

Clinical utility of ^{18}F -fluorocholine positron-emission tomography/computed tomography (PET/CT) in biochemical relapse of prostate cancer after radical treatment: results of a multicentre study

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Objective

To evaluate ^{18}F -fluorocholine positron-emission tomography (PET)/computed tomography (CT) in restaging patients with a history of prostate adenocarcinoma who have biochemical relapse after early radical treatment, and to correlate the technique's disease detection rate with a set of variables and clinical and pathological parameters.

Patients and Methods

This was a retrospective multicentre study that included 374 patients referred for choline-PET/CT who had biochemical relapse. In all, 233 patients who met the following inclusion criteria were analysed: diagnosis of prostate cancer; early radical treatment; biochemical relapse; main clinical and pathological variables; and clinical, pathological and imaging data needed to validate the results. Criteria used to validate the PET/CT: findings from other imaging techniques, clinical follow-up, treatment response and histological analysis. Different statistical tests were used depending on the distribution of the data to correlate the results of the choline-PET/CT with qualitative [T stage, N stage, early radical prostatectomy (RP) vs other treatments, hormone therapy concomitant to choline-PET/CT] and quantitative [age, Gleason score, prostate-specific antigen (PSA) levels at diagnosis, PSA nadir, PSA level on the day of the choline-PET/CT (Trigger PSA) and PSA doubling time (PSADT)] variables. We analysed whether there were independent predictive factors associated with positive PET/CT results.

[Correction added on 12 February 2015 after first online publication: Co-author, Dr. Juan Carlos Alonso-Farto and his affiliation has been added to the author byline]

Results

Choline-PET/CT was positive in 111 of 233 patients (detection rate 47.6%) and negative in 122 (52.4%). Disease locations: prostate or prostate bed in 26 patients (23.4%); regional and/or distant lymph nodes in 52 (46.8%); and metastatic bone disease in 33 (29.7%). Positive findings were validated by: results from other imaging techniques in 35 patients (15.0%); at least 6 months of clinical follow-up in 136 (58.4%); treatment response in 24 (10.3%); histological analysis of lesions in 17 (7.3%); and follow-up plus imaging results in 21 (9.0%). The statistical analysis of qualitative variables, corresponding to patients' clinical characteristics, and the positive/negative final PET/CT results revealed that only whether or not early treatment with RP was done was statistically significant ($P < 0.001$), with the number of positive results higher in patients who did not undergo a RP. Among the quantitative variables, Gleason score, Trigger PSA and PSADT clearly differentiated the two patient groups (positive and negative choline-PET/CT: $P = 0.010$, $P = 0.001$ and $P = 0.025$, respectively). A Gleason score of <5 or ≥ 8 clearly differentiated positive from negative PET. Trigger PSA: mean of 8 ng/mL for positive PET/CT vs 2.8 ng/mL for negative PET/CT; PSADT: mean of 8 months for positive vs 12.6 months for negative. The optimal threshold values were: 3 ng/mL for Trigger PSA level and 6 months for PSADT (Youden index/receiver operating characteristic curve). Analysing these two variables together showed that PSADT was more conclusive in patients with lower Trigger PSA levels. Analysing variables by location showed that only PSADT was able to differentiate between those with disease confined to the prostate compared with the other two

locations (lymph nodes and bone), with shorter PSADT in these two, which was statistically significant ($P < 0.002$). In the patient group with a PSA level of <1.5 ng/mL, 30.8% had the disease, 7% of whom had metastatic bone disease. In the multivariate logistic regression, the risks factors that were clearly independent for those with positive PET/CT were: PSA level of >3 ng/mL, no early RP, and Gleason score of ≥ 8 .

Conclusion

Our results support the usefulness of ^{18}F -fluorocholine PET/CT in biochemical relapse of prostate cancer after radical

treatment, with an overall disease detection rate close to 50%, and it can be recommended as first-line treatment. As mentioned above, besides Trigger PSA levels, there are other clinical and pathological variables that need to be considered so as to screen patients properly and thus minimise the number of nodular lesions and increase the diagnostic accuracy of the examination.

Keywords

PET/CT, fluorocholine, prostate cancer, recurrence

Introduction

Prostate cancer is one of the main health problems affecting the male population and one of the three malignant neoplasms with the highest incidence and mortality in Spain [1]. Although radical treatments [radical prostatectomy (RP) and radiotherapy (RT)] have had a high cure rate, there is a non-negligible risk of tumour relapse, which is about 20–30% over a 10-year follow-up after RP and 53% over a 5-year follow-up after RT. During follow-up after treatment, monitoring of serum PSA levels is the most useful tool for detecting early recurrence. Once biochemical relapse has been diagnosed, the most important point is whether clinical relapse is local or systemic, as this will determine treatment options. In this situation, neither increase in PSA levels, which come before clinically detectable disease, nor conventional imaging techniques (CIT): bone scintigraphy, CT, MRI, have been shown to be useful in disease location or discrimination between local and distant disease [2–5]. In the last few years, many studies have focused on determining the role of functional imaging techniques in this context, specifically positron-emission tomography (PET)/CT with ^{18}F -fluorocholine (choline-PET/CT), and on the correlation between the range of detection of choline-PET/CT and different clinical/pathological variables, with the aim of minimising the number of false negatives and improving the diagnostic cost-efficiency of the examination.

In 2012, in view of the published results in other countries and growing interest, the PET group of the Spanish Society of Nuclear Medicine and Molecular Imaging (SEMINIM) decided to conduct a multicentre study to analyse the diagnostic efficiency of choline-PET/CT in patients with biochemical relapse after initial radical treatment.

Our objectives were: (i) to evaluate the detection rate of choline-PET/CT in biochemical prostate cancer relapse after radical treatment and (ii) to correlate the range of detection with some clinical variables to be taken into consideration for appropriate patient selection, in order to increase the diagnostic efficiency of the examination.

Patients and Methods

We conducted a retrospective study with the participation of six Spanish hospitals (Hospital Universitario La Paz, Hospital Universitario Gregorio Marañón, and Clínica Quirón, Madrid; Hospital General Universitario, Ciudad Real; Hospital Universitario Virgen de las Nieves, Granada; and Hospital San Jaime, Alicante) that recruited 374 patients between January 2010 and October 2012; the coordinating site was Hospital Universitario La Paz, Madrid. The inclusion criteria were: having received initial radical treatment (RP, RT or both); presenting biochemical relapse at the time of the study, according to European Association of Urology (EAU) clinical guidelines [6]; availability of the main clinical and pathological variables considered in the study; availability of the clinical, pathological and imaging information required for validation of the results. Finally, 233 patients met these criteria and were included in the study.

Patient characteristics are shown in Table 1. Other clinical variables considered in the study were: patients' PSA levels at diagnosis, lowest PSA level value after initial radical treatment (nadir PSA), PSA level at PET/CT examination (Trigger PSA) and a PSA kinetic parameter, PSA doubling time (PSADT), which is the time it takes for the PSA level to double its value; this value was automatically calculated by software available in the Memorial Sloan-Kettering Cancer Center website (<http://www.mskcc.org>). All these values are shown in Table 2.

Patient preparation for PET/CT consisted of 4–6 h fasting and, in most cases, bladder catheterisation. All patients received a 4 MBq/kg injection of ^{18}F -fluoromethylcholine supplied by InstitutoTecnológico PET, Madrid (ITP). PET/CT examinations used CT for attenuation correction and anatomical location (116 General Electric and 117 Siemens equipment). The acquisition protocol consisted of an early image of the pelvis 2–5 min after radiotracer injection (≈ 2 beds of 3–4 min) and a 15–30 min post-injection study from the orbitomeatal line to the upper third of the lower extremities (6–7 beds, 3–4 min/bed); finally, some patients

Table 1 Characteristics of patients included in the study.

Characteristics	Value
Age, years (<i>n</i> = 222)	
Mean (SD)	68 (7.1)
Range	47–84
Gleason score, <i>n</i> (<i>n</i> = 216)	
≤5	70
=7	95
≥8	51
T stage, <i>n</i> (<i>n</i> = 179)	
T1	20
T2	111
T3	46
T4	2
N stage, <i>n</i> (<i>n</i> = 128)	
Nx	39
N0	80
N1	9
Early treatment, <i>n</i> (<i>n</i> = 233)	
RP	130
Other	103
Other treatments, <i>n</i> (<i>n</i> = 233)	
Yes	77
No	156
Hormone therapy, <i>n</i> (<i>n</i> = 41)	
Yes	11
No	30

Table 2 PSA parameters of patients included in the study.

	Mean	SD	Median	Minimum	Maximum	<i>n</i>
PSA at diagnosis, ng/mL	15.4	21.8	8.9	3.2	167	163
PSA nadir, ng/mL	0.92	1.90	0.12	0	9.89	54
Trigger PSA, ng/mL	5.3	8.7	2.8	0.1	67.5	230
PSADT, months	10.9	16.2	6	0	107	176

PSA nadir, lowest PSA level after early radical treatment; Trigger PSA, PSA level on day of PET/CT; PSADT, PSA level doubling time.

underwent delayed images of the pelvis at 45–60 min after injection (in 163 patients by protocol and in 70 patients if considered necessary).

All PET/CT images were analysed visually by two nuclear medicine specialists. Final PET/CT results were classified as positive or negative; ¹⁸F-fluorocholine deposits with higher-than background activity not explained by physiological phenomena defined a positive study. In case of inter-observer discrepancy final PET/CT result was obtained by consensus. Positive results were validated by: (i) results in other imaging techniques and/or (ii) clinical follow-up for at least 6 months and/or (iii) response to treatment and/or (iv) histological analysis of lesions and (v) follow-up plus imaging results. All negative PET/CT studies were considered false negatives.

Table 3 Positive/negative results of PET/CT.

	<i>n</i> (%)
Positive PET/CT	111 (47.6)
Negative PET/CT	122 (52.4)
Total	233 (100)

We studied the relationship between choline-PET/CT results and different qualitative clinical variables (T stage, N stage, type of initial radical treatment, having received a second treatment or not, receiving hormonal treatment or not at time of examination) and quantitative clinical variables (mean age at diagnosis, Gleason score, PSA at diagnosis, nadir PSA, Trigger PSA, PSADT). We also studied the ability to discriminate between choline PSA and PSADT, and identified the best threshold for both variables; we analysed the relationship between the final result by location and by some of the quantitative variables. Finally, we analysed whether there were independent predictive values associated to a positive PET/CT result.

The statistical analysis consisted of a descriptive study and analysis with different tests according to data distribution: chi-squared or Fisher's exact test to analyse the association of qualitative data; Student's *t*-test and Mann–Whitney *U*-test to compare the quantitative data between positive and negative PET/CT results; ANOVA and Kruskal–Wallis to compare quantitative data according to final result by location; the area under the receiver operating characteristic (ROC) curve (95% CI) to evaluate the discriminatory capacity of some parameters, using the Youden index to establish the best threshold point; and a univariate/multivariate log regression to identify independent factors associated with positive PET/CT results. All statistical tests were two-sided and *P* < 0.05 was considered to indicate statistical significance. SPSS software version 15 for Windows was used (SPSS Inc., Chicago, IL, USA).

Results

Choline-PET/CT identified and located relapse in 111 of 233 patients, representing an overall detection rate of 47.6%. All positive choline-PET/CT studies were validated as positive. In 122 patients (52.4%), choline-PET/CT was not capable of detecting disease (Table 3). Positive vs negative PET/CT results were validated according the results in other imaging techniques in 35 patients (15%), clinical follow-up in 136 (58%), response to treatment in 24 (10%), histological analysis of loco-regional findings in 17 (7%) and follow-up plus imaging results in 21 (9%).

When analysing positive results by location, in 26 patients (23.4%) the disease was limited to the prostate or RP bed; loco-regional and/or distant lymph node disease was detected in 52 patients (46.8%); and metastatic bone disease was found in 33 patients (29.7%) (Fig. 1).

Fig. 1 ^{18}F -fluorocholine PET/CT study of patient with prostate adenocarcinoma, with Gleason score of 7 (4 + 3), treated surgically (RP), PSA nadir 0.04 ng/mL. At 6 years after surgery, PSA levels start to rise progressively. Patient referred for PET/CT due to suspected biochemical relapse, with PSA level of 1.02 ng/mL and PSADT of 6.4 months. **(A)** Maximum intensity projection reconstruction of whole-body ^{18}F -fluorocholine PET study, which revealed multiple hypermetabolic foci in the thoracic region expressing disseminated metastatic bone disease. **(B,C)** Short-axis transaxial PET/CT images and image fusion of chest and pelvis showing bone involvement with high metabolic activity with no morphological alteration in CT.

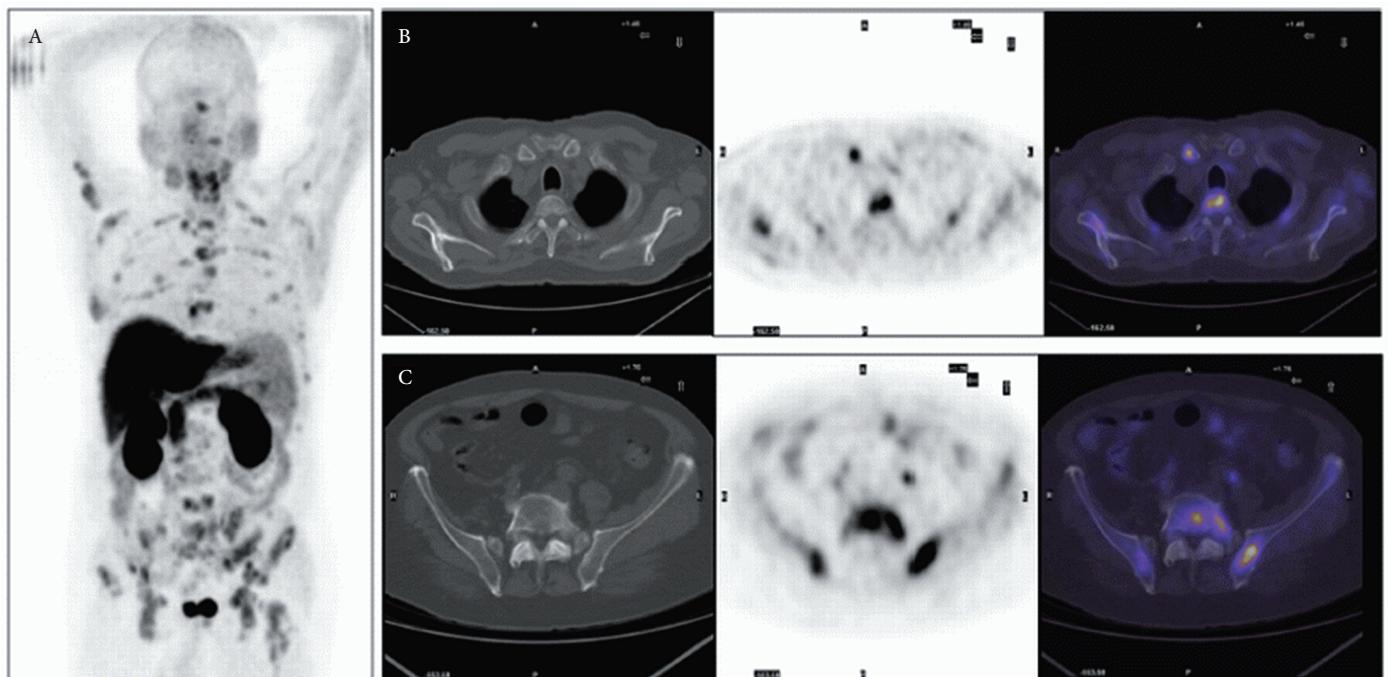


Table 4 Qualitative variable analysis/positive and negative PET/CT.

Characteristics	Total number	Positive, n	Negative, n	P
T1	20	8	12	
T2	111	52	59	
T3	46	20	26	0.464
T4	2	2	0	
NX	39	16	23	
N0	80	33	47	0.171
N1	9	6	3	
RP				
Yes	130	48	82	0.001
No	103	64	39	
Second treatment				
Yes	78	32	46	0.164
No	152	78	74	
Hormone therapy				
Yes	11	2	9	
No	30	7	23	

When analysing the association between qualitative variables and final PET/CT result (Table 4), the only statistically significant factor was having received or not initial treatment with RP ($P < 0.001$), with more positive results in patients without RP. It should be noted that patients with lymph node disease at diagnosis (N1) presented a higher percentage of positive PET/CT results than N0 patients, although the difference was not statistically significant.

Table 5 Quantitative variable analysis/positive and negative PET/CT.

	Mean (SD)		P
	Positive	Negative	
Age, years ($n = 222$)	68.5 (7.4)	67.6 (6.8)	0.322
Gleason ($n = 216$)	7.10 (1.3)	6.7 (0.8)	0.010
Prostate-specific antigen at diagnosis, ng/mL ($n = 163$)	17.7 (23.9)	13.6 (19.9)	0.161
Prostate-specific antigen nadir, ng/mL ($n = 54$)	0.96 (2.0)	0.88 (1.7)	0.332
Trigger prostate-specific antigen, ng/mL ($n = 230$)	8 (11.6)	2.8 (3.2)	0.001
Prostate-specific antigen doubling time, months ($n = 176$)	8.9 (13.4)	12.6 (18.2)	0.025

In the analysis of quantitative variables in relation to PET/CT result (Table 5), there was a statistically significant relationship for Gleason score, Trigger PSA and PSADT. Patients with Gleason ≤ 5 or ≥ 8 had more positive PET/CT results than those with Gleason > 5 or < 8 ($P < 0.010$). Positive patients had a mean Trigger PSA of 8 ng/mL vs 2.8 ng/mL in negative patients ($P < 0.001$; Fig. 2). We established several threshold points for Trigger PSA level and studied the detection rate for each one: Trigger PSA ≤ 1 ng/mL, detection rate 38.2%; Trigger PSA 1–2 ng/mL, 23.5%; Trigger PSA 2–3 ng/mL, 31.4%; Trigger PSA ≥ 3 ng/mL, 66%; we found that there is nearly a

Fig. 2 Box plot showing the distribution of Trigger PSA levels in both patient groups with positive PET/CT ($n = 110$) on the right and negative PET/CT ($n = 120$) on the left.

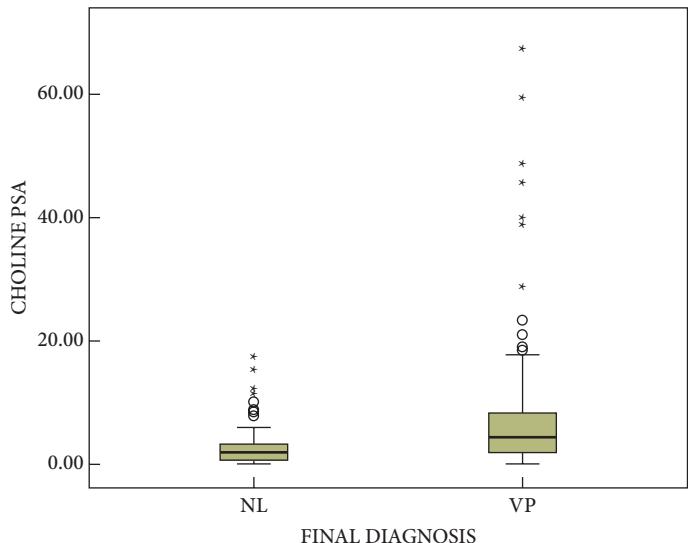
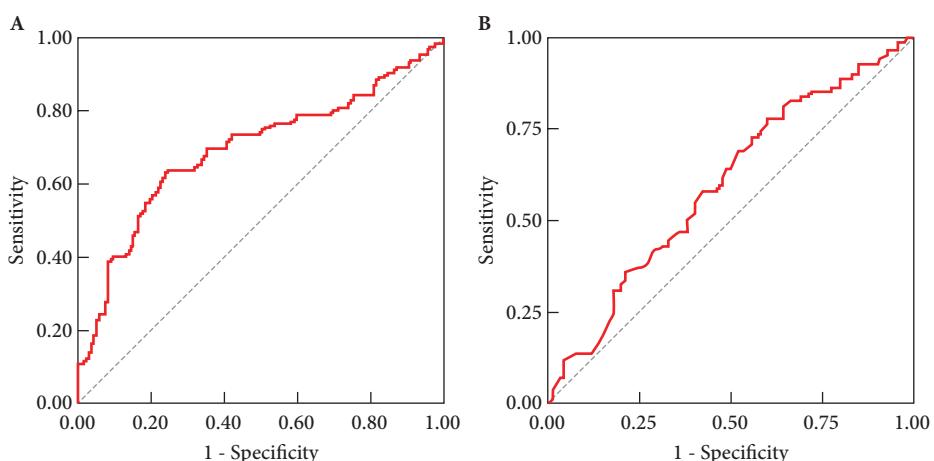
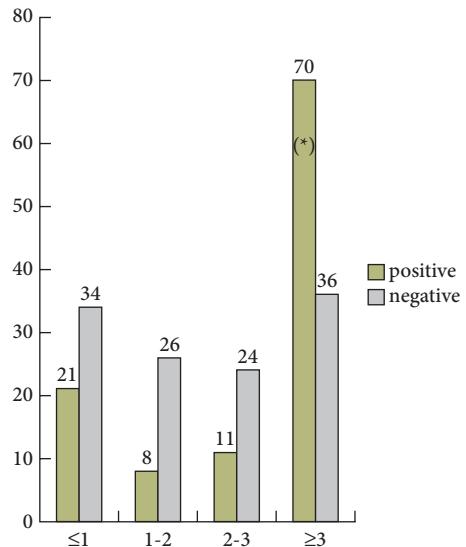


Fig. 3 Number of patients with positive and negative PET/CT in relation to Trigger PSA levels in ascending order.



linear progression as the PSA level increases, and that detection rate is >60% in patients with a Trigger PSA of >3 ng/mL at the time of PET-CT examination (Fig. 3). PSADT also showed significant differences, being shorter in the positive group, an average of 8.9 months, than in the negative group, 12.6 months ($P < 0.025$).

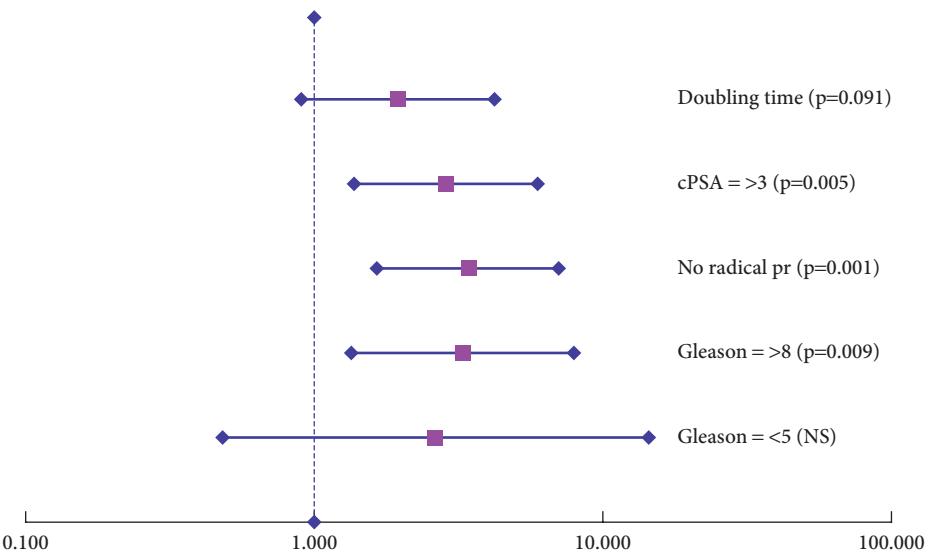
In the ROC curve evaluating the capacity of Trigger PSA and PSADT to discriminate between positive and negative PET/CT results we found that the best threshold value for Trigger PSA was 3.5 ng/mL; the sensitivity and specificity for this threshold was 64% and 76%, respectively (Fig. 4). For PSADT, the best threshold point was 6 months, with both a sensitivity and specificity of 58%. When analysing the best association between the two parameters (Trigger PSA and PSADT), we found that when Trigger PSA was <3 ng/mL, disease detection

rate was greater for patients with a shorter PSADT (<6 months) than for those with longer duplication times (>6 months), 40% vs 23% ($P < 0.001$). We found no differences between PSADT > or <6 months in the group with Trigger PSA levels of ≥3 ng/mL.

In the analysis of positive PET/CT results by location, PSADT was significantly shorter in patients with disease outside the prostate or prostate bed: 8.4 months in patients with metastatic bone disease, or 5.7 months with lymph node disease, vs 16.2 months for local relapse ($P < 0.002$). The Trigger PSA level was not capable of distinguishing between localised or distant disease.

In the group of 68 patients with a relatively low Trigger PSA level (≤ 1.5 ng/mL), 21 (31%) presented disease

Fig. 5 Multivariate logistic regression analysis of positive PET/CT predictive factors.



(metastatic bone disease in four of them). In this group of patients we found no variable capable of predicting PET/CT result; only PSADT showed a tendency towards significance ($P < 0.072$).

In the log regression analysis (Fig. 5), the following variables were independent predictive factors for positive results: Trigger PSA level of ≥ 3 ng/mL, not having received RP treatment, Gleason score of ≥ 8 .

Finally, although the study was not designed to compare choline-PET/CT with other imaging techniques, we found that from 33 patients with metastatic bone disease in choline-PET/CT, 12 had also undergone bone scintigraphy in the previous 6 months. From these patients, five were positive in both techniques, four were negative and three doubtful in bone scintigraphy.

Discussion

Prostate cancer is the second most common cause of death from cancer in men aged > 50 years, with an incidence of 78.9/100 000/year in the European Union, and a mortality rate of 30.6/100 000/year [7]. Its biological evolution is variable, from indolent to highly aggressive intraprostatic tumours. Treatment options in the most aggressive forms include surgery or RT (external RT, brachytherapy and intensity modulated RT). After the initial radical treatment, patients are subject to strict monitoring of PSA levels. Tumour recurrence is common and evaluated by progressive PSA elevation, which typically precedes detectable clinical recurrence. Patient management in this situation basically depends on whether disease progression is confined to the prostatic bed or has spread to other locations.

Although PSA and its related parameters have been proposed as indices for predicting local or distant recurrence, only

imaging techniques are able to show the two scenarios. In this context, CIT are useful in the different stages of the disease, but have shown low sensitivity, with 5–10% detection rates of disease at the site of relapse after primary treatment [2–5].

In this respect, development of functional imaging techniques, such as PET and PET/CT, have arisen as powerful tools for recurrence detection in patients with prostate cancer and biochemical relapse. Simultaneously, the appearance of new PET radiotracers has helped to widen the indications. Of all the new tracers studied in prostate cancer, choline marked with ^{11}C or ^{18}F , a substrate for the synthesis of phosphatidylcholine (a phospholipid present in the cell membrane), have shown the most promising results.

In the last few years, studies have shown that choline-PET is particularly useful for restaging patients with prostate cancer with biochemical relapse after radical treatment [8–12], with a greater range of disease detection than CIT. Due to the lack of Spanish series, this multicentre study was designed to analyse the results of this diagnostic method, recently introduced into our country.

Consistent with previous publications, our present results show that choline-PET/CT is a useful technique for location of clinical disease in patients with prostate cancer with biochemical relapse after initial radical treatment, with a disease detection rate close to 50%. Published results are heterogeneous, with reported overall sensitivity ranging from 38% to 98%. The high degree of discrepancy between different studies could be due to differences in the groups of patients. The most relevant factors are: previous treatments, Trigger PSA level threshold values, presence or absence of hormonal treatment and different validation criteria for choline-PET/CT studies, with few histological confirmations. The first published studies [13,14] report very high disease detection rates ($\approx 70\%$), as they included patients with advanced

metastatic disease and very high PSA levels, as well as groups of patients with different indications. In 2003, Picchio et al. [15] published the first large prospective study on the utility of choline-PET in restaging patients with prostate cancer, with a detection rate of 47%. They confirmed its superiority over PET-fluorodeoxyglucose and its complementarity to other CIT, with the advantage of restaging disease in a single step. In 2006, Cimitan et al. [12], in another study in 100 patients, reported a detection rate of 54%, with a clear indication in a selected group of patients excluding distant disease, in order to plan salvage treatment. Castellucci et al. [16] published a retrospective study in 190 patients, with a choline-PET detection rate of 38.95%, clearly influenced by PSA level and its parameters (PSADT and PSA velocity). In the last few years, Giovacchini et al. [17,18], published two studies, with 170 and 358 patients respectively, reporting detection rates of 44% and 45%, very similar to our present results.

Regarding location of disease by choline-PET/CT, our present findings are also consistent with previous publications [19], as lymph node disease is the most common site, although in our present study this was followed by metastatic bone disease, ahead of recurrence in the post-surgical or prostate bed. One possible explanation of the relatively low local recurrence values detected would be lesions size (smaller than the equipment's resolution limit), urinary elimination of the radiotracer despite catheterisation, and the partial volume effect, which is greater in this anatomical region. In the prostatic fossa, delayed images were useful to differentiate inflammatory changes or urine contamination after RP from viable tumour.

Recently, many studies have focused on the correlation between PET/CT detection rate and Trigger PSA levels. The first study published by Krause et al. [20] showed a significant correlation between choline-PET/CT disease detection rate and PSA levels, establishing several threshold values and finding progression in the detection rate, which was 73% in a group of patients with PSA levels of ≥ 3 ng/mL. Our present results show statistically significant differences in mean PSA levels between positive (8 ng/mL) and negative (2.8 ng/mL) studies, and a clear, practically linear progression between PSA levels and positive PET/CT results, with a detection rate of >60% in patients with a Trigger PSA level of >3 ng/mL at the time of the examination. In this respect, the study by Giovacchini et al. [18] including 358 patients, describes a detection rate close to 80% for PSA levels of 3–5 ng/mL, reaching a plateau for higher levels (84% for PSA level of >10 ng/mL), showing that 80–85% is close to the technique's upper limit of disease detection. Many studies have shown that Trigger PSA level is the most powerful predictive factor of positive choline-PET/CT [15,17,20,21].

Absolute PSA level at the time of examination is not the only determining factor in choline-PET/CT results. Taking into account that rapid changes in PSA parameters (PSADT and

PSA velocity) before or after treatment are indicative of a worse prognosis, we found that choline-PET/CT detection rates were significantly higher in patients with shorter PSADT: mean PSADT in positive choline-PET/CT was 8.9 months vs 12.6 months in negative studies. In 2009, Castellucci et al. [16] investigated the relationship between PET detection rate and PSA kinetic parameters in a group of 190 patients, finding statistically significant differences between positive and negative groups and concluding that PSA kinetics should always be considered before performing PET. Another study in 2010 [17] confirmed these results, finding that patients with a positive choline-PET/CT presented a significantly shorter PSADT [mean (SD) 6.45 (5.71)months] than negative patients [mean (SD) 11.75 (7.54) months]. More recent studies [11,22,23] have also found statistically significant differences between positive and negative choline-PET/CT studies according to PSADT, concluding that this parameter and the absolute PSA level should be taken into account before requesting the examination. In our present study, both Trigger PSA level and PSADT were significant predictors of positive choline-PET/CT.

Several PSA level and PSADT threshold values have been proposed to predict choline-PET results. In our present study, the best threshold value for Trigger PSA level was 3.5 ng/mL (sensitivity and specificity of 64% and 75%, respectively) and for PSADT it was 6 months (sensitivity and specificity 58%). Perhaps a PSA threshold value of 3.5 ng/mL is too high, but this finding could be related to a high mean Trigger PSA level (5.34 ng/mL) of the patients referred for the exploration. On the other hand, it has been observed that patients with a PSADT of ≤ 6 months most probably have systemic metastases, although this is not always so and in some instances patients can benefit from local treatment. Castellucci et al. [16] found a PSA level threshold value of 2.43 ng/mL, for similar sensitivity and specificity values; other authors [18,24] obtained lower threshold values. Specifically, Giovacchini et al. [18] found that the best threshold for the PSA level was 1.4 ng/mL, with sensitivity and specificity values of 73% and 72%, respectively. Graute et al. [24] found a PSA level threshold value of 1.74 ng/mL and a PSADT value of 3.2 months, although the latter was not statistically significant. Castellucci et al. [11] reported a threshold for PSADT of 7.25 months (sensitivity and specificity of 93% and 74.5%, respectively).

It is known that in patients with lower PSA levels that PSADT has a strong influence. In our present analysis, when PSA levels were <3 ng/mL, the detection rate was higher for patients with a shorter PSADT; we found no significant differences for PSADT in patients with higher PSA levels (>3 ng/mL). PSADT became statistically weaker with higher PSA levels. On the other hand, it should be taken into consideration in patients with lower PSA levels at the time of the examination [24,25].

As well as PSA values, other quantitative parameters have been identified as predicting positive choline-PET/CT. In our present results, we only found a statistically significant relationship for Gleason score. In the univariate analysis, a Gleason score of <5 or >8 correlated with positive choline-PET/CT; while in the multivariate analysis, a Gleason value of >8 was an independent predictive factor for positive choline-PET/CT. Although most studies considered the Gleason score as a possible independent predictor of positive choline-PET, the results are not conclusive. Giovacchini et al. [18] found statistical significance in the univariate analysis for a Gleason >7, but not in the multivariate analysis. In other studies, Gleason score did not show statistical significance for predicting positive choline-PET/CT [11,17,24,26]. We found no significance for the other analysed quantitative variables; of special interest is advanced age at diagnosis; although in our present study it was not significantly related to PET/CT results, it is clearly related to biochemical failure and earlier onset of bone metastasis and increased cancer mortality [27,28]. Giovacchini et al. [18], in a study with the largest number of patients reported to date, found that advanced age was a notable independent predictor of positive choline-PET/CT.

In the analysis of quantitative variables by location, PSADT was significantly shorter in patients with disease outside the prostate; as described in other studies [17], absolute PSA value was not capable of distinguishing between localised or distant disease.

Different papers have also suggested other qualitative variables as predictors of positive choline-PET/CT, such as advanced stage, lymph node disease at diagnosis, type of initial treatment, having received multiple therapies due to previous biochemical relapse, and receiving hormonal treatment or not at the time of the choline-PET examination. Advanced disease stage and a history of previous biochemical relapse, and therefore having received treatment with two different types of therapy, are intuitively related to more aggressive disease and poorer prognosis. Many studies report statistical significance for advanced T stage [17,18,24] and lymph node disease at diagnosis (N+) [11]; in our present analysis, neither of the two variables showed statistical significance, although there was a tendency towards significance for N+ patients. This might have been due to the few patients in our group with N+ at diagnosis. In those patients who had received more than one type of therapy, we found no differences in choline-PET/CT results compared with those treated with a single therapy; however, there was clear statistical significance in the paper published by Giovacchini et al. [18], which is logical if we consider the disease's natural evolution, as a second relapse is more common in patients who have already had a previous one.

Special attention should be paid to the type of initial radical treatment received. Most publications include homogenous

groups of patients who have only received radical treatment with RP. A few papers discuss a less clear role of choline-PET/CT in patients treated with initial radical RT [29,30]. In our present study, a determining parameter was having received RP or not, and it was in the group with other initial treatment (RT, brachytherapy, etc.) where we found the largest number of positive choline-PET/CT. This was statistically significant, and an independent risk predictor in the multivariate analysis. Other papers also include patients from different therapeutic categories [12,15,20], although there are no formal statistical studies.

The effect of antiandrogen hormonal therapy on choline uptake represents one of the most significant controversial aspects in the published literature. Some studies suggest a negative impact of hormonal therapy on the efficacy of choline-PET [18]. Many studies have reported higher detection rates of choline-PET studies in hormone-resistant patients, which could be related to the greater aggressiveness of these tumours [17,20,31–33]. Our present study includes patients receiving and without hormonal treatment at the time of choline-PET/CT; the small size of the two groups did not enable us to reach statistical conclusions about the influence of antiandrogen treatment on PET results.

We considered it particularly interesting to analyse a subgroup of 68 patients with Trigger PSA levels of ≤ 1.5 ng/mL, as they could benefit from prompt treatment or on the other hand, if distant disease was detected, they could avoid unnecessary treatments that increase morbidity. In this group of patients, choline-PET/CT showed disease in 31%; four of them also presented bone metastases. Marzola et al. [26] found 25.5% of unexpected distant metastasis in a group of 64 patients with PSA levels of 1.5 ng/mL; interestingly, in the subgroup of patients with PSA levels of <0.5 ng/mL, the detection rate was 29%. Castellucci et al. [11] also reported a disease detection rate of 28% for choline-PET/CT in a group of patients with PSA levels of <1.5 ng/mL; 13 patients presented bone metastases. In that study, they also found that PSADT was a significant independent predictive factor for positive PET, concluding that it would appear to be reasonable to consider that parameter, together with N stage at diagnosis, when requesting choline-PET/CT for this group of patients with relatively low PSA levels. In the present study, we found no variable capable of predicting a positive/negative result of the examination although, consistent with the previous paper, only PSADT showed a tendency towards significance. One possible explanation would be our relatively small group size; perhaps with a larger study population this finding would have been confirmed.

Although we do not have any experience in prostate-specific membrane antigen (PSMA)-PET/CT, according to the current available preliminary data, this novel tracer, which is more tumour specific, might improve detection of lesions of recurrent prostate cancer.

There are several limitations of the present study including the retrospective and multicentre design of the analysis making the group heterogeneous for initial treatment and Trigger PSA, and this could affect diagnostic accuracy. Another related point of conflict in our present results is the fact of having used different study evaluation/validation criteria, which could over/underestimate the number of positive results. Other limitations to be considered are the lack of a histological 'gold standard'. Histological validation would have been preferable in the present study because only 17 patients had histological analysis. However, histological confirmation of choline-PET/CT findings is rarely available, because loco-regional biopsy presents a low positive detection rate, especially for PSA levels of <1 ng/mL; salvage pelvic lymph node dissection is not routinely performed in patients with biochemical recurrence and evidence of nodal disease; and biopsy at the bone level is not commonly performed. In most studies, follow-up and CIT examinations are used to confirm PET findings, as in our present study. Finally, evaluation was made by patient and not by lesion; although most published restaging studies present very few biopsies due to ethical and logistic considerations.

In conclusion, as previously published in numerous studies, choline-PET/CT has been shown to be useful for restaging patients diagnosed with prostate cancer with biochemical relapse, detecting clinical disease in a high percentage of patients referred for the examination. One of its main advantages is that it provides information about multiple anatomical sites in a single study, and it can be recommended as a first-line tool. Although the evidence shows that choline-PET/CTs detection rate increases with increasing PSA levels, other variables should also be considered when selecting candidates for this examination, in order to reduce the number of false negatives and increase its diagnostic cost-efficiency. These include patient risk at diagnosis (Gleason score), initial treatment, and others, the most significant being PSADT especially in patients with lower PSA levels at the time of the examination. Future research should consider the real impact of choline-PET/CT results on patient's therapeutic management.

Conflicts of Interest

None disclosed.

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Abbreviations: choline-PET/CT, ¹⁸F-fluorocholine positron-emission tomography/computed tomography; CIT, conventional imaging techniques; PET, positron-emission tomography; PSADT, PSA doubling time; ROC, receiver operating characteristic; RP, radical prostatectomy; RT, radiotherapy.