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ORIGINAL ARTICLE

# Prostate-specific antigen kinetics parameters are predictive of positron emission tomography features worsening in patients with biochemical relapse after prostate cancer treatment with radical intent: Results from a longitudinal cohort study

MAURO GACCI[1], TOMMASO CAI[2], GIAMPAOLO SIENA[1], ANDREA MINERVINI[1], MOZHGAN FAYAZ TORSHIZI[3], MATTEO BARTOLINI[3], GIANLUCA GIANNÌ[3], CALOGERO SAIEVA[4], MAURO CEROTI[4], BEATRICE DETTI[5], LORENZO LIVI[5], ALBERTO PUPI[3] & MARCO CARINI[1]

*[1]Department of Urology, [3]Nuclear Biomolecular Medicine and, [5]Department of Radiation Therapy, University of Florence, Careggi Hospital, Florence, Italy, [2]Department of Urology, Santa Chiara Regional Hospital, Trento, Italy, and, and [4]Institute for Study and Prevention of Cancer (ISPO), Florence, Italy*



**Abstract**

*Objective.* The aim of this study was to identify prostate-specific antigen (PSA) kinetics parameters predictive of [$^{18}$F] fluorocholine positron emission tomography/computed tomography ($^{18}$FC PET/CT) features worsening in a cohort of patients with biochemical failure after prostate cancer treatment. *Material and methods.* This longitudinal cohort study comprised 103 consecutive patients. All patients underwent two $^{18}$FC PET/CT scans: one at baseline (PET1) and one after 6 months (PET2). Total PSA (tPSA), PSA velocity (vPSA), PSA doubling time (PSAdt), absolute variation in PSA values between PET2 and PET1 (ΔPSA), and percentage variation in PSA between the two PSA measurements (PSA%) were measured in each patient. Progression of disease on $^{18}$FC PET/CT findings was compared with the PSA kinetics parameters. The major outcome measure was disease progression at PET2. *Results.* $^{18}$FC PET/CT progression between PET1 and PET2 was reported in 64 patients (62.1%), while in 39 cases it remained unvaried. The following PSA kinetic parameters correlated with worsened $^{18}$FC PET/CT findings: ΔPSA >5 ng/ml [odds ratio (OR = 6.44, 95% confidence interval (CI) 1.04–39.6; $p = 0.04$], vPSA >6 ng/ml/month (OR = 5.2, 95% CI 0.9–29.8; $p = 0.05$) and PSAdt <6 months (OR = 5.2, 95% CI 0.4–5.4; $p = 0.03$). From receiver operating characteristics (ROC) analysis, the combination with the three PSA kinetics parameters for predicting worsened $^{18}$FC PET/CT findings resulted in a sensitivity of 86% (95% CI 77–92%) and specificity of 77% (95% CI 65–85%). *Conclusion.* PSA kinetics is strictly related to $^{18}$FC PET/CT findings. In patients with biochemical relapse, ΔPSA >5 ng/ml, PSAdt <6 months and vPSA >6 ng/ml/month are highly predictive of $^{18}$FC PET/CT features worsening, independently from the treatment received.

**Key Words:** *biochemical failure, positron emission tomography, prostate neoplasm, prostate-specific antigen, ROC curve*

## Introduction

Biochemical failure after a treatment with radical intent for localized prostate cancer may occur in 15–77% of all patients during the first 5 years after treatment [1,2]. Prostate-specific antigen (PSA) relapse indicates evidence of illness and it is mandatory at this step to establish whether the disease is locally confined or systemic [3]. However, among the conventional imaging techniques, such as bone scan, computed tomography (CT) and magnetic resonance imaging (MRI), the most appropriate diagnostic

Correspondence: T. Cai, Department of Urology, Santa Chiara Regional Hospital, Largo Medaglie d'Oro 9, Trento, Italy. Tel: +39 0461 903306. Fax: +39 0461 903101. E-mail: ktommy@libero.it

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investigation for asymptomatic men with biochemical failure is currently undefined [4,5]. In addition, conventional imaging is not useful when PSA is lower than 5 ng/ml and PSA doubling time greater than 10 months [6]. For this reason and because of the low accuracy shown by these techniques, the attention of several authors has been directed to other imaging techniques, and molecular imaging in particular [7]. [$^{18}$F]Fluorodeoxyglucose (FDG) has limited value in prostate cancer imaging owing its low cellular uptake but it may have a role in assessing treatment response to chemotherapy in hormone-resistant disease [6,7]. Radiopharmaceuticals targeting cell membrane lipid metabolism, such as [$^{11}$C]choline, [$^{18}$F]choline or [$^{11}$C]acetate, seem to be more promising for the detection of malignant prostate cancer cells, and all have proved to have a preferential uptake in prostate cancer cells, affected lymphatic ganglia and metastatic processes [8–10]. However, several authors have proposed different PSA cut-off values and/or PSA progression (kinetics) for which prostate cancer patients should be referred to positron emission tomography (tomography PET)/CT, ranging from 1 ng/ml to 5 ng/ml [11,12]. At present, the knowledge of the PSA level may not be sufficient to decide whether referral to [$^{11}$C/$^{18}$F]choline PET/CT is appropriate or not. Furthermore, PSA kinetic parameters predictive of tumour progression on [$^{11}$C/$^{18}$F]choline PET/CT findings are not yet clearly defined.

The aim of this study was to analyse a cohort of patients with biochemical relapse after prostate cancer treatment with radical intent in order to identify PSA kinetics parameters predictive of worsened [$^{18}$F]choline PET ($^{18}$FC PET/CT) features.

## Material and methods

### *Study design*

To identify possible PSA kinetics parameters predictive of $^{18}$FC PET/CT features worsening, all patients with biochemical relapse after radical treatment [radical prostatectomy (RRP) or definitive radiation therapy (RT)] between April 2006 and July 2008 were enrolled in this longitudinal cohort study. This study was planned as a longitudinal cohort study because it is a correlation research study that involves repeated observations of the same variables over long periods, in a specific group of people [13].

### *Study population and schedule*

All patients with biochemical relapse within the study period were enrolled. All patients who met the eligibility criteria underwent two consecutive $^{18}$FC PET/CT scans: one at baseline (PET1) and one at restaging after 6 months (PET2) (Figure 1). All PET images were interpreted by an independent masked committee who had no knowledge of the history of the patients (one nuclear medicine and one radiology specialist and one outside expert to resolve all cases of disagreement among readers). Progression of disease on $^{18}$FC PET/CT findings was compared with the PSA kinetics parameters. Moreover, the $^{18}$FC PET/CT findings were analysed to evaluate which PET findings were predictive of disease progression. All patients were stratified according to D'Amico risk criteria [14].

### *Inclusion and exclusion criteria*

All patients with biochemical failure after treatment with radical intent, for whom information on all the main clinical and pathological features was available, were enrolled. Patients who had undergone RRP who showed positive margins or positive lymph nodes on pathological analysis were excluded, in order to enrol a homogeneous group to evaluate. Moreover, patients treated with neoadjuvant or adjuvant chemotherapy, or combined surgical and radiation therapy, were also excluded.

### *Definition of biochemical relapse*

Biochemical failure was defined as at least two consecutive PSA measurements acquired 3 months apart above 0.2 ng/ml for patients undergoing RRP; and three consecutive values above 0.4 ng/ml, after having reached the nadir, for those undergoing definitive RT [3,15].

### *Radical treatment schedule*

The RRP was performed as described by Walsh in 1998 [16]. RT is performed with a five-field intensity-modulated radiation therapy (IMRT) technique, delivered with a segmented multileaf collimator (MLC) technique also known as "step and shoot". In brief, pretreatment simulation CT was performed, with patient in the supine position, with an empty rectum and a full bladder. The treatment is usually delivered with an Elekta Synergy linear accelerator that is equipped with imaging tools, including three-dimensional cone-beam imaging. Image control during the treatment consisted of a cone beam for the first 5 days of treatment and then weekly, after correction of the position based on the mean error. All patients were treated with 80 Gy in standard fractions (2 Gy/day) [17–19].

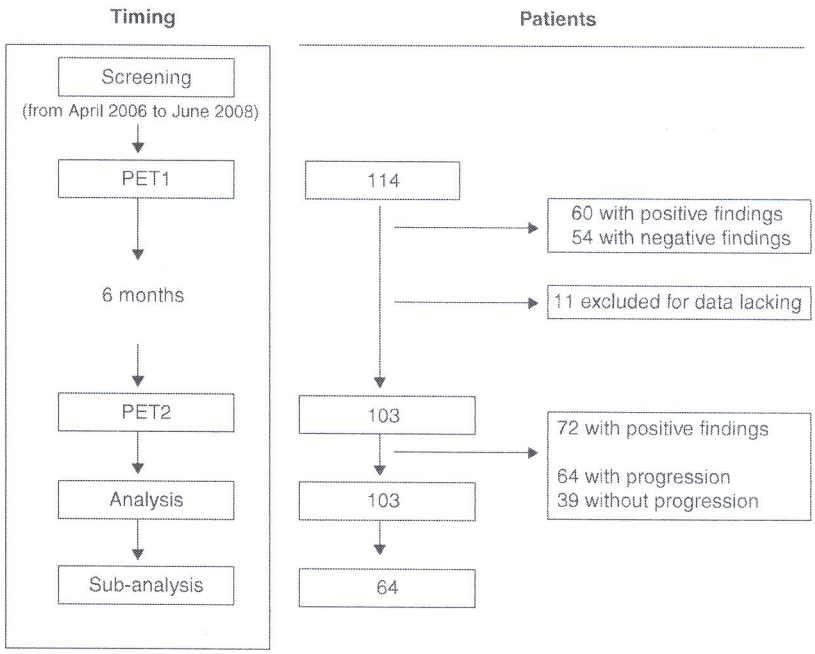


Figure 1. Study schedule flowchart and study design.

*Determination of prostate-specific antigen and prostate-specific antigen kinetics*

At least five PSA measurements were available from each patient: pretreatment PSA, two consecutive PSA measurements at biochemical failure, and one each at PET1 and PET2. The following PSA values were measured in all patients: total PSA (tPSA), PSA velocity (vPSA) according to the formula (PSA2 – PSA1)/Δ time, PSA doubling time (PSAdt) according to the formula ln(2) × Δ time/[ln(PSA2) – ln(PSA1)], absolute variation in PSA values between PET2 and PET1 (ΔPSA) according to the formula PSA2 – PSA1, and percentage variation in PSA values between PET2 and PET1 (PSA%) according to the formula PSA2/PSA1 × 100. All PSA kinetics parameters were calculated in accordance with D'Amico et al. [20] and international guidelines [3]. PSA values were obtained either at Careggi Hospital or at a laboratory local to the patient. All PSA measurements were taken at the same place for each patient.

*[$^{18}$F]Choline positron emission tomography/computed tomography procedures and imaging analysis*

[$^{18}$F]Choline (ACOM, Macerata, Italy) (dose 4 MBq/kg) was injected in an antecubital vein with the patient positioned on the PET/CT bed (Philips GXLGemini GXL PET/CT; Philips Healthcare, Netherlands). The protocol included an early dynamic scan of the pelvis (4 min postinjection) and a delayed whole-body scan (60 min postinjection). Images were reconstructed with a proprietary algorithm and visually examined. Where necessary, [$^{18}$F]choline lesion uptake was quantified by comparison with the uptake in surrounding soft tissues. $^{18}$FC PET/CT findings predictive of disease progression were the presence of an increased number of pathological [$^{18}$F]choline uptake sites (NoPS) and increased uptake intensity (UPI) (Figure 2). In line with Wahl et al., a change of 20% in tumour UPI was considered clinically significant [21]. Patients with negative $^{18}$FC PET/CT findings at PET1 but with positive findings at PET2 were considered to have disease progression. The independent masked committee evaluated the $^{18}$FC PET/CT images in consensus using a dedicated software package (Syngo Leonardo; Siemens Medical Solutions, Erlangen, Germany). During follow-up, $^{18}$FC PET/CT findings were verified as true positive by comparing the PET1 with the PET2 data, or if needed by high-dose CT, bone scintigraphy or MRI. Only true-positive findings on $^{18}$FC PET/CT were included for PSA correlation.

*Statistical analysis*

Descriptive statistics involved non-parametric measures; all quantitative data are expressed as mean ± SD. Comparisons of continuous variables

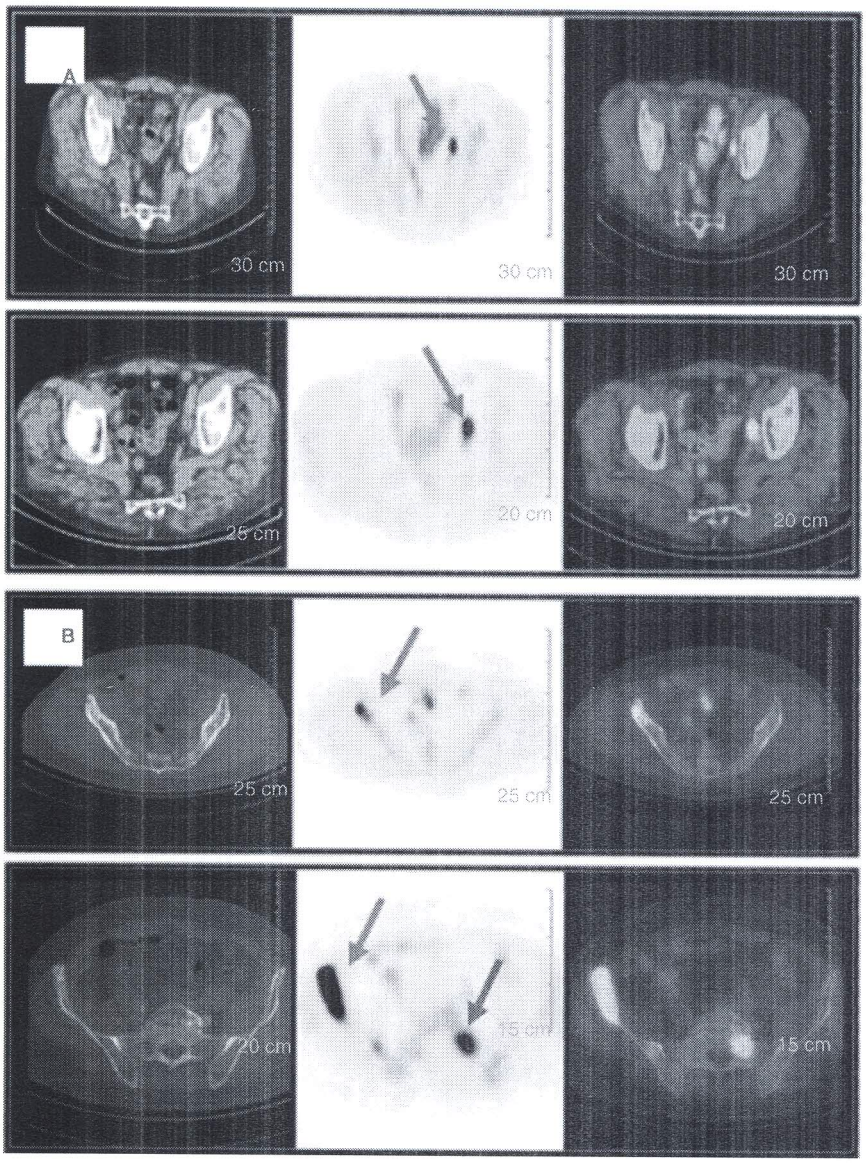


Figure 2. [$^{18}$F]Fluorocholine positron emission tomography/computed tomography ($^{18}$FC PET/CT) findings: (A) increased uptake intensity; (B) increased number of pathological 18F-choline uptake sites.

between two groups were performed using the *t* test. Comparisons of continuous variables were performed using one-way analysis of variance (ANOVA). The chi-squared test was used for categorical variables. The *t* test was used to evaluate the differences in PSA parameters between men presenting unvaried PET and those presenting worsened PET; appropriate non-parametric tests (chi-squared or Wilcoxon test) were used to assess the differences between men with an improvement in the number of lesions and those with an improvement number of lesions and UPI. The association between clinical, pathological and laboratory features and $^{18}$FC PET/CT findings was assessed using univariate and multivariate analysis using the log-rank test (Mantel Cox) for multivariate analysis. The parameters considered for univariate and multivariate analysis were chosen in accordance with Giovacchini et al. [22] and are as follows: age, Gleason score at biopsy, PSA before radical treatment, clinical stage, type of radical treatment, pathological stage (for surgery only), Gleason score at surgery, time to PSA nadir, time to biochemical progression, tPSA at biochemical progression, tPSA, PSAdt, vPSA, ΔPSA and PSA%. Furthermore,

Table I. Clinical and instrumental characteristics of all enrolled patients.

| Enrolled patients | 103 |
|---|---|
| Age (years) | 64.8 ± 6.5 |
| Gleason score (biopsy) | |
| 6 | 23 (22.4) |
| 7 (3+4) | 42 (40.7) |
| 7 (4+3) | 33 (32.1) |
| 8 | 5 (4.8) |
| PSA pretreatment | 9.8 ± 7.3 |
| Clinical TNM | |
| cT1N0M0 | 12 (11.6) |
| cT2N0M0 | 91 (88.4) |
| Comorbidity Charlson Index | 2.1 ± 0.9 |
| Radical treatment and hormonal therapy | |
| Radical prostatectomy | 83 (80.5) |
| With hormonal therapy | 15 (18) |
| Without hormonal therapy | 68 (82) |
| Radiation therapy | 20 (19.5) |
| With hormonal therapy | 18 (90) |
| Without hormonal therapy | 2 (10) |
| Pathological stage (surgery) | |
| pT2a | 12 (14.4) |
| pT2b | 19 (22.9) |
| pT2c | 23 (27.7) |
| pT3a | 19 (22.9) |
| pT3b | 10 (12.1) |
| N0 | 103 |
| N1–2 | – |
| Positive margins | – |
| Gleason score (surgery) | |
| 6 | 6 (7.2) |
| 7 (3+4) | 34 (40.9) |
| 7 (4+3) | 40 (48.2) |
| 8 | 3 (3.7) |
| Time to PSA nadir (months) | 6.9 ± 4.9 |
| Time to biochemical progression (months) | 20.1 ± 11.3 |
| tPSA at biochemical progression | 0.9 ± 0.4 |
| Interval: primary therapy to PET/CT 1 (months) | 19.8 ± 9.7 |
| Interval: PET/CT 1 to PET/CT 2 (months) | 6.9 ± 1.1 |

The table shows all patient anamnestic characteristics, clinical and laboratory data at the time of enrolment. Data are shown as mean ± SD or *n* (%).
PSA = prostate-specific antigen; TNM = tumour, node, metastasis; tPSA = total PSA; PET = positron emission tomography; CT = computed tomography.

the receiver operating characteristics (ROC) analysis was generated by plotting sensitivity versus 1 – specificity, with judgement of the optimal cut-off values for tPSA and PSA kinetics to predict worsened $^{18}$FC PET/CT scan results [23]. All tests were two sided. Statistical significance was taken at $p < 0.05$. All statistical analyses were performed using the SAS program (version 9.1).

Written informed consent for the execution of the $^{18}$FC PET/CT scan and the anonymous publication of disease-related information was signed by each patient. The study was conducted in line with good clinical practice guidelines and with the ethical principles laid down in the latest version of the Declaration of Helsinki.

## Results

From April 2006 to July 2008, 114 patients met the criteria and 103 were finally enrolled into this longitudinal cohort study and followed for 6 months, after the first $^{18}$FC PET/CT time. Eleven patients were excluded owing to missing clinical or laboratory data (Figure 1). The patients' characteristics are summarized in Table I.

### *[$^{18}$F]Choline positron emission tomography/computed tomography and prostate-specific antigen results*

At PET1, 60 patients (58.3%) showed positive findings (45 RRP group and 15 RT group). On an anatomical basis, pathological uptake was observed in lymph nodes (19 patients, 31.7%), in the prostatectomy bed (15 patients, 25%) and in the skeleton (26 patients, 43.3%). At PET2, 72 patients (69.9%) (66 RRP and 16 RT group, respectively) had positive findings (26 lymph nodes, 24 prostatectomy bed and 22 in the skeleton). Overall, PET progression between PET1 and PET2 was reported in 64 patients (62.1%), while in 39 cases PET findings remained unvaried (Figure 1). According to the type of treatment, 45 (54.2%) patients who had undergone RRP showed positive findings at PET1 and 66 (79.5%) at PET2, while among all patients who had undergone RT, 15 (75%) showed positive findings at PET1 and 16 (80%) at PET2. Moreover, among all patients who had undergone RRP, 64 (77.1%) showed progression of disease on $^{18}$FC PET/CT findings, as did 11 (55%) of those who had undergone RT. A comparison analysis according the type of treatment was not carried out, as this was not a study aim. Only the results are described here.

### *Correlation between positron emission tomography findings and prostate-specific antigen kinetics parameters*

Table II shows all PSA kinetics parameters according to the PET changes between PET1 and PET2. ROC analysis identified the optimal threshold of ΔPSA for prediction of PET features worsening as greater than

Table II. Prostate-specific antigen (PSA) kinetics parameters according to positron emission tomography (PET) changes between PET1 and PET2.

| | All patients | Patients with progression | Patients without progression | $p^a$ (df; $t$) |
|---|---|---|---|---|
| No. of patients | 103 | 64 | 39 | |
| tPSA (ng/ml) | | | | |
| Mean | 0.9 | 1.0 | 0.9 | 0.14 |
| Median | 0.8 | 0.9 | 0.8 | (101; 1.4) |
| SD | 0.4 | 0.6 | 0.2 | |
| vPSA (ng/ml/month) | | | | |
| Mean | 4.8 | 6.4 | 4.1 | < 0.001 |
| Median | 6.3 | 6.3 | 3.9 | (101; 12.0) |
| SD | 1.2 | 0.9 | 1.0 | |
| PSAdt (months) | | | | |
| Mean | 5.9 | 6.2 | 4.9 | < 0.001 |
| Median | 6.1 | 6.1 | 4.7 | (101; 7.3) |
| SD | 1.3 | 0.7 | 1.1 | |
| ΔPSA (ng/ml) | | | | |
| Mean | 4.9 | 5.4 | 3.9 | < 0.001 |
| Median | 5.2 | 5.3 | 3.7 | (101; 8.8) |
| SD | 1.3 | 0.5 | 1.2 | |
| ΔPSA% (ng/ml) | | | | |
| Mean | 9.8 | 10.7 | 9.9 | 0.32 |
| Median | 9.9 | 10.5 | 9.6 | (101; 0.9) |
| SD | 3.2 | 3.4 | 4.8 | |

[a]$p$ Value calculated on the mean; df = degrees of freedom; $t$ = $t$ value; tPSA = total PSA; vPSA = PSA velocity; PSAdt = PSA doubling time; ΔPSA = change in PSA; ΔPSA% = percentage variation in PSA between the two PSA measurements.

5 ng/ml, resulting in a sensitivity of 63% [95% confidence interval (CI) 58–68%] and a specificity of 79% (95% CI 77–2%). An increase in PSA value (ΔPSA) greater than 5 ng/ml at PET2 compared to PET1 related to a six-fold higher risk of worsened PET findings [odds ratio (OR) = 6.44, CI 1.04–39.6; $p = 0.04$. ROC analysis revealed that the optimal cut-off of vPSA for the prediction of PET features worsening was greater than 6 ng/ml/month, resulting in a sensitivity of 72% (95% CI 67–81%) and a specificity of 78% (95% CI 75–82%). Moreover, the ROC analysis yielded an optimal cut-off when the doubling time was less than 6 months (sensitivity 78%, 95% CI 73–81%; specificity 79%, 95% CI 73–85%). There was also a significant risk of PET findings worsening in the case of vPSA greater than 6 ng/ml/month and PSAdt less than 6 months, of five times (OR = 5.2, CI 0.9–29.8; p = 0.05) and 10 times higher (OR = 5.2, CI 0.4–5.4; $p = 0.03$), respectively. In multivariate analysis, ΔPSA greater than 5 ng/ml, PSAdt less than 6 months and vPSA greater than 6 ng/ml/month

Table III. Univariate and multivariate analysis results of factors affecting worsening positron emission tomography (PET) features.

| Categories (variables) | Univariate analysis ($p$) | Multivariate analysis ($p$) |
|---|---|---|
| Age | 0.11 | 0.45 |
| PSA at diagnosis | 0.09 | 0.16 |
| GS > o = 7 at biopsy | 0.12 | 0.07 |
| Clinical stage | 0.54 | 0.23 |
| Type of treatment | 0.40 | 0.51 |
| Pathological stage[a] | 0.36 | 0.27 |
| GS > o = 7 at biopsy[a] | 0.22 | 0.09 |
| PSA nadir | 0.08 | 0.10 |
| PSA% | 0.25 | 0.12 |
| ΔPSA >5 ng/ml | 0.38 | 0.003 |
| PSAdt <6 months | 0.08 | 0.04 |
| vPSA >6 ng/ml/month | 0.45 | 0.02 |
| Adjuvant hormonal therapy | 0.09 | 0.07 |
| Charlson Index | 0.09 | 0.09 |
| Time to biochemical progression | 0.33 | 0.41 |
| tPSA at biochemical progression | 0.42 | 0.45 |

[a]Calculated among patients who had undergone surgical treatment. PSA = prostate-specific antigen; GS = Gleason score; PSA % = percentage variation in PSA between the two PSA measurements; ΔPSA = absolute variation in PSA values between the two PSA measurements; PSAdt = PSA doubling time; vPSA = PSA velocity; tPSA = total PSA.

remained independently associated with PET features worsening ($p = 0.003$, $p = 0.041$ and $p = 0.021$, respectively) (Table III). From ROC analysis, the combination of the three PSA kinetics parameters for predicting worsened PET findings resulted in a sensitivity of 86% (95% CI 77–92%) and a specificity of 77% (95% CI 65–85%) (Figure 3).

### *Subanalysis in patients with [$^{18}$F]choline positron emission tomography/computed tomography progression*

In one out of 64 patients an increase in UPI alone was recorded, while in 63 an increase in both NoPS and NoPS/UPI on PET2 findings was recorded. Of those, 13 out of 63 patients (20.4%) showed exclusively an increase in the NoPS, whereas 50 out of 63 (79.6%) showed an increase in both NoPS and UPI. Mean PSAdt was 0.4 ± 2.4 months and 3.9 ± 8.8 months for patients with NoPS/UPI increase and for patients with NoPS increase, respectively ($p = 0.01$). Mean ΔPSA was −2.30 ± 13 ng/ml and 14.7 ± 32 ng/ml for patients with an increase in NoPS alone and patients with an increase in NoPS/UPI, respectively ($p = 0.04$). vPSA and PSA2/PSA1 did not show any statistical difference between the two subgroups ($p = 0.11$ and 0.28, respectively).

Using the D'Amico risk criteria, 22 patients were stratified as low risk (21.4%), 74 as intermediate risk

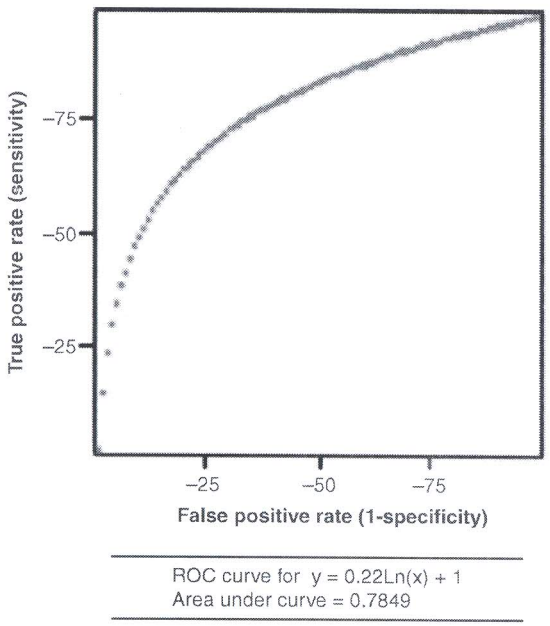


Figure 3. Receiver operating characteristics (ROC) curve.

(71.8%) and seven as high risk (6.8%). However, no correlation was found between different risk groups and PET/CT findings at the PET1 or PET2 evaluation.

## Discussion

Some authors have related the PSA kinetics parameters to poor clinical outcome in prostate cancer patients and argued that PSAdt could be used for stratification of patient treatment and prognosis [22]. Subsequently, the clinical implications of PSA kinetics parameters have become a major focus of research in prostate cancer. Moreover, the treatment of prostate cancer patients with biochemical relapse relies on the distinction between local and systemic disease and on pathological and clinical information, including PSA levels and PSA kinetics [24].

In the present cohort of patients, attention was focused on the PSA kinetics parameters for predicting the worsened $^{18}$FC PET/CT findings in patients with biochemical failure after treatment with radical intent. In recent years, several authors have focused their research on this field of interest. Giovacchini et al. reported that high PSA and short PSAdt were significant predictors of positive PET [22]. Indeed, they report that the percentage of patients who displayed pathological [$^{11}$C]choline uptake in the skeleton increased significantly from 3% for PSAdt greater than 6 months to 52% for PSAdt less than 3 months [22]. Recently, Rybalov et al. found that tPSA and vPSA have significant effects on the detection rates of [$^{11}$C]choline PET/CT in patients with biochemical progression after RRP or external beam radiotherapy, highlighting the role of PSA kinetics parameters in predicting positive results at PET evaluation [25].

The aim of the present study was to evaluate which PSA parameters are predictive of [$^{18}$F]choline PET (FC PET/CT) features worsening in a cohort of patients affected by biochemical failure after prostate cancer treatment with radical intent. In this cohort of patients it was found that PSA kinetics is strictly related to $^{18}$FC PET/CT findings, and in patients with biochemical relapse, a ΔPSA greater than 5 ng/ml, a PSAdt less than 6 months and a vPSA greater than 6 ng/ml/month are highly predictive of $^{18}$FC PET/CT features worsening, independently from the treatment received. To the authors' knowledge, this longitudinal cohort study is the first to show that some PSA kinetics parameters are useful in predicting the $^{18}$FC PET/CT features worsening in patients who have undergone surgery or radiation therapy. This aspect is extremely important to make the results clinically relevant. Patients who had undergone radical prostatectomy with lymph-node dissection and those who had undergone radiation therapy were analysed.

Graute et al. identified the optimal tPSA threshold of 1.74 ng/ml for the presence of $^{18}$FC PET/CT-detectable lesions, in 82 consecutive patients with biochemical relapse after radical prostatectomy [11]. Although some authors have found that at biochemical relapse PET findings are related to tPSA at the time of scanning, in the present study population the tPSA was not predictive of PET features worsening at PET2 evaluation [11]. Even if the tPSA alone is a crucial indicator of disease progression, in this study population it was not able to predict the detectable modification of PET features, while other PSA parameters were more effective in predicting that result. These results need to be confirmed by other experiences before entering daily clinical practice. Furthermore, as reported by several authors, patients with positive $^{18}$FC PET/CT had shorter PSAdt and faster vPSA than patients with negative $^{18}$FC PET/CT [26,27]. Indeed, it was found that a PSAdt less than 6 months was associated with a 10-fold higher risk of worsened PET findings and a five-fold greater risk of faster vPSA (>6 ng/ml/month).

On the basis of the image patterns, a statistically significant difference was observed in terms of PSAdt for patients with NoPS/UPI increase and for those with NoPS increase alone. The significant relationship between PSAdt and the image pattern is highly indicative of how an increased UPI associated with increased NoPS is more likely to happen in the case of more aggressive diseases and has a higher accuracy than the increased NoPS alone.

A couple of limitations of this study should be taken into account: the short follow-up period and the limited number of patients. However, the progression at the $^{18}$FC PET/CT was used as a surrogate of overall survival, which requires a shorter follow-up. The limited number of patients is due to the cost of the methods used. Moreover, the study enrolled the minimum number of patients needed to obtain statistically significant results.

In conclusion, in this study cohort of patients with biochemical recurrence of prostate cancer after radical treatment, ΔPSA greater than 5 ng/ml, PSAdt less than 6 months and vPSA greater than 6 ng/ml/month are predictive of $^{18}$FC PET/CT features worsening. This implies potentially important clinical consequences because in those patients with ΔPSA greater than 5 ng/ml, PSAdt less than 6 months and vPSA greater than 6 ng/ml/month, the therapy could be individualized owing to the high risk of $^{18}$FC PET/CT features worsening and disease progression.

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