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ORIGINAL ARTICLE

Comparison of choline influx from dynamic ^{18}F-Choline PET/CT and clinicopathological parameters in prostate cancer initial assessment

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Abstract

Aim The aim of the study was to compare the kinetic analysis of ^{18}F-labeled choline (FCH) uptake with static analysis and clinicopathological parameters in patients with newly diagnosed prostate cancer (PC).

Materials and methods Sixty-one patients were included. PSA was performed few days before FCH PET/CT. Gleason scoring (GS) was collected from systematic sextant biopsies. FCH PET/CT consisted in a dual phase: early pelvic list-mode acquisition (from 0 to10 min post-injection) and late whole-body acquisition (60 min post-injection). PC volume of interest was drawn using an adaptative thresholding (40% of the maximal uptake) on the late acquisition and projected onto an early static frame of 10 min and each of the 20 reconstructed frames of 30 s. Kinetic analysis was performed using an imaging-derived plasma input function. Early kinetic parameter (K1 as influx) and static parameters (early SUVmean, late SUVmean, and retention index) were extracted and compared to clinicopathological parameters.

Results K1 was significantly, but moderately correlated with early SUVmean ($r=0.57$, $p<0.001$) and late SUVmean ($r=0.43$, $p<0.001$). K1, early SUVmean, and late SUVmean were moderately correlated with PSA level (respectively, $r=0.36$, $p=0.004$; $r=0.67$, $p<0.001$; $r=0.51$, $p<0.001$). Concerning GS, K1 was higher for patients with GS $\geq 4+3$ than for patients with GS $<4+3$ (median value 0.409 vs 0.272 min^{-1}, $p<0.001$). No significant difference was observed for static parameters.

Conclusions FCH influx index K1 seems to be related to GS and could be a non-invasive tool to gain further information concerning tumor aggressiveness.

Keywords ^{18}F-Choline · Positron emission tomography · Prostate cancer · Kinetic analysis

Introduction

Prostate cancer (PC) is the most commonly diagnosed cancer in male worldwide [1]. A number of studies have shown the usefulness of ^{18}F-labeled choline (FCH) derivatives tracers for non-invasive positron emission tomography/computed tomography (PET/CT) in PC [2, 3]. Indeed, choline is a precursor of the biosynthesis of phosphatidylcholine, which is located on the cell membrane phospholipids and highly expressed in cancer, especially in PC [4–6]. To date, FCH PET/CT is mainly used for patients with recurrence of PC [7].

Concerning newly diagnosed PC, FCH PET/CT is mainly used to assess imaging abnormalities seen during intermediate-to-high-risk PC staging with pelvic magnetic resonance (MR), CT, and/or bone scan [8]. In general, for newly

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diagnosed PC, staging and therapeutic options depends on the extent of the tumor (TNM), prostatic-specific antigen (PSA) level, Gleason Scoring (GS), number of biopsies involved with cancer, percentage of each biopsy involved with cancer, PSA doubling time, and life expectancy [9]. However, the utility of integrating novel prognostic factors into an updated risk stratification schema is still source of debate [10]. Indeed, overtreatment is a concern, because many of these cancers are not life-threatening. FCH PET/CT is a non-invasive procedure which could help in newly diagnosed PC to identify aggressive tumors, especially during active surveillance [11]. Therefore, FCH PET/CT could be added to the risk stratification schema in further studies.

Usually, the imaging protocol for FCH PET/CT consists in a dual-phase procedure: a pelvic kinetic acquisition starts immediately after tracer injection followed by a late scan covering the base of the skull through the superior portion of the thighs [12–14]. The early phase is mainly used to detect pelvic lesions before radioactive urine appears in the excretory pathways [12, 15, 16]. Moreover, this early acquisition could also be used to extract an FCH influx index using pharmacokinetic modeling [17–20]. Similar to the kinetic modeling of ^{18}F-Fluorodeoxyglucose (FDG) PET/CT used for several cancers [19, 21–23], the kinetic modeling of FCH PET/CT in PC could add further information concerning tumor aggressiveness [24].

The aim of this study was to characterize the uptake of FCH using kinetic analysis in comparison with usual static parameters and GS in newly diagnosed PC.

Materials and methods

Patients

From October 2015 to April 2017, 61 patients with newly histologically proven PC and before any treatment referred to the nuclear medicine department to perform an FCH PET/CT were included. The study was approved by the institutional review board (2016.CE11). Before inclusion, each patient signed a written informed consent form after verbal and written explanations. All patients underwent ^{18}F FCH PET/CT at least 14 days after US-guided biopsies to avoid any biopsy effect. Results of PSA test performed few days before FCH PET/CT were collected. GS were obtained from systematic extended-sextant 12-core biopsies, based on the Gleason System on ISUP criteria 2014 and stratified by categorization into low-grade ($GS \leq 3+4$) and high-grade malignancies ($GS > 3+4$), respectively.

FCH PET/CT data

FCH was synthesized in Austria (IASOcholine; IASON GmbH, Austria). Each patient underwent a CT scan followed by a 10-min dynamic PET scan using list-mode acquisition with the field of view centered over the pelvic region. At the start of the PET acquisition, 3 MBq/kg were intravenously administered using an automated injector and flushed with 40 mL of saline. Two different PET/CT instruments were used: a Siemens Biograph mCT 64 camera and a Siemens Biograph mCT40 camera (Siemens, Knoxville, TN). Both systems have similar PET detector characteristics. All patients fasted at least 6 h before the FCH PET/CT scanning. A whole-body PET/CT scan was performed 1 h post-injection (p.i). PET data were reconstructed using point spread function based on time-of-flight 3D-ordered subsets expectation maximization iterative algorithm (2 iterations, 21 subsets) with corrections (attenuation, dead time, randoms, scatter, and decay) and 2 mm kernel convolution filter. Voxel size was $4 \times 4 \times 2$ mm^3. Twenty frames of 30 s and 1 static frame of 10 min were reconstructed from the list-mode acquisition. Time-activity curve (TAC) from a volume of interest (VOI) was generated with the Syngo.via software (Siemens) by a nuclear medicine physician. The PC VOI was manually drawn on the late acquisition. Metabolic tumor volume was defined using an adaptative thresholding method based on the signal to noise ratio described by Daisne et al. [25]. The VOI was projected onto the early static frame of 10 min and each of the 20 reconstructed frames of 30 s. The standardized uptake value (SUV) was calculated and adjusted by means of an injected dose according to tissue activity concentration and patient body weight. The SUVmean of the metabolic tumor volume was measured on the early static frame of 10 min (early SUVmean) and on the late acquisition (late SUVmean). SUVmean parameter was preferred to SUVmax, because a lower number of counts is detected during the short duration of kinetic reconstructed frames. The retention index (%) was calculated as $100 \times$ (late SUVmean − early SUVmean)/early SUVmean. For the kinetic analysis, an imaging-derived arterial input function was estimated from a manually-drawn VOI within the largest arterial blood-pool structures available on the early PET image when the peak blood-pool activity was the highest. For the tracer kinetic modeling, the reversible one-tissue compartment model with blood volume parameter was adopted, like recently published [17, 26]. Verwer et al. have suggested that this model is suitable for FCH kinetic modeling due to its robustness and consistency in shorter examinations [26]. Kinetic parameters were extracted with PMOD software version 3.8 (PMOD Technologies; Zürich, Switzerland). K1 (min^{-1}) represented the influx between plasma compartment and tissue compartment.

Statistical analysis

The Pearson's correlation test was performed to measure the statistical association between K1 and SUVs and between imaging parameters and PSA level. To compare imaging parameters and GS, a Mann–Whitney *U* test was performed. A p value < 0.05 was considered as statistically significant. A commercial program was used for all statistical analysis [Wolfram Research, Inc., Mathematica, Version 11.1, Champaign, IL (2017)].

Results

Patients

Median age was 65 years +/− 7 (range 45–87). Thirty-nine patients showed tumor stage < T3 (8 as T1 and 31 as T2) and 22 patients showed tumor stage ≥ T3 (21 as T3 and 1 as T4). At the time of FCH PET/CT, the median PSA level was 13.4 +/− 53.1 ng/mL (range 2.7–298). GS varied between 3 + 3 and 5 + 4 (15 as 3 + 3, 11 as 3 + 4, 15 as 4 + 3, 9 as 4 + 4, 9 as 4 + 5 and 2 as 5 + 4). Figure 1 shows TAC obtained in a 66 years old man.

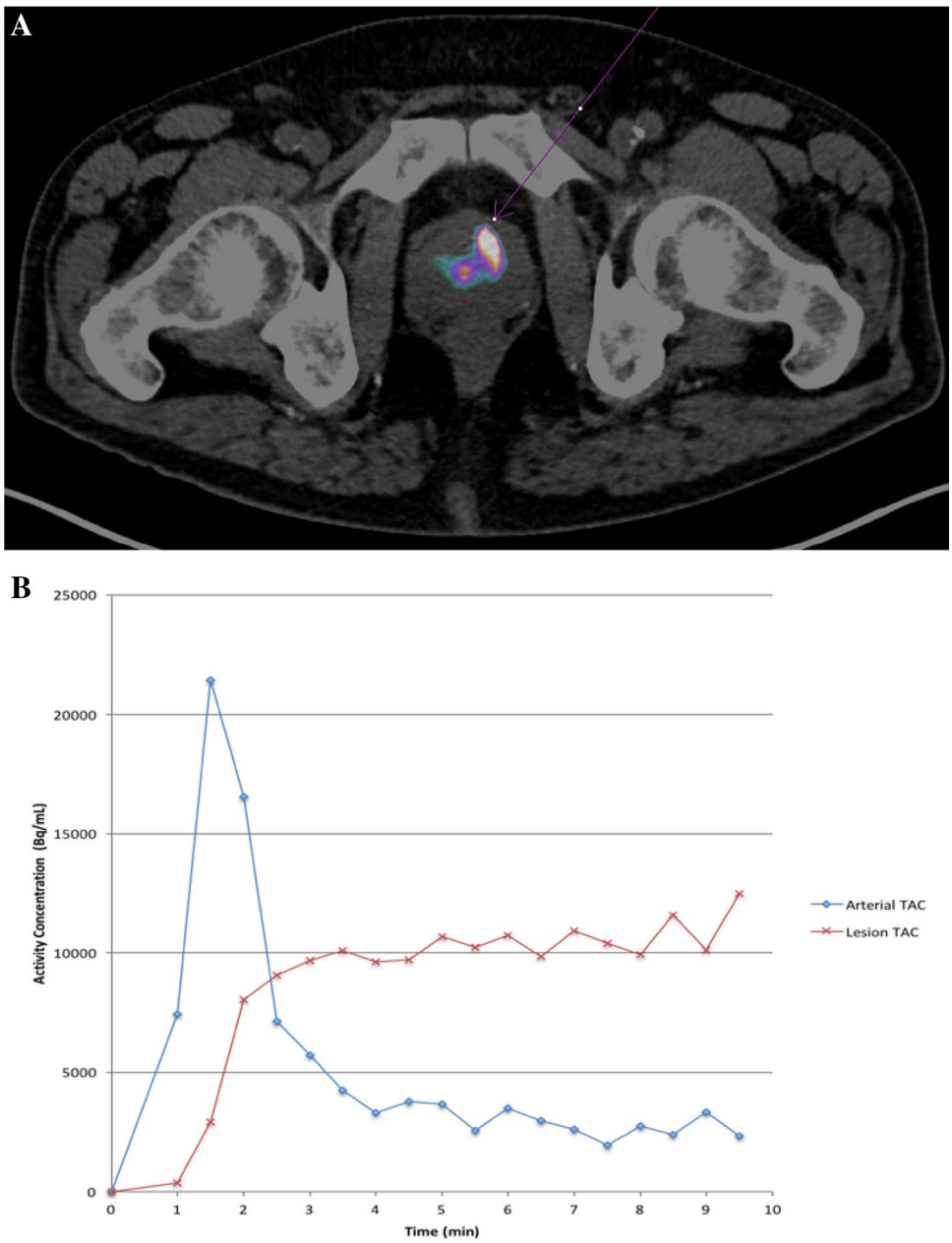

Fig. 1 A 66-year-old man with PSA level = 29 ng/mL. Fused axial early static frame FCH PET/CT (**a**) demonstrates prostatic uptake (purple arrow) with corresponding time-activity curves (**b**). FCH PET/CT parameters are: K1 = 0.344 min^{-1}; early SUVmean = 2.2; late SUVmean = 3.4 and retention index = 55%. Anatomo-pathological report from systematic sextant biopsies showed Gleason score = 3 + 4

Correlation between kinetic and static FCH PET/CT parameters

Results showed that K1 was moderately correlated with early SUVmean ($r=0.57$; $p<0.001$) and late SUVmean ($r=0.43$; $p<0.001$). No significant correlation was observed between K1 and retention index ($r=-0.11$; $p=0.396$) (Fig. 2).

Comparisons between FCH PET/CT parameters and clinicopathological characteristics

K1, early SUVmean, and late SUVmean were moderately correlated with PSA level (respectively, $r=0.36$, $p=0.004$; $r=0.67$, $p<0.001$; $r=0.51$, $p<0.001$) (Fig. 3). Concerning GS, the results of the Mann–Whitney U test showed that K1 was significantly higher for patients with GS ≥ 4 + 3 than for patients with GS < 4 + 3. No significant difference was observed for static parameters. Concerning the sub-group of patients with GS = 7 (26 patients), only K1 parameter was also significantly higher for patients with GS = 4 + 3 than for patients with GS = 3 + 4 (Table 1).

Discussion

In this study, results show that FCH influx (K1) was the only FCH PET/CT parameter that is related to GS. To the best of our knowledge, only two studies with a lower number of participants compared kinetic FCH parameters and GS. Schaefferkoetter et al. demonstrated that FCH influx was significantly higher in tumors with GS of 4 + 3 than tumor with GS of 3 + 4 or 3 + 5 [24], which are consistent with the results of our study [24]. However, on the other hand, Choi et al. showed no difference between high and low GS [17]. Controversial results could be explained by a different kinetic modeling used between these studies (Schaefferkoetter et al. were using the one-tissue compartment model and Choi et al. were using the the two-tissue compartment

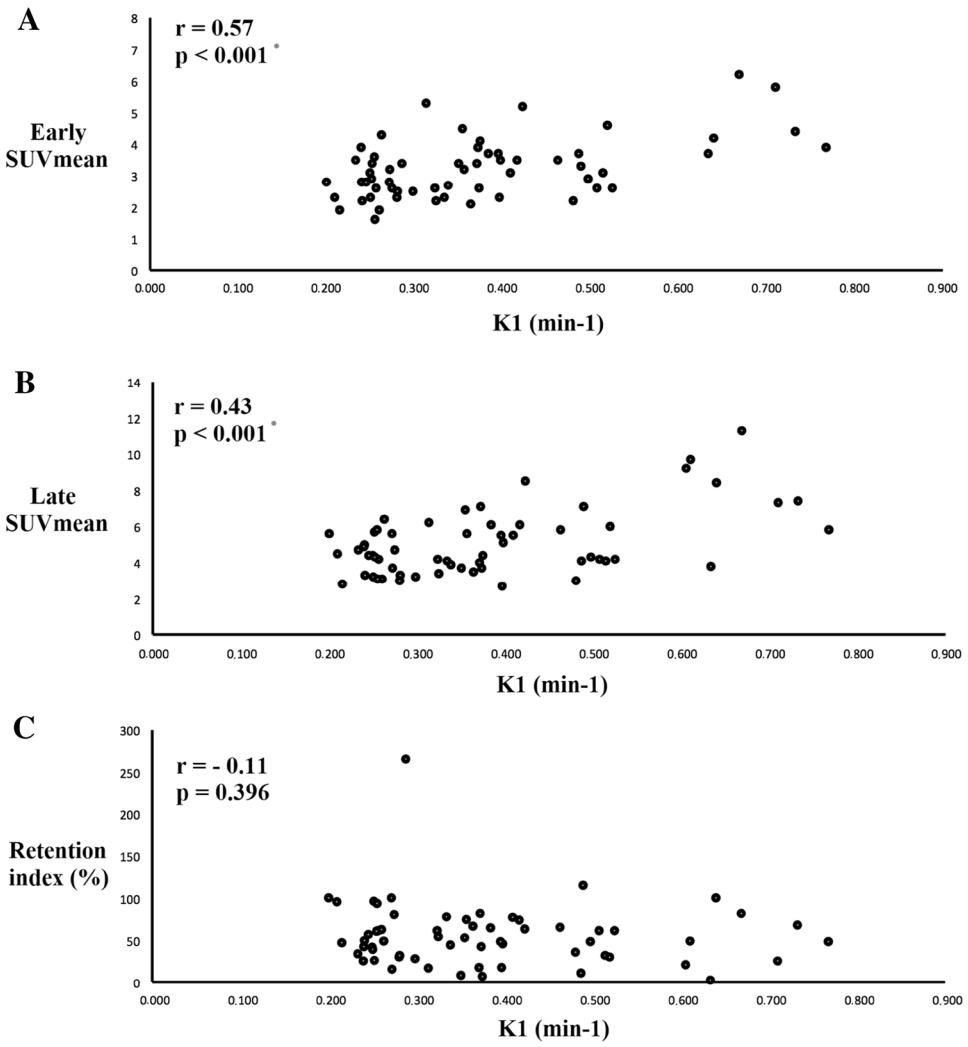

Fig. 2 The Pearson's correlation analysis showing moderate but significant association between early SUVmean (**a**), late SUVmean (**b**) and K1. No significant association was observed between retention index and K1 (**c**)

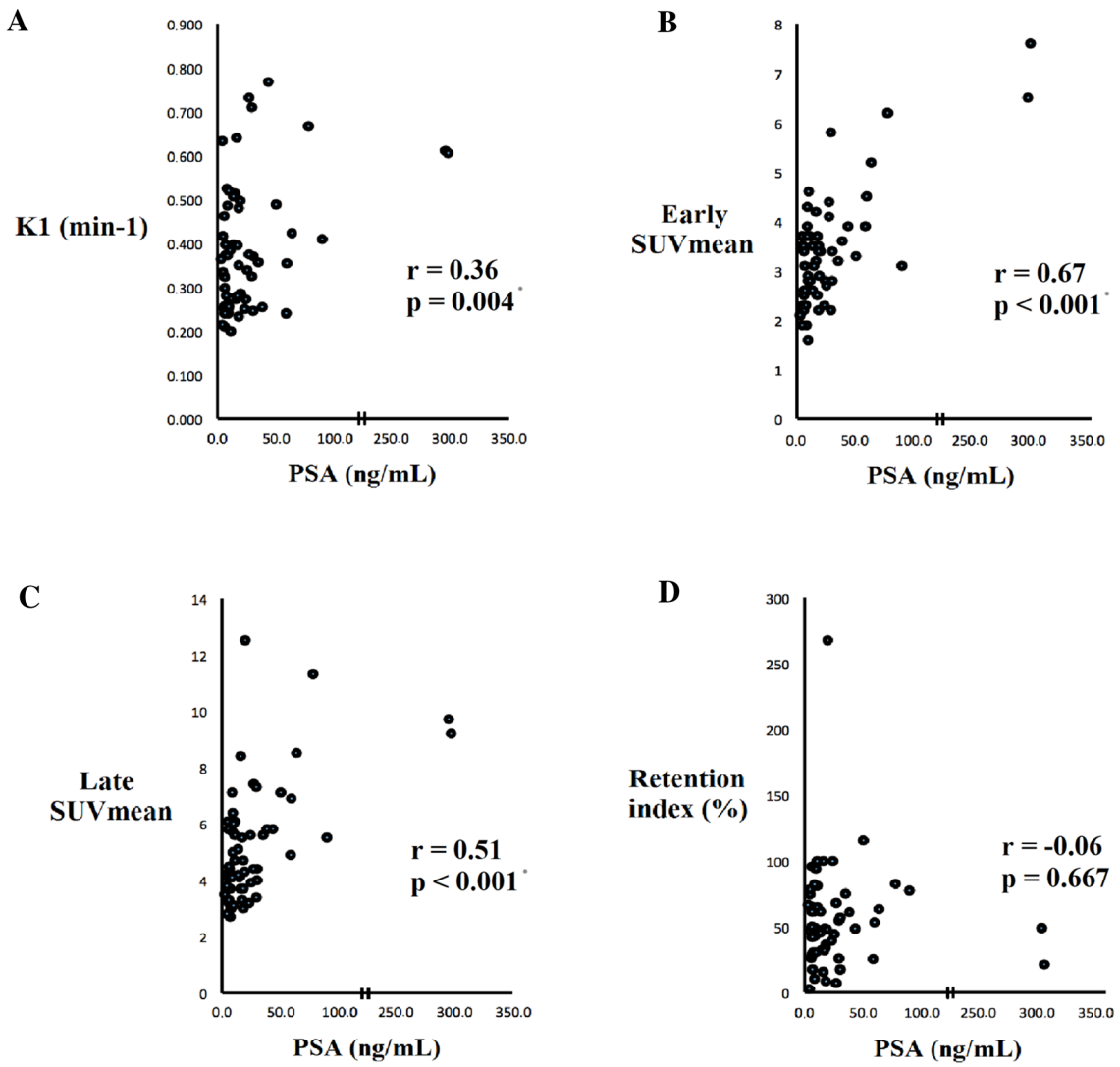

Fig. 3 Pearson's correlation analysis showing moderate but significant association between K1 (**a**), early SUVmean (**b**) and late SUVmean (**c**) and PSA level. No significant association was observed between retention index and PSA level (**d**)

Table 1 Comparison of FCH PET/CT parameters and Gleason scoring

	All of Gleason score			Gleason score = 7		
	≥4 + 3	<4 + 3	*p*	4 + 3	3 + 4	*p*
K1 (min^{-1})	0.409	0.272	< 0.001*	0.438	0.281	0.027*
Early SUV mean	3.4	2.8	0.120	3.3	3.5	0.812
Late SUVmean	5.5	4.4	0.06	5.0	4.7	0.242
Retention index (%)	62	44	0.131	49	39	0.421

Statistical analysis was performed with the Mann–Whitney *U* test

* *p* value < 0.05 = statistically significant

model). Furthermore, only 10 and 12 participants, respectively, were included.

Concerning static parameters and GS, results remain also controversial. In contrast to the results of our study, Schaefferkoetter et al. showed that 60-min SUV were higher for GS of 4 + 3 than GS of 3 + 4 or 3 + 5 [24]. However, studies with a larger group of patients showed consistent results with our study. Indeed, Beheshti et al., De Perrot et al., and Choi et al. found no significant correlation between static parameters and Gleason scores [17,

27, 28]. The lack of significance could be explained by a reduced number of participants.

In the current study, we observed a significant but moderate correlation between K1 and early SUVmean. This result is consistent with the results from the study of Verwer et al. who recently reported showing poor correlation between K1 and SUV ($r=0.30$) [26]. Furthermore, Takesh et al. showed also a poor correlation between K1 and SUVmean ($r=0.28$) [20]. In the same way, Choi et al. did not show any significant correlation between K1 with other PET imaging parameters [17]. This poor correlation between kinetic and static parameters could explain the difference of correlation with GS for these two kinds of PET parameters. These results confirm that kinetic parameters may provide different metabolic information from static parameters.

Concerning PSA level at the time of FCH PET/CT examination, results showed that K1, early SUVmean and late SUVmean are correlated with PSA level. Many studies already showed correlations between static parameters and PSA level concerning FCH PET/CT for patients with recurrence of PC [17, 29–31]. That could explain why FCH PET/CT studies showed a low sensitivity to detect lesions in patients referred for recurrent PC with PSA level < 1 ng/mL [29, 32].

Then, it is relevant to notice in our study that prostatic tumors showed a median retention index as 50%. These results are consistent with dual-phase FCH PET/CT studies [27, 33], showing higher retention for cancers than for benign lesions. However, our results indicate that K1 values were not significantly correlated with retention index. These results confirm that retention index and K1 represent two different molecular interactions. Indeed, Takesh et al. supposed that FCH uptake at later time points is linked to choline kinase activity whereas K1 is linked to perfusion [20]. In the current study, perfusion through K1 is correlated with GS, whereas choline kinase activity through the retention index is not. Further studies are needed to investigate the eventual correlation of K1 with angiogenesis and, under this suggestion, to assess if K1 could be a tool to predict the tumor aggression.

The current study presents limitations. First, an imaging-derived arterial input function was used for the kinetic modeling instead of a conventional plasma-derived input function. In traditional kinetic modeling, a plasma-derived input function is usually obtained from arterial sampling with a metabolite correction, which is relatively invasive and complex to perform in a routine clinical setting. However, Verwer et al. recently reported that the use of an imaging-derived plasma input function was feasible for a kinetic analysis [26]. Second, an easy homogenous time sampling (20 frames of 30 s) for dynamic PET data was preferred to be adapted for clinical assessment. This time sampling is not optimized for the imaging-derived plasma input function, but kinetic parameters were compared in patients who performed the same FCH PET/CT protocol.

Conclusions

The results of this study showed that FCH influx index K1 seems to be related to GS. Further analyses are required to confirm that K1 could distinguish well-differentiated from least-differentiated and could be a non-invasive tool to gain further information concerning tumor aggressiveness. FCH PET/CT is useful in detecting metastases in patients with biochemical recurrence, but it may play an important role also in initial tumor staging similar to and in conjunction with MRI-supported biopsy and potentially improve patient management with dose escalation for PC lesions with higher K1 using intensity-modulated radiotherapy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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