

¹¹C-Choline PET/CT and PSA kinetics

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SUMMARY

The potential role of PET/CT with radiolabeled Choline in patients with treated prostate cancer, has not been established yet and no precise indications exist about the use of this emerging modality. According to the literature, the most useful application of Choline PET/CT is represented by the restaging of the disease in case of biochemical relapse for the detection of local and/or, lymph-nodal and/or distant recurrence. Aim of this brief review is to summarize the results of the most relevant published studies with particular interest to a better understanding of the relationship between PSA, PSA kinetics and Choline PET/CT sensitivity and the potential use of PSA kinetics for an optimal selection of the patient population who may benefit the most from this diagnostic procedure especially early after the biochemical recurrence.

Key words: Prostatic Neoplasms; Prostate-Specific Antigen; Positron-Emission Tomography and Computed Tomography; Choline; Neoplasm Recurrence, Local; Diagnostic Imaging

INTRODUCTION

Prostate cancer (PC) is the second most common cause of cancer death in men over the age of 50 years old. Within the European Union, the incidence rate is 78.9 per 100,000 per year (1). This tumor shows variable biological behavior, from a clinically silent intra-prostatic tumor to an aggressive malignancy (2). In case of aggressive PC surgery or radiation therapy (brachytherapy; EBRT; IMRT) are the two more commonly used therapeutic procedures as primary treatment. During follow up patients are followed with a strict monitoring of PSA levels. In case of increased PSA levels the goal is to distinguish whether disease relapse is localized in the prostate gland or bed or whether metastatic disease is present (3). Several Conventional Imaging (CI) modalities are available: Trans Rectal Ultra Sound (TRUS) with or without biopsy, Magnetic Resonance (MR), Computerized Tomography (CT) and Bone Scintigraphy (BS). Each modality has a particular goal in the natural history of the disease. It is well known however that the above mentioned modalities, have very low sensitivity in the detection of the site of relapse after primary treatment (4-8).

In the last few years Positron Emission Tomography (PET) showed good results in oncology (9).

Different radio-pharmaceuticals have been used to image with PET/CT prostate cancer patients however promising results were obtained by Choline, labeled with ¹¹C or ¹⁸F, a substrate for the synthesis of phosphatidyl-Choline, which is the major phospholipids in the cell membrane (10). Choline PET/CT imaging has been proposed to detect primary prostate cancer, to stage the disease and to detect tumour recurrence in case of biochemical relapse (11). This last application is by far the most useful in the clinical setting (Figure 1 and 2).

Aim of this short review is to summarize the results of the most relevant published studies with particular interest to a better understanding of the relationship between PSA, PSA kinetics and Choline PET/CT sensitivity and the potential use of PSA kinetics for an optimal selection of the patient population who may benefit the most from this diagnostic procedure especially early after the biochemical recurrence.

PSA and PSA kinetics

As remembered above, monitoring PSA serum level is the best way to follow PC patients after treatment and to detect recurrence of the disease. In case of biochemical relapse (PSA > 0.2 ng/mL), it is crucial to distinguish between, the presence of a single versus the presence of multiple lesions and to correctly detect the site or sites of relapse in order to establish a correct therapy. However, in this scenario, CI have a limited role due to their known lack of accuracy (4-8). This condition ends up in an enormous number of negative (false negative) investigations performed in this setting of patients. In a large retrospective study (292 patients) Choueiri et al (5) tried to identify parameters that were predictive of positive findings at imaging. Authors found that age, PSA and PSA_{dt} were significantly associated with imaging results. They concluded that CT, MR and BS are unlikely to be useful when PSA is lower than 5 ng/mL and PSA_{dt} is slower than 10 months. Summarizing the results of this study, what is discouraging is the very low overall sensitivity showed by CI that was only 11% (31/292). It is to underline that the 31 positive patients at imaging, showed a mean PSA value of 23ng/mL, while the remaining 261 negative patients a mean PSA of 6 ng/mL. It is questionable which impact on the clinical and therapeutic flow chart should have such late detection of the sites of relapse.

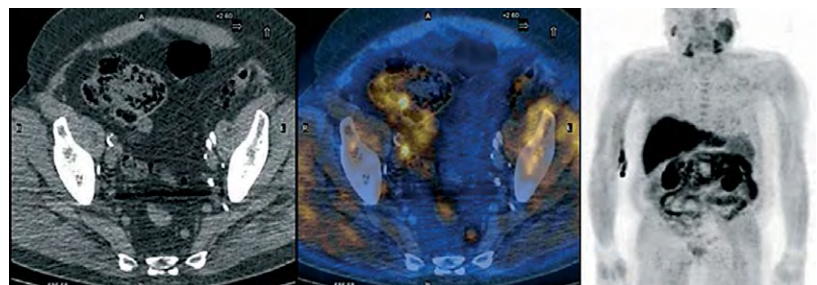


Figure 1. Seventy-five y.o. patient. Two years after radical prostatectomy, PSA rapidly increased, up to 1.4 ng/mL (PSA_{dt} 6 months). ¹¹C-Choline PET/CT, performed 5 minutes after the administration of 380MBq of ¹¹C-Choline, showed a positive lymph node in the left internal iliac chain

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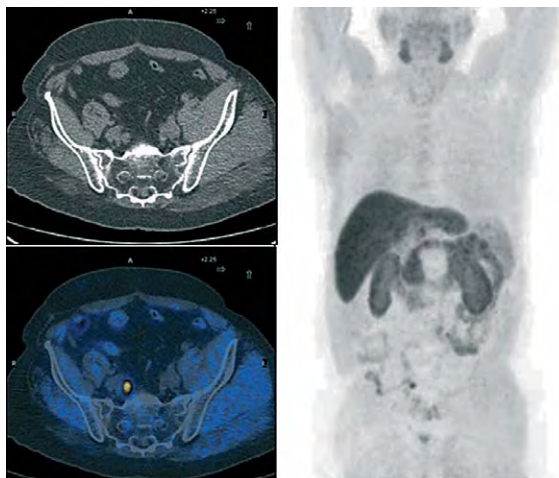


Figure 2. Sixty-four y.o. patient. One year after radical prostatectomy, PSA increased up to 1.0 ng/mL (PSAdt 4 months). ^{11}C -Choline PET/CT, performed 5 minutes after the administration of 345MBq of ^{11}C -Choline, showed a positive lymph node in the right common iliac chain

The study of tissue metabolism using PET/CT could play an important role in this context. Many studies have focused their attention to the possible correlation between the detection rate of ^{11}C -Choline PET/CT and the serum PSA level. Krause et al (12) evaluated with ^{11}C -Choline PET/CT sixty-three PC patients with biochemical relapse (PSA mean 5,9 ng/mL) after primary treatment. Authors demonstrated a significant and strict correlation between PET/CT detection rate and PSA serum level: the detection rate was 36% for a PSA value <1 ng/mL, 43% for a PSA value 1-<2 ng/mL, 62% for a PSA value 2-<3 ng/mL and 73% for a PSA value ≥ 3 ng/mL. The overall detection rate for PET/CT was 59%. The strict relationship between PSA values and positive ^{11}C -Choline PET/CT findings was confirmed by Giovacchini et al (13) in a large population of 358 PC patients (mean PSA 3.7ng/mL) studied after RP or RT.

Castellucci et al (14) investigated the relationship between the detection rate PET/CT and other PSA derivatives in particular PSA kinetics (PSA velocity and PSA doubling time). Authors enrolled 190 patients who showed an increase in PSA (mean 4.2 ng/mL). Authors demonstrated that PSAdt and PSAvel values were statistically different between patients with PET/CT-positive and PET/CT-negative findings. PET/CT detection rate was 20%, 40%, 48%, and 60%, respectively, in patients with PSAdt >6 mo (45 patients), 4 < PSAdt ≤ 6 mo (20 pts), 2 < PSAdt ≤ 4 mo (31 pts) and PSAdt ≤ 2 mo (10 pts). Authors concluded that PSA kinetics should always be taken into consideration before performing a PET/CT in patients with biochemical failure because it is the most relevant factor for a PET/CT positive result. Giovacchini et al (15) confirmed these data. They evaluated the influence of PSAdt on the PET/CT detection rate in 170 patients after RP who showed a biochemical failure (mean PSA 3.2 ng/mL, median PSAdt 7.0 mo). The study showed an overall detection rate of 44% and an overall accuracy of ^{11}C -Choline PET/CT of 88%. Multivariate logistic regression found that high PSA and fast PSAdt were the only significant predictors of positive PET/CT scan. Moreover their results demonstrated that PSAdt can distinguish patients with pathological ^{11}C -Choline uptake in the skeleton from patients with pathological ^{11}C -Choline uptake in the prostatic fossa.

To better understand the relationship between PSA, PSA kinetics and PET detection rate Castellucci et al (16) evaluated 102 consecutive patients previously treated by RP who presented a only a mild increase of PSA serum levels < 1.5 ng/mL (mean 0.86 +/- 0.40 ng/mL). Overall, ^{11}C -Choline PET/CT showed positive findings in 29/102 patients (28% of cases). Main finding of this study is that only PSAdt and initial N status were found to be significant and independent predictive factors at multivariate analysis. Mean PSAdt in PET/CT-positive patients was 4.34 months (SD 2.82) while in PET/CT-negative patients it was 13.30 months (SD 9.75) ($p = 0.0001$). The optimal threshold for PSAdt established by ROC analysis was 7.2 months (AUC 0.85; 95% CI 0.77-0.91) providing 93% sensitivity, 74% specificity, 60% PPV, and 96% NPV. Using this cut off value for PSAdt of 7.25 months, there were only 2/56 (only 3%) positive ^{11}C -Choline PET/CT in patients with a PSAdt slower than the cut off while 27/46 (58%) positive ^{11}C -Choline PET/CT in patients with a faster PSAdt value ($p < 0.001$).

DISCUSSION

According to the data mentioned above, the routine application of CI methods in case of early biochemical recurrence it is questionable. In fact, despite their low cost and wide availability, in most cases they do not provide useful information to clinicians. According to recently published guidelines from the European Association of Urology (17) the use of any diagnostic procedure in case of biochemical relapse should not be recommended if PSA levels are lower than 20ng/mL. We kindly disagree with this approach since the results showed so far by Choline PET/CT are encouraging. It is true, however that larger studies are needed to better understand the impact of such method on patients management. The good results showed by PET/CT with choline are probably in accordance with the uptake mechanism of Choline (10), that is linked to the metabolic activity of the cell. The advent of this hybrid molecular imaging technique in the field of prostate cancer seems to open a new approach to the use of imaging in case of biochemical recurrence, making it available and suitable even in patients with very early biochemical relapse. Moreover, considering the very poor results of CI in this setting of patients, it could be possible to suggest the performance of PET/CT with Choline as first diagnostic procedure in case of biochemical recurrence especially in case of low PSA and fast PSA kinetics.

Finally Choline PET/CT could be used to guide targeted therapies such as image guided IMRT or image guided lymph node dissection as suggested by different published studies (18–21). Such new approaches could be particularly useful in young, oligometastatic patients (one or two lesions) with a long life expectancy were an image guided targeted treatment, could delay the administration of systemic Hormonal Therapy or chemo therapy in order to reduce toxicity, increase life quality and delay resistance to the hormonal treatments.

CONCLUSION

PET/CT with ^{11}C Choline has proven a significantly higher detection rate of lymph-nodal or distant metastasis as compared to other imaging modalities, in particular in case of low PSA values. In our opinion PET/CT with ^{11}C Choline could be suggested as a first diagnostic procedure in patients with biochemical relapse showing fast PSA kinetics. In such patients PET/CT with ^{11}C Choline could be used to guide personalized targeted therapies

with the main aim to delay the administration of Hormonal Treatment or Chemotherapy.

Conflict of interest

We declare no conflicts of interest.

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