed by the local centre enrolling the patient)

Version 2 from 2020-03-09

Form completed	*(dd/mm/yyyy)*	Today
Patient information		
01.01 Institution		Brasil - Quanta Diagnostico e Terapia
01.02 Patient Initials		
01.03 Age *(at the time of the scan)*		
Clinical Information		
02.01 TNM		
02.02 R	◯Not applicable ◯Negative surgical margin ◯Positive margin	
Pathological data		
03.01 Gleason Score		*Expressed as primary + secondary GS (e.g. 4+3)*
03.02 Initial PSA before primary therapy		
03.03 Radical therapy	◯Radical prostatectomy ◯Primary radiotherapy	
03.04 Date of primary treatment		*(dd/mm/yyyy)*
03.05 RT-Adjuvant	◯No ◯Yes	
03.06 Date RT		*(dd/mm/yyyy)*
03.07 Site RT	◯Prostate bed ◯Pelvic lymph nodes ◯Prostate bed + lymph nodes ◯Not applicable	
03.08 ADT Adjuvant	◯Hormonal therapy after primary treatment with adjuvant intent ◯No ADT	
Biochemical Relapse Data		
04.01 Androgen deprivation therapy (ADT) during biochemical relapse	◯No ◯Yes	
04.02 On-going ADT	◯1 ADT on-going at the time of the scan ◯No ADT	
04.03 Salvage therapy	◯Salvage RT ◯Salvage PLND ◯ Other salvage procedures ◯No salvage therapy during BCR	
04.04 Date of salvage therapy		*(dd/mm/yyyy)*
04.05 Site salvage	◯Prostate Bed ◯Pelvic LNs ◯Retroperitoneal and distant LNs ◯Prostate Bed + LNs ◯Other	
04.06 Time to relapse		*(in months)*
04.07 PSA PET *(ng/mL)*		*At the time of the scan (+-2weeks)*
04.08 Date of PSA performed for PSMA-		*(dd/mm/yyyy)*
04.09 PSA doubling time *(in months)*		*At the time of the scan*
PSMA PET/CT Results and Findings		
05.01 Date of PSMA scan		*(dd/mm/yyyy)*
05.02 CT of PET/CT	◯Low dose ◯Diagnostic ◯ CECT	
05.03 PET results	◯Positive for suspected PCa lesions ◯Negative for suspected PCa lesions	
05.04 PET indeterminate finding	◯An indeterminate for suspected PCa lesions ◯No indeterminate PCa lesions	
05.05 Prostate bed	◯Prostate/prostate bed relapse ◯No relapse	

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05.06 dlocal		*Transverse view, dimension of the biggest lesion, e.g.: 2 x 2 cm*
05.07 SUVmax local		*Of the lesion with highest uptake*
05.08 Number of local lesions	Select number...	
05.09 LN local	◯ Pelvic LNs suspected for PCa relapse ◯ No suspected pelvic LNs	
05.10 dLN local		*Transverse view, dimension of the biggest lesion, e.g.: 2 x 2 cm*
05.11 SUVmax LN local		*Of the lesion with highest uptake*
05.12 Number of lymph nodes	Select number...	
05.13 Bone	◯ Bone lesions ◯ No bone lesions	
05.14 dbone		*Transverse view, dimension of the biggest lesion, e.g.: 2 x 2 cm*
05.15 SUVmax Bone local		*Of the lesion with highest uptake*
05.16 Bone number lesion		*Site of the lesion*
05.17 Other	◯ No ◯ Lung ◯ Liver ◯ Other	
05.18 If other, please specify	◯ 0-10 ◯ > 10	
05.19 Other lesion dimension		*Transverse view, dimension of the biggest lesion, e.g.: 2 x 2*
05.20 SUVmax other		*Of the lesion with highest uptake*
05.21 Doubtful findings	◯ Yes ◯ No	
05.22 If yes, please specify		
Correlative Imaging		
06.01 MR	◯ Not performed ◯ Negative scan ◯ Positive scan	
06.02 CT	◯ Not performed ◯ Negative scan ◯ Positive scan	
06.02.01 If positive scan showed	◯ Less PCa lesions than PSMS ◯ Same lesions as PSMA ◯ More PCa lesions than PSMA	
06.03 Bone scan	◯ Not performed ◯ Negative scan ◯ Positive scan	
06.03.01 If positive scan showed	◯ Less PCa lesions than PSMS ◯ Same lesions as PSMA ◯ More PCa lesions than PSMA	
06.04 TRUS	◯ Not performed ◯ Negative scan ◯ Positive scan	
06.04.01 If positive scan showed	◯ Less PCa lesions than PSMS ◯ Same lesions as PSMA ◯ More PCa lesions than PSMA	
06.05 PET Choline	◯ Not performed ◯ Negative scan ◯ Positive scan	
06.05.01 If positive scan showed	◯ Less PCa lesions than PSMS ◯ Same lesions as PSMA ◯ More PCa lesions than PSMA	
06.06 PET Fluoride	◯ Not performed ◯ Negative scan ◯ Positive scan	
06.06.01 If positive scan showed	◯ Less PCa lesions than PSMS ◯ Same lesions as PSMA ◯ More PCa lesions than PSMA	
Intent to Treatment		
07.01 Salvage Radiotherapy	◯ No ◯ Yes	
07.02 Site S-RT *(site of irradiation)*	◯ Prostate bed ◯ Pelvic LNs ◯ Prostate bed + Pelvic LNs	
07.03 Salvage lymphadenectomy	◯ No ◯ Yes	
07.04 Site S-PLND	◯ Pelvic-LND ◯ Extended-PLND	
07.05 Other surgery	◯ No ◯ Yes	
07.05.01 If yes, please specify		
07.06 Chemotherapy	◯ No ◯ Abiraterone ◯ Enzalutamide ◯ Other	
07.06.01 If other, please specify		
07.07 Hormone therapy	◯ No ◯ Yes	
07.08 Radio nuclide therapy	◯ No ◯ 223Ra ◯ 177-Lu	
07.09 Further imaging required	◯ No ◯ TRUS ◯ CT ◯ MR ◯ Choline PET ◯ Fluoride PET	
07.10 Further biopsy required	◯ No ◯ Yes	
07.10.01 If yes, please specify		

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Follow-up Data	
08.01 Follow-up *(date)*	*(dd/mm/yyyy)*
08.02 PSA	*report all the PSA values assessed during patient follow-up*
08.03 Progression	◯No ◯Yes
08.04 Date of progression	*(dd/mm/yyyy)*
08.05 Death	◯No ◯Yes
08.06 Date of death	*(dd/mm/yyyy)*
08.07 Histology Prostate Bed	◯Histological confirmation of the prostate bed relapse obtained ◯No histological confirmation
08.08 Histology LNs	◯Histological confirmation of LNs relapse obtained ◯No histological confirmation
08.09 Histology Bone	◯Histological confirmation of bone lesion obtained ◯No histological confirmation
08.10 Histology other	◯Histological confirmation of other lesion obtained ◯No histological confirmation
08.10.01 If other, please specify	
08.11 MDT	◯Metastasis directed therapy performed according to PSMA results ◯No MDT
08.12 Salvage Radiotherapy	◯No ◯Yes *(dd/mm/yyyy)*
08.13 Site S-RT *(site of irradiation)*	◯Prostate bed ◯Pelvic LNs ◯Prostate bed + Pelvic LNs
08.14 Site S-PLND	◯Pelvic-LND ◯Extended-PLND
08.15 Other surgery	◯No ◯Yes *(dd/mm/yyyy)*
08.15.01 If other, please specify	
08.16 Chemotherapy	◯No ◯Abiraterone ◯Enzalutamide ◯Other
08.16.01 If yes, the date	*(dd/mm/yyyy)*
08.16.02 If other, please specify	
08.17 Hormone therapy	◯No ◯Yes if yes, provide starting date *(dd/mm/yyyy)*
08.18 Radio nuclide therapy	◯No ◯223Ra ◯177-Lu if yes, provide date *(dd/mm/yyyy)*
08.19 Further imaging required	◯No ◯TRUS ◯CT ◯MR ◯Choline PET ◯Fluoride PET

Validate Data | Submit Data

Supplemental Table 1: Table of studies reporting on PSMA positivity in early recurrence prostate cancer at different PSA levels:

Studies reporting on imaging in early recurrent prostate cancer at PSA level ≤ 0.2 ng/mL			
Author (year)	**Standard of reference**	**N**	**Sensitivity (%)**
Meredith et al. (2016)	PET/CT result alone	124	11.3%
Dietlein et al. (2017)	Clinical and imaging follow-up, histology	9	22.2%
Sachpekidis et al. (2016)	PET/CT result alone	4	25.0%
Schmuck et al. (2017)	Clinical and imaging follow-up histology in a minority of patients (n=112)	18	38.9%
Afshar-Oromieh et al. (2017)	PET/CT result alone	69	46.4%
Afshar-Oromieh et al. (2015)	Clinical and imaging follow-up, histology in a minority of patients (n=42)	17	47.1%
Gupta et al. (2017)	PET/CT result alone	12	41.7%
Hope at al. (2017)	Clinical and imaging follow-up	12	58.3%
Kranzbuhler et al. (2018)	PET/CT result alone	9	44.4%
Miksch et al. (2020)	Clinical and imaging folllow-up	18	27.0%
Sonni et al (2020)	Clinical follow-up	24	42.0%

		Total: 316	Mean: 36.8

Studies reporting on imaging in early recurrent prostate cancer at PSA level ≤ 0,5 ng/mL

Author (year)	Standard of reference	N	Sensitivity (%)
Dietlein et al. (2017)	Clinical and imaging follow-up	NA	11.0%
Sanli et al. (2017)	Clinical and imaging follow-up	10	20.0%
Sachpekidis et al. (2016)	PET/CT result alone	8	37.5%
Calais et al. (2018)	Histology, clinical and imaging follow-up in a minority of patients	153	40.5%
Afshar-Oromieh et al. (2017)	PET/CT result alone	177	46.3%
Afshar-Oromier et al. (2015)	Histology in a minority of patients (n=42)	27	48.1%
Morigi et al. (2015)	Histology in a minority of patients (n=9)	16	50.0%
Lengana et al. (2018)	Clinical and imaging follow-up	11	55.0%
Rauscher et al. (2018)	Histology in a minority of patients	134	55.0%
Eiber et al. (2015)	PET/CT result alone	19	58.0%
Meredith et al. (2016)	PET/CT result alone	206	17.5%

Gupta et al. (2017)	PET/CT result alone	28	42.9%
Schmuck et al. (2017)	Histology, clinical and imaging follow-up in a minority of patients (n=112)	52	50.0%
Berliner et al. (2017)	Histology in a minority of patients (n=2)	33	51.5%
Derlin et al. (2018)	Clinical and imaging follow-up, histology	24	20.8%
Hope et al. (2017)	Clinical and imaging follow-up	26	61.5%
Grubmuller et al. (2018)	Clinical and imaging follow-up, histology	NA	65.0%
Fendler et al. (2019)	Clinical, PSA and imaging follow-up	52	38.0%
Deandreis et al. (2020)	Clinical and imaging follow-up, histology when feasible	79	23.2%
Ceci et al. (2019)	Clinical and imaging follow-up, histology	138	37.9%
Farolfi et al. (2019)	PET/CT result alone	119	34.4%
Miksch et al. (2020)	Clinical and imaging folllow-up	28	55.0%
Hoffmann et al (2020)	Clinical and imaging follow-up, histology in a minority of patients	27	40.0%
Kraft et al (2020)	Clinical and imaging follow-	151	59.0%

	up, histology when feasible		
Bianchi et al. (2020)	Clinical follow-up	249	35.8%
Sonni et al. (2020)	Clinical follow-up	21	62.0%
Calais et al. (2019)	Clinical and imaging follow-up, histology in a minority of patients	26	46.0%
McCarthy et al. (2019)	PET/CT result alone	63	50.8%
		Total: 1877	**Mean: 43.3**

Studies reporting on imaging in early recurrent prostate cancer at PSA level ≤ 1,0 ng/mL

Author (year)	Standard of reference	N	Positivity rate
Derlin et al. (2018)	Clinical and imaging follow-up, histology	38	18.4%
Sanli et al. (2017)	Clinical and imaging follow-up	14	21.4%
Sachpekidis et al. (2016)	PET/CT result alone	11	36.4%
Verburg et al. (2016)	Histology in a minority of patients (n = 18), follow-up in a minority of patients (n = 7)	27	44.4%
Calais et al. (2018)	Histology, clinical and imaging follow-up in a minority of patients	270	49.0%

Berliner et al. (2017)	Histology in a minority of patients (n = 2)	44	52.3%
Afshar-Oromieh et al. (2015)	Histology in a minority of patients (n = 42)	51	52.9%
Schmuck et al. (2017)	Clinical and imaging follow-up, histology in a minority of patients (n = 112)	81	53.1%
Afshar-Oromieh et al. (2017)	PET/CT result alone	296	57.1%
Rauscher et al. (2018)	histology in a minority of patients	272	64.7%
Eiber et al. (2015)	PET/CT result alone	52	67.3%
Meredith et al. (2016)	PET/CT result alone	258	25.2%
Gupta et al. (2017)	PET/CT result alone	46	37.0%
Hope et al. (2017)	Clinical and imaging follow-up	37	62.2%
Fendler et al. (2019)	Clinical, PSA and imaging follow-up	45	57.0%
Ceci et al. (2019)	Clinical and imaging follow-up, histology	92	53.6%
Miksch et al. (2020)	Clinical and imaging folllow-up	77	68.0%
Hoffmann et al. (2020)	Clinical and imaging follow-up, histology in a minority of patients	48	61.5%
Kraft et al. (2020)	Clinical and imaging follow-	141	79.0%

	up, histology when feasible		
Bianchi et al. (2020)	clinical follow-up	164	54.7%
Calais et al. (2019)	Clinical and imaging follow-up, histology in a minority of patients	18	67.0%
McCarthy et al. (2019)	PET/CT result alone	24	66.7%
		Total: 2106	**Mean: 52.2%**

Studies reporting on imaging in early recurrent prostate cancer at PSA level ≤ 2,0 ng/mL

Author (year)	Standard of reference	N	Positivity rate
Sanli et al. (2017)	PET/CT result alone	16	31.7%
Derlin et al. (2018)	PET/CT result alone	60	39.1%
Lengana et al. (2018)	Clinical and imaging follow-up	23	39.1%
Sachpekidis et al. (2016)	None	15	46.7%
Berliner et al. (2017)	Histology in a minority of patients (n = 2)	54	55.6%
Ceci et al. (2015)	Clinical and imaging follow-up, histology	37	56.7%
Verburg et al. (2016)	Histology in a minority of patients (n = 18), follow-up in	46	58.7%

	a minority of patients (n = 7)		
Schmuck et al. (2017)	Clinical and imaging follow-up, histology in a minority of patients (n = 112)	120	59.2%
Morigi et al. (2015)	Histology in a minority of patients (n = 9)	30	60.0%
Afshar-Oromieh et al. (2015)	Histology in a minority of patients (n = 42)	90	61.1%
Afshar-Oromieh et al. (2017)	PET/CT result alone	462	65.2%
Eiber et al. (2015)	PET/CT result alone	124	82.3%
Meredith et al. (2016)	PET/CT result alone	316	35.7%
Gupta et al. (2017)	PET/CT result alone	54	40.7%
Hope et al. (2017)	Clinical and imaging follow-up	60	68.3%
Fendler et al. (2019)	Clinical, PSA and imaging follow-up	75	84.0%
Deandreis et al. (2020)	Clinical and imaging follow-up, histology when feasible	106	49.6%
Ceci et al. (2019)	Clinical and imaging follow-up, histology	102	71.3%
Hoffmann et al. (2020)	Clinical and imaging follow-up, histology in a minority of patients	61	70.0%
Fourquet et al. (2020)	Clinical and imaging follow-up, histology in a minority of	10	70.0%

	patients (n=5)		
Sonni et al. (2020)	Clinical follow-up	38	82.0%
Calais et al. (2019)	Clinical and imaging follow-up, histology in a minority of patients	6	67.0%
McCarthy et al. (2019)	PET/CT result alone	24	62.5%
		Total: 1929	**Mean: 58.9%**