PET/CT with 18F-Fluorocholine in Patients with Prostatic Cancer in Biochemical Recurrence

PET/CT com Fluorocolina-F18 em Doentes com Carcinoma da Próstata em Recidiva Bioquímica

Paula LAPA✉[1], Rodolfo SILVA[1], Tiago SARAIVA[1], Arnaldo FIGUEIREDO[2], Rui FERREIRA[1], Gracinda COSTA[1], João Pedroso LIMA[1]

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ABSTRACT

Introduction: In prostate cancer, after therapy with curative intent, biochemical recurrence frequently occurs. The purpose of this study was to evaluate the impact of PET/CT with 18F-Fluorocholine in restaging these patients and in their orientation, and to analyze the effect of the risk stratification, the values of PSA and the hormone suppression therapy, in the technique sensitivity.

Material and Methods: Retrospective analysis of 107 patients with prostate carcinoma in biochemical recurrence who underwent PET/CT with 18F-Fluorocholine in our hospital, between December 2009 and May 2014.

Results: The overall sensitivity was 63.2% and 80.0% when PSA > 2 ng/mL. It was possible to identify distant disease in 28% of the patients. The sensitivity increased from 40.0%, in patients with low and intermediate risk, to 55.2% in high-risk patients. Without hormonal suppression therapy, the sensitivity was 61.8%, while in the group under this therapy, was 67.7%.

Discussion: PET/CT with 18F-Fluorocholine provided important information even in patients with low levels of PSA, however, with significantly increased sensitivity in patients with PSA > 2 ng/mL. Sensitivity was higher in high-risk patients compared with low and intermediate risk patients, however, without a statistically significant difference. The hormone suppression therapy does not appear to influence uptake of 18F-Fluorocholine in patients resistant to castration.

Conclusions: In this study, PET/CT with 18F-Fluorocholine showed good results in restaging patients with prostate cancer biochemical recurrence, distinguishing between loco regional and systemic disease, information with important consequences in defining the therapeutic strategy.

Keywords: Fluorocholine; Positron-Emission Tomography; Prostatic Neoplasms; Radiopharmaceuticals.

RESUMO

Introdução: No carcinoma da próstata, é frequente, após terapêutica com intuito curativo, ocorrer recidiva bioquímica. O objectivo deste trabalho foi avaliar o impacto da PET/CT com Fluorocolina-F18 no restadiamento e orientação destes doentes e analisar a influência, da estratificação de risco, dos valores do PSA e da terapêutica de supressão hormonal, na sensibilidade da técnica.

Material e Métodos: Análise retrospectiva de 107 doentes com carcinoma da próstata em recidiva bioquímica que realizaram PET/CT com Fluorocolina-F18 no nosso hospital, entre dezembro de 2009 e maio de 2014.

Resultados: A sensibilidade global foi de 63,2% sendo 80,0% quando PSA > 2 ng/mL. Foi possível identificar doença à distância em 28% dos doentes. A sensibilidade aumentou de 40,0% em doentes de risco baixo e intermédio para 55,2% em doentes de alto risco. Sem terapêutica de supressão hormonal, a sensibilidade foi de 61,8% enquanto no grupo sob essa terapêutica, foi de 67,7%.

Discussão: A PET/CT com Fluorocolina-F18 forneceu informações relevantes, mesmo em doentes com baixos valores do PSA, contudo, com incremento significativo da sensibilidade nos doentes com PSA >2 ng/mL. A sensibilidade foi superior nos doentes de alto risco comparativamente com os de risco baixo e intermédio, contudo, sem uma diferença estatisticamente significativa. A terapêutica de supressão hormonal parece não influenciar a captação de Fluorocolina-F18 nos doentes resistentes à castração.

Conclusões: Neste estudo, a PET/CT com Fluorocolina-F18 apresentou bons resultados no restadiamento de doentes com carcinoma da próstata em recidiva bioquímica, distinguindo entre doença loco-regional e sistémica, informação com importantes consequências na definição da estratégia terapêutica.

Palavras-chave: Fluorocolina; Neoplasias da Próstata; Radiofármacos; Tomografia por Emissão de Positrões.

INTRODUCTION

Prostate cancer (PCa) is the most common cancer in males and the second leading cause of cancer death in Europe, with an increasing incidence over the last few decades.[1] Patient's age is a well-recognized risk factor for PCa and therefore with increasing life expectancy it is estimated to become an ever more relevant public health concern.[2]

Follow-up upon therapy with a curative intent is mainly based on serum prostate specific antigen (PSA) levels and biochemical recurrence is a common event.[3]

Patients with locally recurrent cancer have an indication for salvage therapy. Hormonal therapy (HT) is the most commonly used palliative therapy in patients with metastatic cancer.[4] However, with the introduction of tailored therapies new therapies are available and therefore optimized resources are required with an early and accurate identification of the affected locations.

Imaging has assumed an important role in staging and

1. Serviço de Medicina Nuclear. Centro Hospitalar e Universitário de Coimbra. Coimbra. Portugal.
2. Serviço de Urologia. Centro Hospitalar e Universitário de Coimbra. Coimbra Portugal.
✉ Autor correspondente: Paula Alexandra Amado Lapa Matos dos Santos. paula.alexandra.lapa@gmail.com
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re-staging as well as in therapeutic decision. Relevant advances have also occurred in imaging techniques, allowing for a better assessment of patients with PCa, adding to the optimization of therapy. The 18F-fluorocholine (18F-FCH) positron emission tomography/computed tomography (PET/CT) assumed a relevant role in PCa assessment and showed promising results, namely in patients with recurrent disease.[5-16] This is a non-invasive anatomo-functional tomographic imaging technique providing whole-body and multi-organ information, with high accuracy for the identification of local disease, as well as local and distant lymph node involvement, including with bone involvement. It has emerged allowing for the identification of lesions, regardless of any dimensional criteria, leading to an earlier and more sensitive detection, when compared to other imaging techniques, such as CT scan and MRI (magnetic resonance imaging).[17,18]

Choline plays a role in biosynthesis of phospholipid components of cell membrane and enters the cell through a specific transporter and is used in the synthesis of phosphatidylcholine. Phosphorylation of choline into phosphocholine is the first step and is catalyzed by the enzyme choline kinase[19]. 11C- or 18F-labelled choline are therefore considered as useful radiotracers for PCa cells. Both radiotracers (11C-choline and 18F-FCH) provide similar information. Nevertheless, 18F longer half-life time (110 versus 20 minutes for 11-C) allows for a wider use and in locations away from production sites (cyclotrons).[20]

Different sensitivities and specificities, positive and negative predictive values, as well as diagnostic accuracy have been described in literature. Despite this disparity, 18F-FCH PET/CT is probably the best-performing imaging method for staging and re-staging of PCa, for the identification of lymph node involvement[21] as well as the detection of intramedullary bone involvement.[22] It is also useful in the identification of dormancy in PCa, with a 74% success rate, as well as in the differentiation between local and systemic disease.[23] However, issues such as its impact on the approach to the patient with PCa, as well as the influence of PSA levels and HT on information provided need further clarification; optimal trigger PSA level for the use of this technique is also controversial.[7,12-14,24,25]

Different studies have found a good positive correlation between 18F-FCH PET/CT sensitivity and PSA level in recurrent disease. Other variables were also suggested as positive predictive factors, namely patient's age, the stage of disease, Gleason score and the presence of previous biochemical recurrence.[26,27]

The influence of HT on 18F-FCH uptake was assessed in only a few studies and in a limited number of patients. However, current scientific evidence seems to indicate that 18F-FCH uptake is not significantly influenced by HT in

Table 1 – Characteristics of our group of patients

Parameter	Data
Total Number of Patients	107
Average Patient's Age (years)	67.6 ± 7.6 (45 - 84)
Average PSA at Diagnosis (ng/mL)	21.7 ± 40.3 (3.1 - 316.0)
Median Gleason Score	7/1st Q: 6/3rd Q: 7 (5 - 9)
TNM staging	
I	5.7%
IIa	7.1%
IIb	30.0%
III	45.7%
IV	11.4%
Initial therapy	
Prostatectomy	67.6%
Radiotherapy	22.9%
Prostatectomy and Radiotherapy	9.5%
Time between initial treatment and PET/CT in recurrence PCa	
< 6 months	11.2%
6 - 24 months	18.0%
> 24 months	70.8%
Average PSA recurrence level (ng/mL)	8.5 ± 28.8 (0.2 - 280.1)
% of patients under HT at the time when 18F-FCH PET/CT was carried out	36% (unavailable data regarding 37 patients)

patients with castration-resistant disease, although it may be significantly attenuated in hormone-sensitive patients.[28,29]

OBJECTIVE

Our study aimed to assess the impact of 18F-FCH PET/CT in re-staging and therapy orientation of patients with biochemically recurrent PCa.

We also aimed to assess the influence of different factors in 18F-FCH PET/CT sensitivity, namely risk stratification, as well as PSA levels and HT.

MATERIAL AND METHODS

Population

In total, 107 patients (aged 67.6 ± 7.6, 45-84) with PCa from our hospital, submitted to 18F-FCH PET/CT imaging between Dec 2009 and May 2014 due to biochemical recurrence upon therapy with a curative intent were included in the study.

Initial therapy with a curative intent involved prostatectomy or radiotherapy (RT) in 75.7% (81/107) and 33.6% (36/107) of the patients, respectively (10 patients underwent prostatectomy and consolidation RT).

The presence of two consecutive PSA levels >0.2 ng/mL obtained upon prostatectomy or Biochemical recurrence was considered when two PSA consecutive values over 0.2 ng/mL were obtained upon prostatectomy or an increase >2 ng/mL compared to the PSA nadir upon RT.[1,30,31]

At the time when the 18F-FCH PET/CT was performed, 36.0% (31/86) of the patients were under HT (this information was not available for 21 patients). Patients on HT with PSA values in progression were considered as castration-resistant.

The characteristics of our group of patients are shown in Table 1.

Imaging protocol for 18F-FCH PET/CT

Patients who were referred for 18F-FCH PET/CT were previously informed as regards the aims of the scan and the whole procedure and formally accepted it through completion of a written informed consent.

The acquisition protocol involved the intravenous administration of 3MBq/kg of 18F-FCH, with immediate acquisition of a 5-min pelvic dynamic study. This initial acquisition aimed to allow for the study of the pelvic region before the arrival of the radiotracer to the bladder due to its normal urinary excretion, which, due to its proximity, would prevent the assessment of prostate and periprostatic region. Thirty minutes upon the administration of the radiotracer, a whole-body acquisition study was subsequently obtained, in order to search for the presence of any metastatic involvement. Patients assumed the dorsal decubitus position with the arms above the head within a GE Discovery ST PET/CT scanner. CT attenuation and anatomical mapping acquisition parameters were as follows: 120 kV, smart mA: 35 noise index with current values between 10-200mA, pitch 1.5:1, rotation 0.5 s and a 3.75 mm slice thickness. PET emission study was obtained in 3D mode, with a 70 cm Field Of View (FOV) diameter and 3-min acquisition time whole-body studies were acquired per table position. Data were collected in list mode and rebuilt using a 3D Ordered Subset Expectation Maximization (OSEM) iterative reconstruction algorithm, with 20-subset per two iterations, 128 x 128 matrix and one 5-mm Full Width at Half Maximum (FWHM) post-reconstruction filtering.

Image interpretation

Consensus interpretations by two specialists in Nuclear Medicine were obtained and patient's clinical history as well as the available laboratory and imaging data were previously provided.

A semi-quantitative analysis was carried out and the value of the Maximum Standard Uptake Value (SUV_{max}) was calculated for each lesion, based on the creation of a volume of interest completely and solely involving the lesion. SUV_{max} was used as an indicator of the radiotracer's uptake intensity by lesions.

18F-FCH uptake by the prostate and prostate bed was considered as abnormal when uptake intensity was above the background activity.

Lymph nodes with increased 18F-FCH uptake were considered as lymph node metastases, even without any anatomical criteria as lymphadenopathies. Lymph nodes with anatomical criteria as lymphadenopathies and no 18F-FCH uptake were not considered as metastases. Inguinal lymph nodes with mild 18F-FCH uptake and no suspicious morphological criteria were considered as reactive or inflammatory. This interpretation was carried out according to different criteria described in several published studies.[7,10,15]

Skeletal areas of abnormally increased 18F-FCH uptake were considered as malignant according to its uptake intensity, anatomical location and morphological characteristics (tomodensitometric characteristics). These data were also correlated to those obtained in additional tests, such as the 18F-Sodium Fluoride (^{18}F-NaF) bone PET/CT scan, the bone scintigraphy or MRI, whenever available. Discrepancies between 18F-FCH uptake and CT scan morphological characteristics found in PET/CT lead to an additional study through clinical follow-up and, in 16 patients, through a control 18F-FCH PET/CT. In these patients, lesions showing persistent 18F-FCH uptake or with a clinical or laboratory evidence of disease progression were considered as malignant.

The tests of two patients with biochemical recurrence upon RT and prostatectomy are shown in Figure 1-2 and in Figure 3, respectively.

Recurrence diagnosis was histopathologically confirmed in 7.5% (8/107) of the patients and these underwent prostatectomy due to recurrence upon initial RT therapy. Three patients also underwent a pelvic lymphadenectomy, having been removed 19 lymph nodes in total. Histopathological confirmation was not obtained for the remaining 92.5% (99/107) of the patients, in whom lesions with an increased 18F-FCH uptake were considered as malignant, according to the abovementioned criteria. Clinical and laboratory follow-up, as well as the results obtained from several control imaging tests have also contributed to the assignment of any pathological meaning.

Average follow-up time of our patients was 18.7 ± 13.3 months.

Statistical analysis

SPSS (version 20) software was used in statistical analysis. Univariable studies were carried out for the descriptive and frequency analysis. Mann-Whitney's U-test and Chi-square test were used in comparison of quantitative and qualitative variables between groups, respectively. Correlation between quantitative variables was assessed using Spearman's coefficient. Logistic regression test was carried out for assessing the influence of the different variables in the sensitivity of 18F-FCH PET/CT scan. Statistical significance was met for a value of *p* below 0.05 for all tests.

RESULTS

The 18F-FCH PET/CT scan was positive in 63.6% (68/107) of the patients. Prostatic/prostate bed recurrence was found in 38.2% of these patients (26/68) with absence of disease at any other location; isolated lymph node involvement was found in 20.6% (14/68) and isolated bone involvement in 8.8% (6/68) of the patients. Regardless of the presence of any other spread, 60.3% (41/68) of the patients presented with prostatic recurrence, 51.5% (35/68) with lymph node involvement and 26.5% (18/68) with bone involvement.

The presence of local spread of the disease was found in 55.9% (38/68) of the patients, corresponding to prostatic or prostate bed recurrence and/or to pelvic lymph node involvement and 44.1% (30/68) presented with distant spread, corresponding to extra-pelvic lymph node and/or bone involvement.

A false positive result corresponding to prostatitis was found in one of the eight patients from whom we were provided with histology results. In the remaining seven

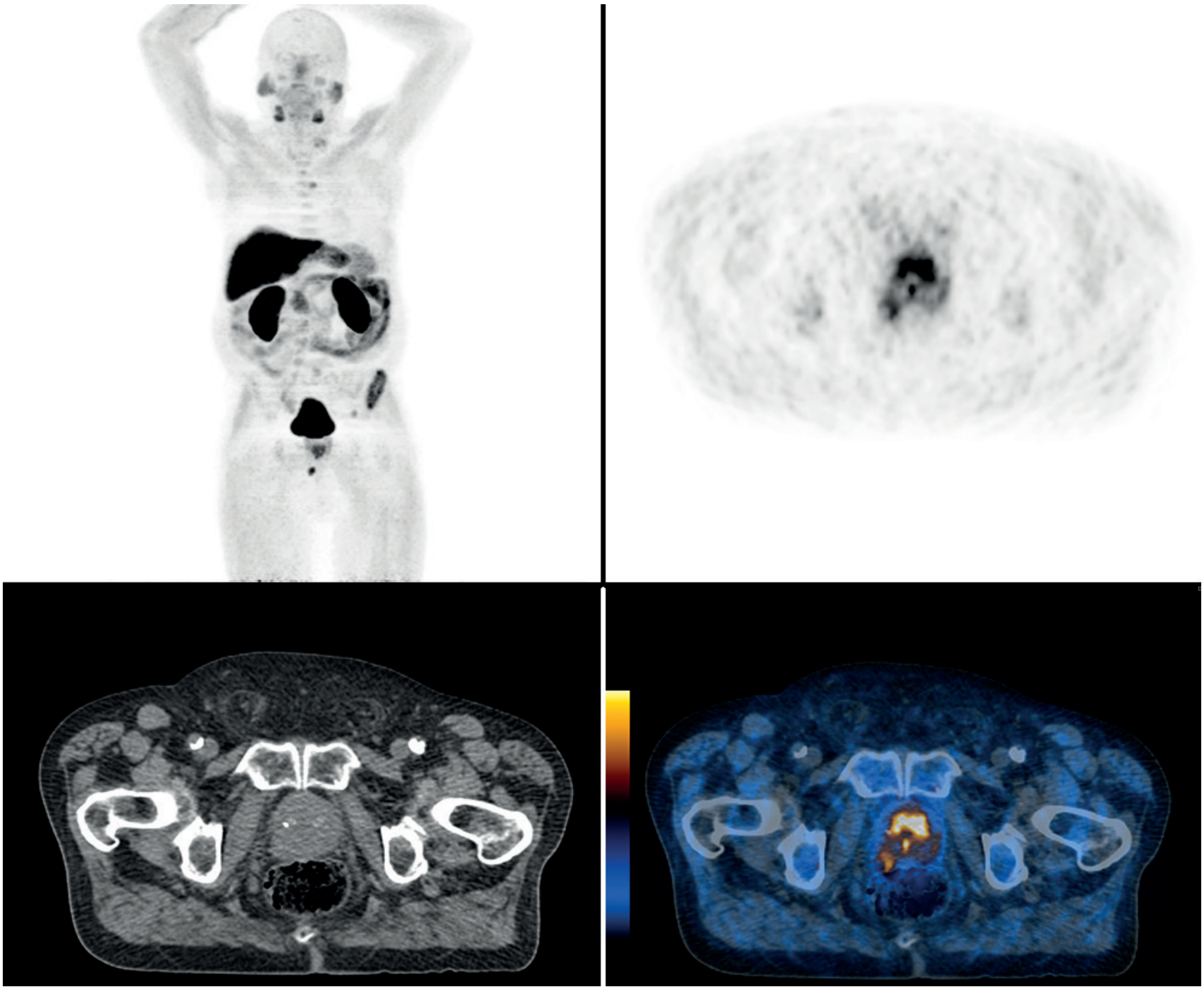

Figure 1 - 18F-FCH PET/CT imaging from patient with prostate cancer who underwent radiotherapy (current PSA level - 81 ng/mL). Abnormally increased prostatic 18F-FCH uptake is shown, suggesting the presence of active prostatic disease. Whole-body study showing local-regional, as well as distant metastatic involvement is shown in Fig. 2.

patients the disease was confirmed in the prostatectomy sample, corresponding to true positive results. No lymph node involvement (19 lymph nodes in total) was found in the three patients who underwent pelvic lymphadenectomy, all lymph nodes having been interpreted as negative in the 18-FCH PET/CT and therefore considered as true negative.

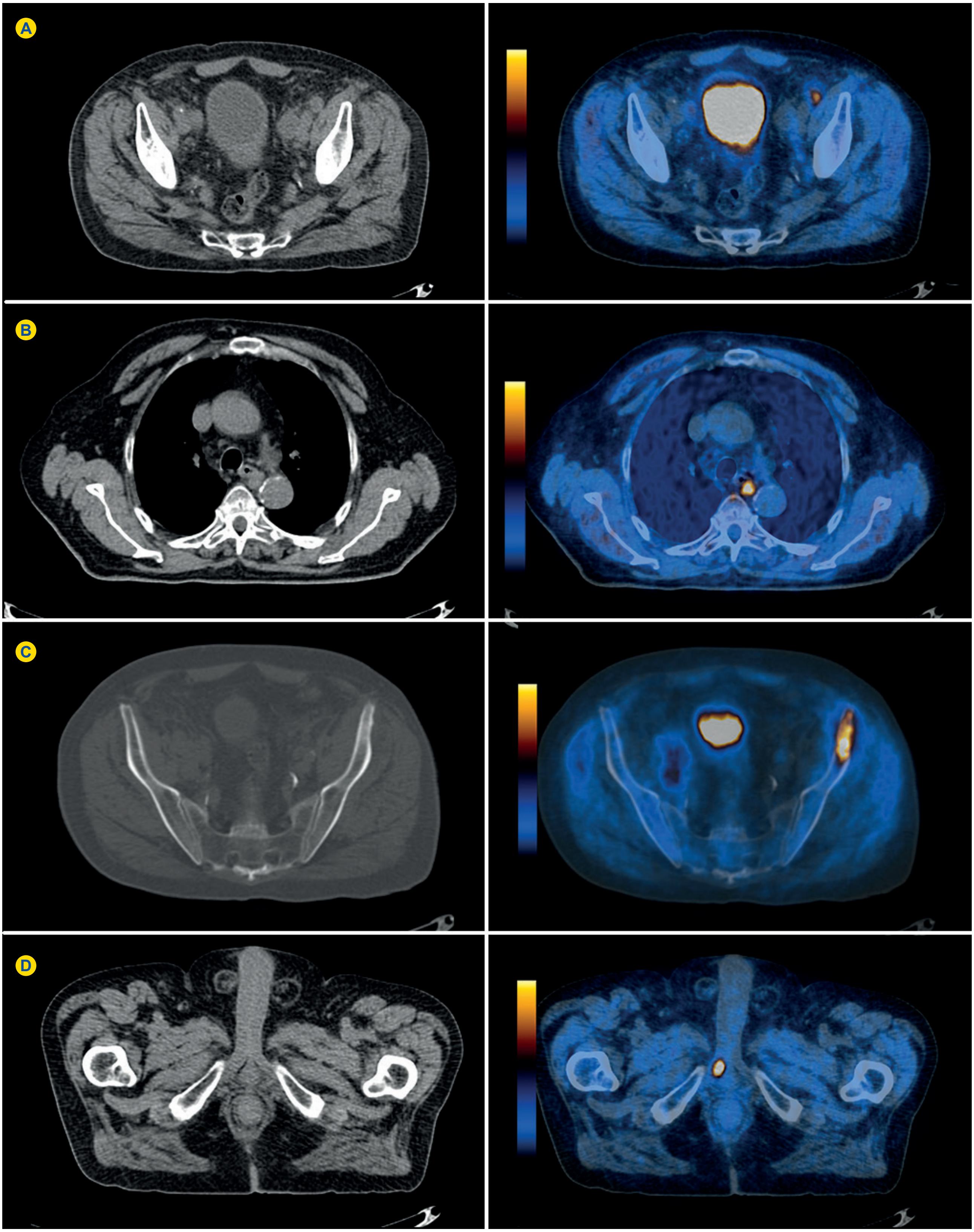

Figure 2 - 18F-FCH PET/CT imaging regarding the same patient as in Fig. 1, showing the presence of lymphadenopathies with abnormally increased prostatic 18F-FCH uptake, suggesting the presence of local-regional (A) and distant (B) lymph node metastatic spreading as well as bone involvement (C), in addition to the involvement of the right corpus cavernosum (D).

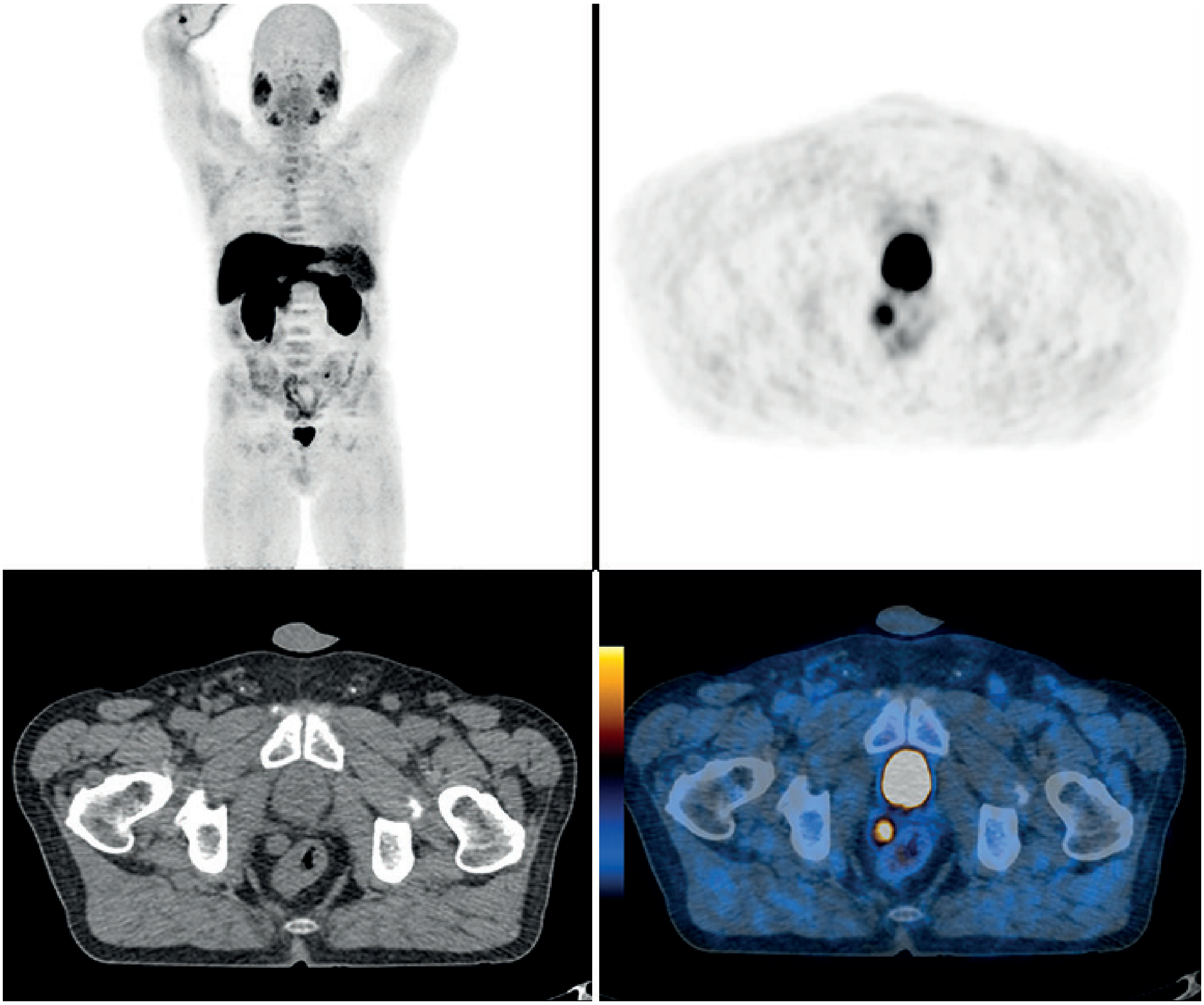

Figure 3 - 18F-FCH PET/CT imaging from patient with prostate cancer who underwent prostatectomy (current PSA level - 8 ng/mL). The presence of one right pararectal lymphadenopathy with abnormally increased uptake of the radiotracer suggesting the presence of lymph node involvement, showing no other suspicious activity at the prostatic bed or at any other location.

A single lesion was detected by the 18F-FCH PET/CT in 54.4% (37/68) of the patients (70.3% with local recurrence, 21.6% with a single lymph node metastasis and 8.1% with a single bone metastasis).

Positive 18F-FCH PET/CT scan and PSA levels

Globally, an average 8.2 ± 29.1 ng/mL(0.2 – 280.1) PSA level was found. An average 2.0 ± 3.5 ng/mL (0.2 - 20) PSA level was found in patients with negative 18F-FCH PET/CT, when compared to 11.8 ± 36.2 ng/mL (0.3 – 280.1) in patients with positive 18F-FCH PET/CT ($p < 0.05$). An average 5.6 ± 6.7 ng/mL (0.4 – 29.1) PSA level was found in patients with local recurrence only and no disease in any other location, 4.5 ± 3.3 ng/mL (0.7 - 14) in patients with lymph node involvement only and 7.3 ± 12.9 ng/mL (1.2 – 33.5) in patients with bone involvement only ($p > 0.05$). An average 7.6 ± 33.9 ng/mL (0.3 – 280.1) PSA level was found in patients with local and regional disease, while a 9.4 ± 12.4 ng/mL (0.4 - 50) level was found in patients with distant spread disease ($p < 0.05$). An average 36.8 ± 86.4 ng/mL (1.1 – 280.1) PSA level was found in patients with local recurrence and lymph node involvement and 0.3 ng/mL (one patient only) in patients with local recurrence and bone involvement; an average 12.7 ± 3.1 ng/mL (9.0 – 16.5) PSA level was found in patients with local recurrence and with both lymph node and bone involvement. These data are shown in Table 2, 3 and 4.

A 40.5% [17/(17 + 25)] sensitivity with the 18F-FCH PET/CT scan was found in patients with PSA ≤ 2 ng/mL and 80% [48/(48 + 12)] in patients with PSA > 2 ng/mL ($p < 0.05$). PSA recurrence level was not available in five patients. (Fig. 4).

An average 13.9 ± 15.8 ng/mL (3.1 – 87.0) initial PSA level was found in patients with negative 18F-FCH PET/CT and 27.1 ± 50.2 ng/mL (4.0 – 316.0) ($p < 0.05$) in those with positive 18F-FCH PET/CT.

Positive 18F-FCH PET/CT scan and SUVmax levels

Average 3.3 ± 2.1 (0.6 – 8.5), 4.0 ± 3.8 (1.1 – 13.5) and 7.0 ± 4.7 (2.2 – 15.2) SUV_{max} levels were found in patients

Table 2 – Average PSA level and positive scan

	Global	Negative PET	Positive PET	*p*
Average PSA level	8.2 ± 29.1	2.0 ± 3.5	11.8 ± 36.2	< 0.05

Table 3 – Average PSA and disease location

	Local recurrence	Lymph node involvement	Bone involvement	*p*
Average PSA	5.6 ± 6.7	4.5 ± 3.3	7.3 ± 12.9	> 0.05

Table 4 – Average PSA level and local-regional versus distant metastases

	Local-regional disease	Distant metastases	*p*
Average PSA	7.6 ± 33.9	9.4 ± 12.4	< 0.05

with local recurrence, lymph node and bone involvement, respectively ($p > 0.05$).

No statistically significant differences were found between SUV_{max} levels in patients with ≤ 2 ng/mL PSA levels *vs.* patients with PSA > 2 ng/mL ($p > 0.05$) nor any statistically significant correlation between PSA recurrence and average SUV_{max} levels ($p > 0.05$).

Positive 18F-FCH PET/CT and HT

At the time when the 18F-FCH PET/CT scan was performed, 29.0% (31/86) of the patients were receiving HT (unavailable data for 21 patients). An average 3.2 ± 3.3 ng/mL (0.2 -14.0) PSA level was found in patients not receiving HT *vs.* 18,3 ± 51.5 ng/mL (0.2 – 280.1) in patients receiving HT ($p < 0.05$).

Average SUV_{max} levels obtained in both groups of patients are shown in Table 5.

Average SUV_{max} levels were slightly higher in patients receiving HT when compared to those not receiving it, even though statistically significant differences were not found (4.7 ± 2.4 *vs.* 4.2 ± 3.4; $p > 0.05$).

A 61.1% [33/(33 + 21)] 18F-FCH PET/CT sensitivity was found in the group of 55 patients not receiving HT, while a sensitivity of 67.7% [21/(21 + 10)] was found in the group of patients receiving HT ($p > 0.05$) (Table 6).

Risk stratification

A 33.3% [3/(3 + 6)] increase in 18F-FCH PET/CT scan sensitivity was found in D'Amico (score of the risk of PCA recurrence) low-to-intermediate-risk patients, while a 55.2% [37/(37 + 30)] increase was found in high-risk patients (missing data from 30 patients made stratification unavailable) ($p > 0.05$).

A 52.6% [20/(20 + 18)] sensitivity was found in high-risk

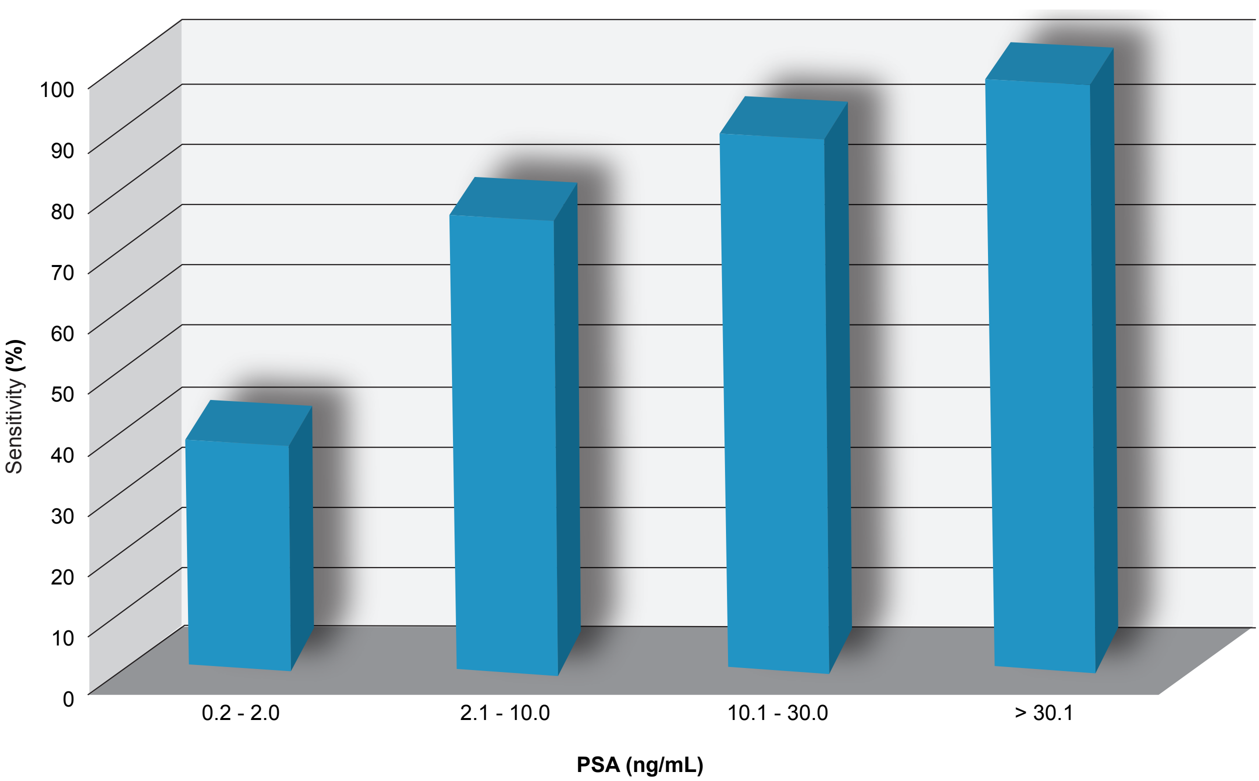

Figure 4 - Variation on 18F-FCH PET/CT sensitivity according to PSA levels.

patients not receiving HT, while a 75% [12/(12 + 4)] sensitivity was found in those receiving it ($p > 0.05$). This analysis was not possible in low-to-intermediate risk patients due to the small number of patients in this group.

The average SUV_{max} of lesions was slightly higher in high-risk patients, when compared to low-to-intermediate risk patients, even though statistically significant differences were not found (4.4 ± 3.4 *vs.* 5.0 ± 3.3) ($p > 0.05$).

Predictive factors and sensitivity of the 18F-FCH PET/CT scan

A logistic regression analysis was carried out in order to assess the impact of different factors in positive 18F-FCH PET/CT scans. Patient's age, PSA recurrence level, level of PSA at diagnosis, Gleason score, tumour staging, HT and time between initial treatment and the 18F-FCH PET/CT scan were the variables included in the model. Gleason score (B = 1.138 and $p = 0.019$) and the level of PSA at recurrence (B = 1.42 and $p = 0.037$) were the only statistically significant variables found in this analysis.

DISCUSSION

Recurrence is a common event in PCa upon initial therapy with a curative intent, with radical prostatectomy or RT.[32]

PSA level is very relevant in follow-up, allowing for an early detection of biochemical recurrence. Nevertheless, it does not allow for the identification of the disease locations, namely the differentiation between a local and regional recurrence and a disease with a distant spread or between a single lesion and a spreading disease,[33] which are crucial for a tailored therapy.[34]

Prostate biopsy has limitations due to its invasive nature as well as to potential sampling errors. Conventional imaging techniques, although well established in clinical practice, have some limitations regarding the detection of disease locations, especially as regards bone involvement.[35] Approximately 70% of lymphadenopathies have small dimensions (long axis < 8 mm).[36] This is a limitation as regards the sensitivity of any imaging technique based on morphological criteria, such as CT or MRI.

An accurate identification of any lymph node involvement is particularly important, due to the influence on 5-year disease-free survival, ranging from 20-30% with multiple lymph node metastases compared to 75-80% with a single metastasis.[37]

Bone scintigraphy has been used in detection of bone involvement. It has however a limited sensitivity and mostly a low specificity and usually there is the need for using other imaging techniques in order to clarify the results of scintigraphy.

The 18F-FCH PET/CT scan is a non-invasive whole-body multi-organ study combining anatomical and functional information, now increasingly being used in imaging PCa assessment.[38] Although it seems useful in the initial clinical staging, it has been shown as especially useful in re-staging of patients with biochemical recurrence.[39] It is mainly useful in the early stage of biochemical recurrence, allowing for the selection of patients that may benefit from salvage therapy, as well as for the assessment of patients with biochemical recurrence receiving HT, due to the likely presence of extra-pelvic involvement.[39]

Different studies have assessed the diagnostic accuracy of this technique in the presence of biochemical recurrence of PCa, showing widely-varying sensitivities ranging between 43 and 95%.[5,7,10,12,14,24,40-43] A recent study has found a high sensitivity and high negative predictive value of 18F-FCH PET/CT scan. In this study, a group of patients with biochemical recurrence remained in complete remission over a 6.5-year follow-up, upon removal of a single lymphadenopathy identified by the 18F-FCH PET/CT scan.[44] These were promising results, although further long-term studies are necessary to confirm these results.

Other studies have assessed the influence of different factors such as the stage of the disease, Gleason score, HT, PSA level and PSA doubling time.[13,25-28,45] The accuracy of 18F-FCH PET/CT scan in biochemical recurrence has been well recognized[46] even though some studies have described that sensitivity is influenced by HT, as well as by the PSA level.[47] This relationship led to a debate on a PSA threshold for this technique to be performed. Different PSA thresholds were described in literature and, as the

Table 5 – Comparison between SUV_{max} levels within different malignancies in patients receiving or not receiving HT

Parameter	Global	Under HT	No HT	*p*
Local recurrence	3.3 ± 2.1	4.0 ± 2.6	5.1 ± 2.7	> 0.05
Lymph node involvement	4.0 ± 3.8	3.7 ± 3.2	4.4 ± 3.5	> 0.05
Bone involvement	7.0 ± 4.7	9.6 ± 3.8	6.7 ± 3.3	> 0.05

Table 6 – Correlation between PSA, SUV_{max} levels and 18F-FCH PET/CT sensitivity in patients receiving or not receiving HT

Parameter	No HT	Under HT	*p*
PSA level	3,2 ± 3,3	18,3 ± 51,5	< 0,05
SUV_{max} level	4,7 ± 2,2	4,2 ± 3,4	> 0,05
Sensitivity	61,1%	67,7%	> 0,05

technique has been increasingly used in clinical practice, these levels have been progressively lowered. In 2006, this procedure was questionable for PSA levels under 5 ng/mL.[48] Even though 2 ng/mL is the most frequently accepted threshold (and therefore also adopted in our study), it is currently recognized that the 18F-FCH PET/CT scan may be useful from 1 ng/mL and we may even consider it with lower PSA levels and high PSA doubling times.[22]

Sound results were obtained in our study with the use of the 18F-FCH PET/CT scan in re-staging patients with PCa and biochemical recurrence, allowing for the identification of metastatic PCa, as well as for metastasis location (lymph node and bone involvement) in a significant percentage of cases (28% of the patients and 44% of positive scans). Globally, a 63.2% sensitivity was found and increased to 80% when considering only the patients with PSA > 2 ng/mL. In total, 38 (35.5%) patients with a single lesion were detected, 26 (68.4%) with local recurrence, eight (21.1%) with lymph node involvement and four (10.5%) with bone involvement, with a clear impact in therapeutic approach.

From the variables included in the logistic regression analysis, (patient's age, PSA recurrence level, PSA at diagnosis, Gleason score, staging of the disease, HT and time between initial treatment and the time when scan was performed), only Gleason score (B = 1.138 and p = 0,019) and PSA recurrence level (B = 1.42 and p = 0.037) were statistically significant.

Pre-clinical studies showed a lower choline accumulation in hormone-sensitive cells upon HT, an effect that was not found in hormone-resistant cells.[49] Different mechanisms were proposed to explain for the reduction in SUV_{max} upon HT, namely 1) reduced volume of the lesion (reducing the signal due to a partial volume effect), 2) reduced levels of cell proliferation and 3) under-regulation of the expression of genes regulating the lipid metabolism, including a lower active choline transporter or lower choline-kinase enzyme activity.[50-55] However, HT did not show the same effects in castration-resistant patients.

In our study, the sensitivity of 18F-FCH PET/CT scan, as well as levels of SUV_{max} were slightly higher in the group of patients under HT, even though statistically significant differences were not found in both parameters ($p > 0.05$). In addition, HT was not found as a positive predictive variable of 18F-FCH PET/CT scan in logistic regression analysis. Nevertheless, it should be mentioned that this analysis was limited by the small number of patients in whom HT was documented.

Despite these limitations, these results suggest that HT does not significantly affect 18F-FCH uptake in castration-resistant patients. Therefore, pre-scan HT withdrawal in patients with biochemical recurrence seems unnecessary. However, further studies are needed to clarify the mechanisms by which 18F-FCH uptake is inhibited by HT.

The major limitations of this study regard its retrospective nature as well as the fact that most of the lesions were not histologically confirmed. Histological confirmation of every lesion is not feasible due to practical and ethical issues. Lesions were considered as malignant based on clinical and laboratory, as well as imaging follow-up. However, different lesions may respond differently to therapy, which may have biased the results.

New advances in PCa imaging are constantly emerging. The PET/CT scan with Prostate Specific Membrane Antigen (PSMA) labelled with ^{68}Ga is a very promising technique, which seems to combine high sensitivity, even in patients with low PSA, with high specificity. In addition, the introduction of beta-emitting (such as the ^{177}Lu) labelled PSMA molecules provides for oriented molecular diagnostic and therapeutic approach (theragnostics) that may change treatment of metastatic PCa.[56]

CONCLUSION

Sound results were found in our study regarding the use of 18F-FCH PET/CT scan in re-staging of patients with biochemical recurrence of PCa. The use of this technique allowed for the distinction between local-regional and systemic disease, an information relevant to therapeutic outcomes.

A strong positive correlation was found between the sensitivity of this procedure and recurrent PSA level. The 18F-FCH PET/CT scan provided for important diagnostic data in patients with low PSA levels and a significant increase in sensitivity was found in patients with PSA > 2 ng/mL.

A slightly higher sensitivity of 18F-FCH PET/CT scan was found in high-risk patients, when compared to low-to-intermediate-risk patients (according to the D'Amico classification), even though a statistically significant difference was not achieved.

Slightly higher sensitivity and SUV_{max} levels were found in the group of patients under HT, even though a statistically significant difference was not found. These results suggest that diagnostic information is not negatively influenced by HT in castration-resistant patients and therefore pre-scan HT withdrawal seems unnecessary in this group of patients.

HUMAN AND ANIMAL PROTECTION

The authors declare that the followed procedures were according to regulations established by the Ethics and Clinical Research Committee and according to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

CONFLICTS OF INTEREST

The authors declare that there were no conflicts of interest in writing this manuscript.

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