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SHORT COMMUNICATION

Androgen deprivation therapy influences the uptake of ^{11}C-choline in patients with recurrent prostate cancer: the preliminary results of a sequential PET/CT study

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Abstract
Purpose The influence of androgen deprivation therapy (ADT) on ^{11}C-choline uptake in patients with prostate cancer (PC) has not yet been clarified. The aim of our study was to investigate this issue by means of sequential ^{11}C-choline positron emission tomography (PET)/CT in patients with recurrent PC.

Methods We retrospectively studied 14 recurrent PC patients (mean age 67 years, range 55–82) during follow-up after radical prostatectomy (RP) with rising serum prostate-specific antigen (PSA) levels. All patients had undergone at least two consecutive ^{11}C-choline PET/CT scans: the first ^{11}C-choline PET/CT before commencing ADT and the second ^{11}C-choline PET/CT after 6 months of ADT administration.
Results The mean serum PSA level before ADT was 17.0± 44.1 ng/ml. After 6 months of ADT administration the PSA value significantly decreased in comparison to baseline (PSA= 2.4±3.1 ng/ml, $p<.025$). Moreover, before starting ADT, 13 of 14 patients had positive ^{11}C-choline PET/CT for metastatic spread, while after 6 months of ADT administration in 9 of 14 patients ^{11}C-choline PET/CT became negative.
Conclusion These preliminary results suggest that ADT significantly reduces ^{11}C-choline uptake in androgen-sensitive PC patients.

Keywords Sequential choline PET/CT · Prostate cancer · Recurrent disease · Androgen deprivation therapy

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Introduction

^{11}C-Choline positron emission tomography (PET)/CT is an emerging highly sensitive technique for restaging patients with suspected recurrent prostate cancer (PC) after primary treatment: in patients who had undergone radical treatment for clinically localized PC, an increasing serum prostate-specific antigen (PSA) level typically anticipates the development of evident metastasis by some years in almost 30–40% of cases [1]. In this setting ^{11}C-choline PET/CT has gained an important role because it proved to be more sensitive than conventional imaging (CI) such as transrectal

ultrasound (TRUS), endorectal MR, abdominal-pelvic contrast-enhanced CT/MR and bone scan [2–11]. Radiotherapy with curative intent is limited to patients with local relapse only, while in cases of systemic spread androgen deprivation therapy (ADT) is given: luteinizing hormone-releasing hormone (LH-RH) analogs or bicalutamide 150 mg/day. Intermittent ADT has been proposed as a potential alternative to continuous therapy, in order to delay the time to hormone-refractory disease, to minimize the side effects and to reduce the costs of prolonged therapy, respectively [12, 13].

An unresolved matter in the literature is the potential influence of ADT in patients who undergo ^{11}C-choline PET/CT. Giovacchini et al. [14] evaluated six PC patients before and after ADT (bicalutamide 150 mg/day; median treatment of 4 months) and reported a significant influence of ADT on ^{11}C-choline PET/CT uptake in patients with PC at presentation; a significant ($p<.05$) negative correlation was detected between maximum standardized uptake value (SUV_{max}) and ADT both at univariate ($r^2=0.24$) and multivariate ($r^2=0.48$) analyses. However, there are no recommendations in the literature about the question of whether ADT should be discontinued before ^{11}C-choline PET/CT. The aim of our study was to investigate this issue.

Materials and methods

Patients

Between September 2003 and September 2010, 1,451 patients were submitted to ^{11}C-choline PET/CT for PC staging before primary treatment ($n=163$) or restaging because of biochemical PSA relapse after primary therapy ($n=1,288$) in our centres. We identified 14 patients who fulfilled the following criteria: (a) patient submitted to at least two ^{11}C-choline PET/CT scans within 12 months in the setting of tumour restaging; (b) the first ^{11}C-choline PET/CT before commencing ADT and the second ^{11}C-choline PET/CT after 6 months of ADT administration to assess the effectiveness of therapy; (c) confirmation of ^{11}C-choline PET/CT results by biopsy and/or subsequent clinical and imaging follow-up; and (d) availability of complete clinical and pathological data for each patient.

Radiopharmaceuticals

^{11}C-Choline was synthesized according to the solid-phase method as described by Pascali et al. [15] using a commercial synthesis module (TRACERlab, GE Healthcare). $^{11}CO_2$ produced by a PETtrace cyclotron (GE Healthcare) was converted into $^{11}CH_3I$ by the conventional $LiAlH_4$/HI reaction. $^{11}CH_3I$ was used for the *N*-methylation of dimethylaminoethanol (60 μl) placed directly on a solid-phase support (C18 Sep-Pak Light, Waters). After a washing step with ethanol and water, ^{11}C-choline retained on a cation exchange resin (Sep-Pak Accell Plus CM, Waters) was eluted with saline, sterilized by a 0.22-μm filter and collected in a final volume of 8 ml.

Radiochemical purity was evaluated by means of a high-performance liquid chromatography radio-detector equipped with a reversed-phase column, and the concentration of organic solvents was measured by gas chromatography. Endotoxin content was measured by the conventional lysosomal acid lipase method (Cambrex Bioscience).

Imaging protocol

All ^{11}C-choline PET/CT scans were accomplished using a dedicated hybrid PET/CT (Discovery STE or Discovery LS, GE Medical Systems, Waukesha, WI, USA). CT attenuation correction acquisition parameters were: 140 kV, 90 mA, 0.8 s tube rotation and 5 mm thickness. The patients fasted at least 6 h before the PET acquisition and received an intravenous injection of 370–555 MBq of ^{11}C-choline. Starting 5 min after injection according to the ^{11}C-choline kinetics results reported by previous papers [16, 17], emission data were acquired at 5–6 bed positions from the base of the skull through the mid-thigh for 5 min at each position; in order to minimize the possible presence of tracer in the urinary pathways, patients were asked to void immediately before being scanned, and the scan started from the pelvis. CT images were used for both attenuation correction of emission data and image fusion.

Image analysis

All ^{11}C-choline PET/CT images were analysed with dedicated software (eNTEGRA, GE Medical Systems, Waukesha, WI, USA) that allowed review of PET, CT and fused image data. PET images were first assessed visually using transaxial, sagittal and coronal views and interpreted by consensus by two experienced nuclear medicine physicians aware of clinical data. At visual inspection any focal uptake of ^{11}C-choline higher than surrounding background was considered suspicious for malignancy. The SUV_{max} was measured and taken into account but no absolute cutoff value was used for the diagnosis.

PET/CT findings were considered as positive if they were confirmed by any one of the following: (a) presence of malignant PC cells at biopsy for local relapse; (b) confirmation of the same lesion by any imaging procedure performed within 6 months including bone scan, TRUS, abdominal-pelvic contrast-enhanced CT/MR; (c) any ^{11}C-choline-positive lesion which disappeared in a follow-up

PET/CT after prolonged ADT administration; and (d) increase of the number and extension of ^{11}C-choline-positive lesions in the follow-up PET/CT.

Statistical analysis

Data were expressed as mean, median and standard deviation (SD). Serum PSA levels measured before and after ADT therapy were compared by the Wilcoxon signed rank test. A p value<.05 was considered statistically significant.

Results

Table 1 shows the characteristics of the patient population: all patients underwent the first ^{11}C-choline PET/CT prior to starting ADT; the mean PSA was 17.0±44.1 ng/ml (median 5.5, range0.25–170). After at least 6 months of ADT, the PSA value significantly decreased compared to baseline (mean PSA=2.4±3.1 ng/ml, median0.55, range0.01–8.4) (p=.025). Of note, before starting ADT in 13 of 14 patients ^{11}C-choline PET/CT showed metastatic spread. Instead, after at least 6 months of ADT, nine patients presented a negative ^{11}C-choline PET/CT and PSA values significantly decreased (Table 1). On the other hand, three patients showed a rising PSA value during ADT and ^{11}C-choline PET/CT demonstrated a progression of disease. One patient showed both a stable PSA value and PET/CT result. Finally, only one patient did not demonstrate a good correlation between PSA value and PET result (patient 9) in whom a decrease in PSA value and a progression of the disease was observed. However, in this case both PSA values, before and after ADT, were high (9.1 and 7.6 ng/ml, respectively; time interval between the two assays=year). These data indicate the presence of a relationship between PSA values and ^{11}C-choline PET/CT results in ADT responders. An example is shown in Fig. 1.

Discussion

In the last few years PET/CT with ^{11}C-choline has emerged as a useful method for the detection of PC [18–22]. However, the background of the increased uptake of choline in human PC is not completely understood. Two hypotheses have been suggested: the first one is based on an increased cell proliferation in tumours; the second one is based on an upregulation of choline kinase [23]. Nowadays there is conflicting evidence whether or not ^{11}C-choline

Table 1 Characteristics of the patient population

ID-age	Primary Tx	TNM	GS	PSA before ADT (ng/ml)	PET before ADT	Type of ADT	PSA during ADT (ng/ml)	PET/CT during ADT	Interval between PET/CT exams (months)
1-70	RP	pT3b N1	4+3	2	Three BM (left iliac bone, D8, D10)	LH-RH agonist	0.5	Neg.	11
2-74	RT	cT2 Nx	4+3	1.3	Presacral LN	LH-RH agonist	0.1	Neg.	8
3-68	RP	pT2 N0	3+4	2.16	Two BM (sternum and left ribs)	LH-RH agonist	4.6	PD	7
4-58	RP	pT3a N0	3+4	5.32	Prostatic fossa and left pelvic LN	LH-RH agonist	8.4	PD	12
5-69	RP	pT3a Nx	3+4	5.77	Left pelvic LN and right ribs	Bicalutamide 150 mg	1.35	Neg.	8
6-70	RP	pT3b N1	5+4	5.0	Prostatic fossa and right pelvic LN	LH-RH agonist	0.32	Neg.	5
7-65	RP	pT3b N0	4+3	7.6	Left LN and one BM (D12)	Bicalutamide 150 mg	0.04	Neg.	8
8-66	RP	pT2c N0	4+4	8.9	Prostatic fossa	LH-RH agonist	2.5	Neg.	11
9-70	RP	pT2c Nx	4+5	9.1	Negative	LH-RH agonist	7.61	PD	12
10-62	RP	pT3a Nx	5+4	0.25	Prostatic fossa	LH-RH agonist	0.38	SD	12
11-82	RT	cT3 Nx	4+4	170	Three BMs (D8, D10 and right rib) and two left pelvic LNs	LH-RH agonist	0.01	Neg.	6
12-65	RP	pT3a N0	3+3	2.4	One BM (ischium)	LH-RH agonist	0.6	Neg.	12
13-71	RP	pT3a N0	4+3	12.1	Multiple LNs	LH-RH agonist	0.01	Neg.	4
14-70	RT	cT2 Nx	5+4	6.9	One retroperitoneal and one iliac LN and one BM (S1)	LH-RH agonist	7.2	PD	9

Tx treatment, *GS* Gleason score, *RP* radical prostatectomy, *LN* lymph node, *RT* radiotherapy, *ADT* androgen deprivation therapy, *BM* bone metastasis, *PD* progressive disease, *SD* stable disease

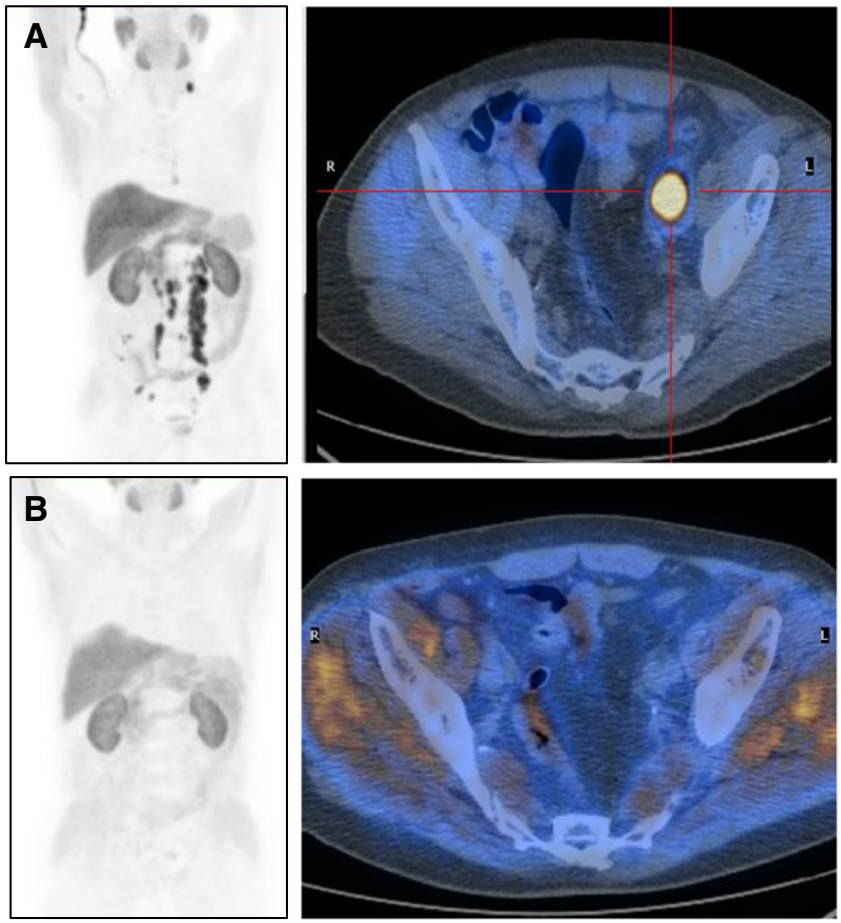

Fig. 1 Patient 13 (see Table 1 indicating patient characteristics). **a** Maximum intensity projection (MIP) image (*left*) and fused PET/CT image (*right*) of ^{11}C-choline PET/CT scan performed after discontinuation of ADT (PSA 12.1 ng/ml). Increased ^{11}C-choline uptake in multiple lymph nodes is observed in the MIP image: a large and hot lymph node (SUV_{max}=8) is evident in the left iliac chain. **b** MIP image (*left*) and fused PET/CT image (*right*) of ^{11}C-choline PET/CT scan performed 6 months after ADT administration. A complete response is evident. PSA dropped down to 0.01 ng/ml

uptake is correlated with proliferation. A study by Breeuwsma et al. [24] published in 2005 about 18 PC patients who underwent radical prostatectomy (RP) showed that ^{11}C-choline does not correlate with cell proliferation (Ki-67 labelling) in vivo. On the other hand, in the same year, another in vitro study by Al-Saeedi et al. [25] affirmed that choline incorporation into PC tumour cells is correlated with proliferation. In addition, the authors suggested the hypothesis that choline uptake could change before and after therapy and consequently it may be indicative of tumour response to therapy. Again, in another study by the same authors [26], it was found that the increased choline content and choline kinase activity in the growing cells is related to cell proliferation that may be involved in membrane synthesis and signalling.

Another unresolved matter in the literature is the potential influence of ADT such as LH-RH analogues or bicalutamide in patients who undergo ^{11}C-choline PET/CT. In two recent studies [21, 22], the administration of ADT proved to be a statistically significant parameter in predicting a positive ^{11}C-choline PET/CT scan at univariate analysis but it was not proven to be an independent predictive factor at multivariate analysis. The authors concluded that ADT did not seem to modify the results of ^{11}C-choline PET/CT exam on a patient basis. However, it should be noted that in the two studies cited above, the number of metastases and their intensity of ^{11}C-choline uptake were not specifically compared in the single patient both before and after ATD administration. Moreover, in a recent study by Giovacchini et al. [14], the authors reported a significant influence of ADT on ^{11}C-choline PET/CT uptake in patients with PC at initial staging and they also discussed the possible mechanisms involved. ATD seems able to induce atrophy of glandular cells, both normal and malignant cells. A time-dependent loss of the prostatic metabolites was observed during ATD and it can be associated with downregulation of the expression of several genes, also genes involved in lipid metabolism. And, finally, ADT could influence the cell cycle inducing an arrest, but this possibility is still uncertain.

These preliminary results suggest that ADT significantly reduces ^{11}C-choline uptake in androgen-sensitive PC patients. Based on these results, it may be suggested that the withdrawal of ADT before the execution of ^{11}C-choline PET/CT could increase the detection rate and the intensity of ^{11}C-choline uptake in metastatic lesions, therefore increasing the sensitivity of the ^{11}C-choline PET/CT scan. Our study could also add a step in the controversial

scenario about the correlation of choline uptake with cell proliferation suggesting a possible relationship between a significant reduction in proliferation as a consequence of therapy response detected by ^{11}C-choline PET/CT

In the present study, for the first time, to the best of our knowledge, the effect of ADT on ^{11}C-choline PET/CT uptake in distant metastases was evaluated in the same patient both before and after ADT administration. It clearly emerged that ADT is able to significantly modify the uptake of ^{11}C-choline in the same lesions after ADT administration. It is worth noting that the major effect of ADT on ^{11}C-choline PET/CT was recorded in patients with non-hormone-resistant PC, similarly to the effect of ADT on PSA. Finally, we want to underline that the main limitation of our study is the limited patient population: our preliminary data need to be confirmed in a larger series of patients.

Conflicts of interest None.

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