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RESEARCH ARTICLE

Diagnostic performance of ^{18}F-choline PET-CT in prostate cancer

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Abstract

Objectives To evaluate the diagnostic performance of ^{18}F-choline PETCT in staging prostate cancer (PC) and whether the use of this imaging modality changes the therapeutic decision in patients previously staged by conventional imaging. The secondary aim was to determine the prognostic factors associated with positive choline PETCT findings in both detection of disseminated disease and in changes in the therapeutic indication.

Materials and methods Multicentre, retrospective, observational study of 269 patients diagnosed with PC. Mean age was 69 ± 9.2 years. Of the 269 patients, 62 (23%) had high-risk localized PC (group 1), 118 (43.9%) biochemical failure after radical prostatectomy (group 2), and 89 (33.1%) biochemical failure after radiotherapy (group 3). None of the patients showed clear evidence of distant disease on computed tomography or bone scans. The following potential prognostic factors were assessed: PSA level at diagnosis; primary and secondary Gleason; Gleason score (GS); clinical and pathologic T and N stage; number of positive cylinders in the biopsy; presence of vascular or lymphatic invasion; status of surgical margins; androgen deprivation therapy (ADT); time to biochemical recurrence; and PSA, PSA doubling time (PSADT), and PSA velocity (PSAV) at failure. Univariate and multivariate analyses were performed, and receiver-operating curves calculated.

Results The mean PSA by groups was, group 1: 31.22 ng/ml, group 2: 2.52 ng/ml and group 3: 5.85 ng/ml. The tumor detection rate with ^{18}F-choline PETCT was 74% (group 1: 85.5%, group 2: 55.1% and group 3: 91%). Prognostic factors for positive ^{18}F-choline PETCT were identified only in group 2: PSA at failure and PSADT. ^{18}F-choline PETCT changed the therapeutic indication in 62.8% (group 1: 71%, group 2: 55.2% and group 3: 70.1%). The prognostic factors for a change in treatment were identified only in group 1: secondary Gleason ≤ 4 and GS ≤ 7 and in group 2: PSA at failure, PSA nadir after surgery and pathologic stage N0. ^{18}F-choline PETCT identified lymph node and/or metastatic disease in 32.7% (group 1: 25.8%, group 2: 29.7% and group 3: 41.6%). Prognostic factors for detecting lymph node/metastasis were identified in the group 2: PSA failure ≥ 1.37 ng/ml and PSADT < 4 months and in the group 3: PSADT < 4.6 months and time to failure < 5 years.

Conclusion These findings support the clinical use de ^{18}F-choline PET-CT in staging high-risk patients with a secondary Gleason ≤ 4 and GS ≤ 7, in restaging patients with biochemical recurrence after RP if PSA at failure ≥ 1.37 ng/ml or PSADT ≤ 4 months and in patients with biochemical failure after RT, if PSADT ≤ 4.6 months and time to failure < 5 years, because it determines a change in the therapeutic indication.

Keywords Prostate cancer · Biochemical failure · ^{18}F-choline PET-CT

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Introduction

Prostate cancer (PC) is the most common cancer and the second leading cause of cancer-related death in men [1]. Although close to 80% of men present with localized disease at diagnosis, the likelihood of developing metastatic disease depends on the initial risk group. Consequently, most clinical guidelines recommend performing computed tomography (CT) and bone scans (BS) as part of routine staging in patients with high-risk disease, in some intermediate-risk patients, and in biochemical failure. However, conventional staging (CT and BS) often fails to detect disseminated disease. For example, in cases with Gleason score (GS) < 8 or prostate-specific antigen (PSA) levels < 20 mg/ml, CT detects nodal involvement in less than 1% of patients. Similarly, the detection rate for bone metastases in patients with PSA < 10 ng/ml is only 2.3%.

Imaging modalities such as multiparametric ultrasound, multiparametric magnetic resonance imaging (MRI), and positron-emission tomography (PETCT) are now routinely used during all facets of PC management [2]. In patients with malignant solid tumors, perhaps the most widely used imaging technique is ^{18}F-fluorodeoxyglucose (18F-FDG) PETCT. However, the sensitivity of this modality is lower in PC. PC cells are characterized by overexpression of choline kinase, which is responsible for the production of cell membrane components in which both acetate and choline are involved. Consequently, alternate radiotracers such as ^{11}C-acetate, ^{11}C- and ^{18}F-choline have been developed. Several studies have found that choline PETCT has a greater sensitivity and specificity than ^{18}F-FDG PETCT in PC [3, 4]. These alternative radiotracers have shown promising preliminary results in localizing recurrent disease [5].

Choline PETCT may provided valuable information in well-selected patients, including the following: patients with high-risk PC, patients with oligometastatic disease, and in patients who develop biochemical failure after local treatment [6].

In this context, the objectives of the present study were to evaluate the diagnostic performance of ^{18}F-choline PETCT in staging prostate cancer and whether the use of this imaging modality changes the therapeutic decision in patients previously staged by conventional imaging. The secondary aim was to determine the prognostic factors associated with positive choline PETCT findings in both detection of disseminated disease and in changes in the therapeutic indication.

Material and methods

This was a multicentre, retrospective, observational study of 269 patients diagnosed and treated for PC. All patients underwent ^{18}F-choline PETCT between January 2010 and November 2016. The mean patient age was 69 ± 9.2 years.

For the purposes of this study, the patients were classified into three distinct groups, as follows: group 1: 62 patients (23%) diagnosed with high-risk PC who underwent conventional staging, but without clear evidence of lymph node involvement or distant metastasis; group 2: 118 patients (43.9%) with biochemical failure after primary surgery (RP) ± radiotherapy (51 patients, 43.2% received RT post-surgery) defined by two consecutive PSA rises ≥ 0.2 ng/ml; and group 3: 89 patients (33.1%) with biochemical failure after primary radiotherapy (RT) defined by nadir of PSA + 2 ng/ml.

The following potential prognostic factors were obtained from the medical records: PSA level at diagnosis; primary and secondary Gleason; Gleason score (GS); clinical and pathologic T and N; number of positive cylinders in the biopsy; presence of vascular or lymphatic invasion; status of surgical margins; androgen deprivation therapy in the primary treatment (ADT); time to biochemical recurrence; and PSA, PSA doubling time (PSADT), and PSA velocity (PSAV) at failure.

Statistical analysis

A descriptive analysis was performed, including measures of central tendency and dispersion for the quantitative variables, and absolute and relative frequencies for the categorical variables. The Student's *t* test and Chi-square test were used, respectively, to compare means and qualitative variables. Univariate and multivariate analyses were performed. Receiver-operating characteristic (ROC) curves were generated to analyze the quantitative variables found to be significant on the multivariate analysis. Statistical significance was set at $p < 0.05$. The SPSS statistical software package (v.22.0; IBM-SPSS; Chicago, IL; USA) was used for all statistical analyses.

The study was approved by the Clinical Research Ethics Committee at our institution and complies with all data protection regulations.

Results

The baseline characteristics of the study population are shown in Table 1.

Table 1 The baseline characteristics of the study population

	Group 1 ($n=62$)	Group 2 ($n=118$)	Group 3 ($n=89$)
Age	69.9 years	66.9 years	71.9 years
PSA basal	31.22 ng/ml	9.3 ng/ml	30 ng/ml
cT/pT			
T1-T2	34 (54.1%)	77 (65.3%)	69 (77.6%)
T3-T4	28 (45.9%)	33 (28%)	20 (22.4%)
Unknown	–	8 (6.8%)	–
cN/pN			
N0	42 (67.7%)	57 (48.3%)	86 (96.7%)
N1	14 (22.6%)	27 (22.9%)	2 (2.2%)
Nx	6 (9.7%)	34 (28.8%)	1 (1.1%)
Gleason score			
≤6	6 (9.7%)	19 (16.1%)	35 (39.3%)
7	17 (27.4%)	60 (50.8%)	29 (32.6%)
≥8	39 (62.9%)	33 (28%)	25 (28.1%)
Unknown	–	6 (5.1%)	–
PSA failure	–	2.5 ng/ml	5.9 ng/ml
Time failure	–	4.6 years	6 years

Correlation between conventional staging and ^{18}F-choline PET-CT

The mean PSA by groups, at the time of the PETCT, was: group 1: 31.22 ± 45.15 ng/ml, group 2: 2.52 ± 3.43 ng/ml and group 3: 5.85 ± 6.46 ng/ml. The tumor detection rate with ^{18}F-choline PETCT by groups was, group 1: 85.5%, group 2: 55.1% and group 3: 91%.

The tumor detection rate with ^{18}F-choline PETCT overall was 74% versus only 48.7% with conventional staging ($p=0.002$). The findings of the ^{18}F-choline PETCT study and conventional staging were only poorly well-correlated (Table 2), coinciding in only 107 cases (39.7%), a statistically significant difference ($p=0.004$).

In conventional staging 16 patients (6%) had oligometastatic disease, but ^{18}F-choline PETCT confirmed it only in 8 patients and identified previously undetected oligometastatic disease in 19 more patients (overall 27 patients (10.1%).

Only, in patients with biochemical failure after surgery several prognostic factors for positive ^{18}F-choline PETCT were identified in univariate analysis: pathologic stage T3, perineural invasion, PSA at failure, PSADT and PSAV. On the multivariate analysis, the PSA at failure and PSADT maintained their significance (Table 3).

Change in the therapeutic indication

Overall, the ^{18}F-choline PETCT finding changed the therapeutic indication in 169 patients (62.8%). By group, in 44

Table 2 Correlation between positive findings obtained by conventional staging (CT and bone scintigraphy) and ^{18}F-choline PET-CT

	^{18}F-choline PET-CT					
	Disease-free	Local	Loco-regional	Oligometastatic	Polymetastatic	Total
Conventional staging, *n* (%)						
Disease-free	48	18	26	13	34	139 (51.6%)
Local disease	13	33	9	2	4	61 (22.8%)
Loco-regional	6	6	12	1	11	36 (13.4%)
Oligometastatic	2	1	1	8	4	16 (6%)
Polymetastatic	2	1	4	3	7	17 (6.3%)
Total	71 (26.4%)	59 (22%)	52 (19.4%)	27 (10.1%)	60 (22.4%)	269

Table 3 Univariate and multivariate analysis of the prognostic factors for positive ^{18}F-choline PET-CT in patients with biochemical failure after surgery

Prognostic factors	^{18}F-choline PET-CT			Univariate	Multivariate	
	n	Negative	Positive	*p*	*p*	Odds ratio (95% CI)
Stage pT						
pT2	78	41 (52.6%)	37 (47.4%)	0.016	0.755	0.682 (0.062–7.54)
pT3-pT4	40	12 (30%)	28 (70%)			
Perineural invasion						
No	36	21 (58.3%)	15 (41.7%)	0.014	0.924	1.13 (0.092–13.920)
Yes	42	13 (31%)	29 (69%)			
PSA failure (ng/ml)	118	0.94 ± 0.78	3.72 ± 4.09	0.000	0.037	4.15 (1.09–15.80)
PSADT (months)	91	13.7 ± 23.48	5.56 ± 5.48	0.016	0.024	0.567 (0.346–0.928)
PSAV (ng/ml/month)	58	0.16 ± 0.33	0.48 ± 0.65	0.041	0.121	0.011 (0.00–3.267)

PSADT: PSA doubling time; *PSAV* PSA velocity

patients (71%) in group 1, 64 patients (55.2%) in group 2, and 61 patients (70.1%) in group 3.

On the univariate analysis, the significant prognostic factors for a change in the therapeutic indication based on the ^{18}F-choline PETCT results are (Table 4): in high-risk: secondary Gleason ≤ 4 and GS ≤ 7, and in biochemical failure after surgery: pathologic stage N0, PSA nadir after surgery, and PSA at biochemical failure. On the multivariate analysis, the PSA at failure maintained their significance. In group 3 no prognostic factor was identified.

Lymph node involvement and/or metastatic disease

^{18}F-choline PETCT identified lymph node and/or metastatic disease in a total of 88 patients (32.7%), distributed as follow: group 1: 16 patients (25.8%); group 2: 35 patients (29.7%); and group 3: 37 patients (41.6%).

In the group 1, no significant prognostic factors were found for the detection of nodal involvement or metastatic disease. In group 2, the following were significant prognostic factors on the univariate analysis (Table 5): pathologic stage ≥ pT3, ADT, PSA level at failure, PSADT and PSAV. On the multivariate analysis, the PSA at failure and PSADT remained significant.

As Fig. 1 shows, the ROC curve for PSA failure—nodal/metastatic disease was significant. The sensitivity and specificity rates for the diagnosis of metastatic disease by ^{18}F-choline PETCT were 65.5% and 73.6% for PSA at failure = 1.37 ng/ml.

The ROC curve for PSADT-nodal/metastatic disease was significant (AUC 0.763, typical error 0.056, $p = 0.000$). The sensitivity and specificity rates for diagnosing metastatic disease on the ^{18}F choline PETCT were, respectively, 72.3% and 65.4% for PSADT = 4 months.

In group 3, the following variables were significant prognostic factors on the univariate analysis (Table 5): primary Gleason, GS, perineural invasion, ADT, PSADT, PSAV and time from completion of RT to failure. On the multivariate analysis, only PSADT remained statistically significant.

The ROC curve for PSADT-metastatic disease was significant (AUC 0.877, typical error 0.047, $p = 0.000$). The sensitivity and specificity for the diagnosis of metastases on choline PETCT were 87.1% and 64% for PSADT = 4.3 months.

The ROC curve for PSAV-metastatic disease was significant (AUC 0.886, typical error 0.055, $p = 0.000$). The sensitivity and specificity rates for detecting the presence of metastasis by choline PETCT according to the PSAV values were, respectively, 100% and 60% for PSAV = 0.22 ng/ml/month.

The ROC curve for time from completion of RT to failure-metastatic disease was significant (AUC 0.739, typical error 0.062, $p = 0.001$). The sensitivity and specificity for diagnosing metastatic disease on the choline PET-CT were, respectively, 78.1% and 60% in cases with a time to failure of 5 years.

Discussion

In the treatment of PC, correct staging is essential to select the most appropriate treatment. Conventional imaging scans are unable to detect metastatic disease in patients with low PSA levels. In addition, in patients with oligometastatic disease, these tests are insufficient to ensure that no additional lesions are present. In this context, we sought to determine

Table 4 Univariate and multivariate analysis significant prognostic factors for a change in the therapeutic indication based on the ^{18}F-choline PETCT

Group	Prognostic factors	^{18}F-choline PET-CT change in the therapeutic indication			Univariate	Multivariate	
		n	No	Yes	*p*	*p*	Odds Ratio (95% CI)
Group 1 high-risk	Secondary Gleason						
	≤ 4	48	10 (20.8%)	38 (79.2%)	0.007	0.072	3.60 (0.893–14.505)
	5	13	8 (61.5%)	5 (38.5%)			
	Gleason score						
	≤ 7	22	2 (9.1%)	20 (90.9%)	0.008	0.081	4.44 (0.832–23.73)
	≥ 8	39	16 (41%)	23 (59%)			
Group 2 biochemical failure after surgery	Stage pN						
	pN0	55	19 (34.5%)	36 (65.5%)	0.037	0.412	2.67 (0.62–11.37)
	pN1	27	14 (51.9%)	13 (48.1%)			
	Lymphadenectomy not performed	26	15 (57.7%)	11 (42.3%)			
	PSA nadir, post-operative (ng/ml)	58	0.32 ± 0.39	2.38 ± 4.46	0.026	0.153	2.18 (0.74–6.36)
	PSA failure (ng/ml)	118	1.45 ± 2.01	3.41 ± 4.07	0.003	0.028	2.01 (1.08–3.76)

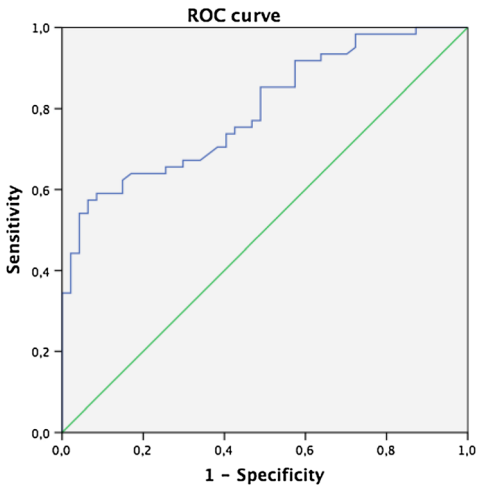
Table 5 Univariate and multivariate analysis of the prognostic factors for 18F-choline PET-CT for the diagnosis of nodal-metastatic disease

Group	Prognostic factors	Nodal-metastatic disease detected on ^{18}F-choline PET-CT			Univariate	Multivariate	
		n	No	Yes	*p*	*p*	Odds ratio (95% CI)
Group 2 biochemical failure after surgery	Stage pT						
	pT2	78	62 (79.5%)	16 (20.5%)	0.003	0.999	0.999 (0.155–6.446)
	pT3–pT4	40	21 (52.5%)	19 (47.5%)			
	ADT						
	No	107	80 (74.8%)	27 (25.2%)	0.003	0.965	0.953 (0.11–8.229)
	Yes	11	3 (27.3%)	8 (72.7%)			
	PSA failure (ng/ml)	108	1.64 ± 2.39	4.57 ± 4.46	0.000	0.042	2.16 (1.027–4.564)
	PSADT (months)	91	11 ± 18.65	3.73 ± 2.76	0.049	0.010	0.617 (0.428–0.892)
	PSAV (ng/ml/month)	58	0.22 ± 0.34	0.62 ± 0.78	0.008	0.057	0.073 (0.005–1.080)
Group 3 biochemical failure after radiotherapy	Primary Gleason						
	≤ 3	46	36 (78.3%)	10 (21.7%)	0.000	0.435	11.060 (0.027–4585)
	≥ 4	41	14 (34.1%)	27 (65.9%)			
	Gleason score						
	≤ 7	63	42 (66.7%)	21 (33.3%)	0.009	0.908	1.217 (0.043–34.289)
	≥ 8	25	9 (36%)	16 (64%)			
	Perineural invasion						
	No	55	38 (69.1%)	17 (30.9%)	0.000	0.645	0.441 (0.014–14.362)
	Yes	19	4 (21.1%)	15 (43.2%)			
	ADT						
	No	44	31 (70.5%)	13 (29.5%)	0.015	0.885	116.78 (0.00–1.395E)
	Yes	44	20 (45.5%)	24 (54.5%)			
	PSADT (months)	56	10.9 ± 7.05	4.06 ± 3	0.000	0.082	0.324 (0.091–1.152)
	PSAV (ng/ml/month)	36	0.22 ± 0.14	0.81 ± 0.85	0.005	0.932	0.793 (0.004–163.593)
	Time from RT to failure (months)	67	83.5 ± 34.3	55.47 ± 34.96	0.001	0.862	0.917 (0.918–1.075)

ADT androgen deprivation therapy; *PSADT* PSA doubling time; *PSAV* PSA velocity

Fig. 1 ROC Curve the sensitivity and specificity of PSA values for the diagnosis of metastasis by ^{18}F-choline PET-CT in patients with biochemical failure after surgery

PSA value at failure (ng/ml)	Sensitivity (%)	Specificity (%)
0.35	98	26.4
0.40	94.5	35.8
0.51	87.3	43.4
0.60	83.6	50.9
0.70	80	52.8
1.00	72.7	58.5
1.06	69.1	64.2
1.26	67.3	70
1.37	65.5	73.6
1.46	65.5	75.5
1.67	65.5	79.2
1.80	63.6	81.1
2.03	60	83
2.10	60	86.8
2.3	54.5	88.7



if ^{18}F-choline PETCT improves staging and changes the therapeutic indication. Our study has several limitations: retrospective design carried out in six centers with possible different interpretations of the PETCT findings. Our main findings showed that the results of the PETCT changed the therapeutic indication in 63% patients and identified lymph node and/or metastatic disease in 33% patients.

^{11}C- or ^{18}F-choline PETCT have only limited value in diagnosing primary PC due to their low sensitivity and specificity to differentiate between benign and malignant lesions in the prostate. MRI seems to be superior for the detection of primary PC [7]. For patients with intermediate or high-risk PC, commonly used imaging techniques such as CT and MRI have only a limited capacity to identify lymph node metastases because both modalities rely on lymph node size to identify metastases. Several meta-analyses [8, 9] have examined the detection rate of these imaging modalities for nodal metastases, but their use in routine clinical practice for N-staging of high-risk PC cannot be recommended because of limited sensitivity, especially for identifying small metastases and micrometastases [7].

The relative efficacy of ^{11}C- or ^{18}F-choline PETCT for M-staging in primary PC compared to other imaging modalities has been evaluated in several studies [10]. Both of these modalities can be recommended as alternatives to BS in patients with high-risk PC, especially given that studies have found that the results of choline PETCT imaging can change the management of these cases [6]. In our study, ^{18}F-choline PETCT detected the presence of cancer in 85.5% of the high-risk patients; the detection rate for nodal and distant metastases was 25.8% leading to a change in therapeutic indication in 71% of these patients. We were unable to identify any prognostic factors for positive choline PETCT findings or nodal and metastasis detection. Probably, it is due to the small size of the sample. The high-risk group is only 62 patients and node/metastatic disease was detected in only 16 patients. However, in the high-risk group, the prognostic factors for a change in treatment were, secondary Gleason ≤ 4 and Gleason score ≤ 7, which could be the subgroup of patients in which PETCT would be indicated.

In patients with biochemically recurrent PC, both ^{11}C- and ^{18}F-choline PETCT are highly accurate in identifying nodal and distant metastases. The main advantage of PETCT is that it is a single, whole-body examination; however, its accuracy in detecting local recurrence is limited [11]. Evangelista et al. [6] demonstrated that ^{18}F-choline PETCT was more sensitive and specific than BS and CT in the restaging setting. Those authors also found that MRI was more sensitive than choline PETCT, particularly in identifying local recurrences. MRI can detect local recurrence in prostatic bed, but its sensitivity in patients with PSA level < 0.5 ng/ml remains controversial, local recurrence was seen in 37% of men with PSA > 0.3 ng/ml vs 13% if PSA ≤ 0.3 ng/ml [12]. Couñago et al. [13] evaluated tumor recurrences after RP in 38 patients using both ^{18}F-choline PETCT and MRI, finding no differences in the detection rates for local recurrence, nodal recurrence, or bone metastases. A systematic review and meta-analysis included 10 studies (1031 patients) evaluating the diagnostic performance of MRI for the detection of bone metastasis in patients with prostate cancer, newly diagnosed and treated, the median PSA were 2.7–31 ng/ml. The sensitivity and specificity of all studies were 96% and 98%, respectively [14].

A meta-analysis of choline PETCT for the management of PC concluded that choline PETCT changed the treatment indication in 41% of patients [9], in our study this happened in 62.8%. In most patients with PC, the goal of treatment is to administer a risk-adjusted, patient-specific treatment to maximize cancer control while minimizing adverse effects. Modern radiation techniques such as intensity-modulated radiotherapy and image-guide radiotherapy enable the application of high-dose radiation to the primary intraprostatic lesion, to a nodal recurrence isolated after RP, or to loco-regional nodal metastases. They also require more accurate imaging tools to reliably identify not only the primary lesion and potential nodal involvement, but more importantly, to reliably detect or rule out the presence of distant disease [15]. In this sense, choline PETCT can help to distinguish between localized, regional, and distant recurrence to better inform decision-making for improved disease management. Small areas of local recurrence may be amenable to salvage radiotherapy, while early detection of distant disease would enable the timely administration of ADT [16]. ^{18}F-choline PETCT has a limited role in evaluating prostatic gland/fossa recurrence due to the physiological biodistribution of the radiopharmaceutical agent. However, in 70–90% of patients with PSA levels > 2 ng/ml (regardless of the GS), focal uptake is compatible with a true local recurrence [17]. In our study, ^{18}F-choline PETCT confirmed local and loco-regional disease in 22.7% and 13.4% of patients, respectively.

The advent of ^{18}F-choline PETCT has led to the identification of a new subgroup of metastatic PC patients: oligometastatic disease [18]. This subgroup could eventually be managed by treating all active lesions with local therapy, either surgery or ablative stereotactic body radiotherapy [19]. We found that choline PETCT identified oligometastatic disease in 10% in our sample, a finding that implied a change in the treatment indication.

One study involving 1000 patients who underwent ^{18}F-choline PETCT after biochemical failure found that 645 of the PETCT were positive for recurrent disease. In addition, the choline PETCT findings were positive in 81% of patients with PSA ≥ 2 ng/mL, 43% with PSA from 1 to 2 ng/mL, and 31% with PSA ≤ 1 ng/mL while 78.8% of patients with positive PETCT findings had a GS > 7 [20]. In contrast, we found no correlation between GS and positive choline

PETCT; however, we did find a highly significant correlation between the detection rate and PSA failure after surgery.

In our sample, findings from the ^{18}F-choline PETCT study were positive in 55% and 91%, respectively, of patients with biochemical failure after RP or RT. Kwee et al. [21] evaluated 50 patients treated with RP or RT, with rising PSA levels at follow-up, finding that the ^{18}F-choline PETCT was positive in 62% of patients overall. In that study, the sensitivity rate in patients with a PSA ≥ 1.1 ng/mL was 88%.

Fuccio et al. [22] retrospectively evaluated 123 consecutive-treated patients with biochemically recurrent PC after RP, finding that ^{11}C-choline PETCT was positive in 34.1%. The mean PSA value in the ^{11}C-choline PETCT negative patients was 2.7 ng/ml versus 3.8 ng/ml in those with a positive result. In our sample, the mean PSA value in the post-RP biochemical failure group was 0.94 ng/ml for those with a negative choline PETCT versus 3.72 ng/ml in those with a positive PETCT.

Choline PETCT identified nodal and/or metastatic involvement in 30% of the patients with biochemical failure after RP and the significant prognostic factors were: PSA failure ≥ 1.37 ng/ml and PSADT ≤ 4 months. Schillaci et al. [23] evaluated the influence of PSA, PSAV, and PSADT on ^{18}F-choline PETCT in restaging patients with rising PSA after RP. The author to conclude that ^{18}F-choline PETCT is recommended in patients with PSA > 2 ng/ml, PSADT ≤ 6 months and PSAV > 2 ng/ml per year.

Chiaravalloti et al. [24] investigated the performance of ^{18}F-choline PETCT in 79 patients with biochemical failure after RP. Findings on the ^{18}F-choline PETCT were positive in 55%. In patients with a PSADT ≤ 6 months the detection rate was 65%, and in patients with PSAV > 1 ng/ml/yr the rate was 67%.

Jadvar, conducted a study to summarize the findings of systematic reviews and meta-analyses, finding that the overall pooled detection rate for choline PETCT in restaging PC was 58%, increasing to 65% when PSADT was ≤ 6 months and to 71% and 77% when the PSAV was > 1 or > 2 ng/ml/yr, respectively [25].

In another study, Chondrogiannis et al. [26] performed ^{18}F-choline PETCT to evaluate 46 patients with biochemical failure after RT, finding a positive detection rate in 80.4% of the sample, which increased in line with increase in the trigger PSA. The detection rate was 54.5% in patients with PSA levels between 1.0 and 2.0 ng/ml; 81% between 2.0 and 4.0 ng/ml; and 89% between 4–6 ng/ml, and 100% in patients with PSA > 6.0 ng/ml. In the overall series, patients with a negative PETCT had a mean PSA of 2.3 ng/ml vs 7.5 ng/ml in the positive PETCT group. Of the PETCT positive patients, 59% had local relapse confined to the prostatic bed while 22% presented lymph node and distant metastases. In contrast, in our study, the detection rate was 91% in patients with biochemical failure after RT, and the detection rate for nodal and distant metastases was 41.6%. The PSA level was not a prognostic factor; the only prognostic factors were: PSADT ≤ 4.6 months, PSAV 0.22 ng/ml/month, and time to failure < 5 years.

Table 6 Prostate specific antigen cut-off and detection rates (*) of choline PETCT and 68 Ga-PSMA PETCT in the restaging setting

PSA (ng/ml)	Choline PETCT	68 Ga-PSMA PETCT
< 0.5	–	49% (48–50)
< 1	20% (7–31)	–
< 2	46% (43–56)	68% (67–69)
> 2	80% (72–81)	90% (88–92)

*Median (range)

The 68 Ga-prostate-specific membrane antigen (68 Ga-PSMA) has been recently developed as a ligand in PETCT to detect the presence of PC. This technique is more effective in detecting metastases, nodal involvement, and recurrent PC than ^{18}F-choline PETCT and CT. It is effective in patients with low PSA levels and is positively associated with rising PSA levels and tumor size [27]. Bluemel et al. [28] investigated the value of 68 Ga-PSMA PETCT in patients with biochemical recurrence but negative finding on ^{18}F-choline PETCT, finding that this imaging modality detected recurrent disease in 43.8% of those patients. Detection rates were 28.6, 45.5, and 71.4%, respectively, for PSA levels ≥ 0.2 to < 1 ng/mL, 1 to 2 ng/mL, and > 2 ng/mL. Table 6 summarizes prostate specific antigen cut-off and detection rates of choline and 68 Ga-PSMA PETCT in the restaging setting [6]. The 68 Ga-PSMA is recommended for evaluating biochemical relapse after prostatectomy for the superiority over choline for PSA levels < 1 ng/ml, however, at this time in Spain we do not have availability to perform PSMA [29].

Conclusions

The tumor detection rate with ^{18}F-choline PET-CT was 74%, detecting oligometastatic disease in 10.1%, lymph node/metastatic disease in 33%, and changed the therapeutic indication in 62.8% of the sample. Our findings support the clinical use de ^{18}F-choline PET-CT in staging high-risk patients with a secondary Gleason ≤ 4 and GS ≤ 7, in restaging patients with biochemical recurrence after RP if PSA at failure ≥ 1.37 ng/ml or PSADT ≤ 4 months and in patients with biochemical failure after RT if PSADT ≤ 4.6 months and time to failure < 5 years, because it determines a change in the therapeutic indication.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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