

# Somatostatin receptors over-expression in castration resistant prostate cancer detected by PET/CT: preliminary report of in six patients

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**Abstract:** Prostate cancer (PC) is usually characterized by an excellent prognosis, largely due to little biological aggressiveness and the power of hormonal deprivation therapy. In spite of these favorable characteristics, however, a significant quota of patients does not respond to androgen deprivation therapy (ADT) and develop a progressive disease. Castration-resistant prostate cancer (CRPC) is defined by disease progression in spite of ADT. This progression may show any combination of a rise in serum prostate-specific antigen (PSA), clinical and radiological progression of pre-existing disease, and appearance of new metastases. This event is a striking change in the clinical scenario, since the power of treatment for CRPC patients with distant metastases is very limited. Somatostatin is a hormone produced by neuroendocrine cells. Its distant effects are mediated by the binding to five specific receptors, which are the most striking parameter for neuroendocrine. Various synthetic somatostatin agonists able to bind to the receptors have been synthesized during the past two decades for diagnostic and therapeutic purposes. Octreotide, the most popular of these, is widely used to treat patients affected by neuroendocrine tumors. A number of researches carried out in the past evaluated the possible neuroendocrine differentiation (NED) of PC cells in the castration resistant phase. If proved, the presence of a specific class of receptor on cell's surfaces should give a potentially biological target to be used for therapy. However, these studies led to contradictory results. Aim of our phase III diagnostic trial was to study "*in vivo*" the over-expression of somatostatin receptors (SSTRs) in CRPC patients by PET/CT after the administration of the somatostatin analog [<sup>68</sup>Ga-DOTANOC,1-Nal(3)]-octreotide labeled with <sup>68</sup>Ga. Every area of increased uptake corresponding to a metastasis detected with other methods was considered as SSTRs expressing. False positivity to SSTRs expression was considered those localizations with a suspicious uptake not confirmed by other radiologic procedures. On the other hand, metastatic lesions lacking the radiopharmaceutical's uptake were considered not SSTRs expressing metastases. The preliminary results in 6 of the 67 patients scheduled by our phase III trial showed metastases with a variable SSTRs expression in 2 patients.

**Keywords:** Castration resistant prostate cancer (CRPC); neuroendocrine differentiation (NED); somatostatin receptors (SSTRs); <sup>68</sup>Ga-DOTANOC; PET/CT

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## Introduction

The meaning of neuroendocrine differentiation (NED) and somatostatin receptors (SSTRs) expression in castration resistant prostate cancer (CRPC) (1,2) has still not an established meaning (3-5). On the other hand, the possible presence of SSTRs on CRPC cell surface should provide a good therapeutic chance in patients with few treatment options to the oncologist. Serum chromogranin A (CgA) test has been the main surrogate parameter to define the SSTRs positivity. However, serum CgA raise in serum suffers of a low specificity (6-8), and moreover, it is not synonymous of SSTR expression (9). In summary, the raise of CgA does not guarantee the SSTR expression. Thus, a reliable and easy to use method to study *in vivo* SSTR presence should help significantly.

<sup>68</sup>Ga-DOTANOC is a radiopharmaceutical analog for SSTR2, SSTR3 and SSTR5, usually employed to image the neuroendocrine carcinomas (NET) with PET/CT. Aim of our phase IIIA trial to the study of CRPC is to detect their SSTRs overexpression by <sup>68</sup>Ga-DOTANOC PET/CT. Here we present the preliminary results of the first six patients recruited.

## Material and methods

Six patients with CRPC were enrolled in this phase III trial (EUDRA CT number 2010-021026-35) granted by Regione Lombardia. The local Ethical Committee approved the trial design. All the patients gave their written informed consent before the enrollment in the study.

CRPC was defined a rise in serum prostate-specific antigen (PSA) and/or progression of pre-existing disease and/or appearance of new metastases despite androgen deprivation therapy (ADT). Basically, our recruitment criteria encompassed: (I) asymptomatic non-metastatic

CRPC; (II) asymptomatic metastatic CRPC with prior treatments; (III) symptomatic, metastatic CRPC with prior treatments. For the first group of patients, the PSA was in unremitting raise for more than three consecutive evaluations during ADT. No measurable lesions, KPS >80%, life expectancy >3 months, good hematologic parameters and a wash-out time from the last chemotherapy of at least one month were requested. The main exclusion criterion was age (less than 18 and more than 85 years old).

One week after the patients were declared eligible for the trial, they were admitted to our hospital.

PET/CT was carried one hour after the i.v. administration of nearly 185 MBq of <sup>68</sup>Ga-DOTANOC, synthesized following the procedures reported in the literature (10). PET/CT scan was carried out with a Siemens Biograph 6 PET/CT scanner (Siemens Healthcare, Italia), and the acquisition parameters for the CT were: kV =130; effective mAs =70; maximum reconstructed width =5 mm without overlap; pitch 1.5 mm; standard reconstruction algorithm. PET was performed from the lower thighs, with 6 bed positions (3 min per bed) and reconstructed using standard algorithms provided by Siemens.

Following our trial's specifications, only one <sup>68</sup>Ga-DOTANOC PET/CT examination was carried out in these patients.

## Results

The main clinical characteristics of the six patients at diagnosis of PC are summarized in *Table 1*. The main clinical characteristics of the six patients at the onset of castration resistance are summarized in *Table 2*.

The five patients with bone metastases had diffuse multiple localization patterns at CT and bone scan. One of these had also an impressive lung involvement with

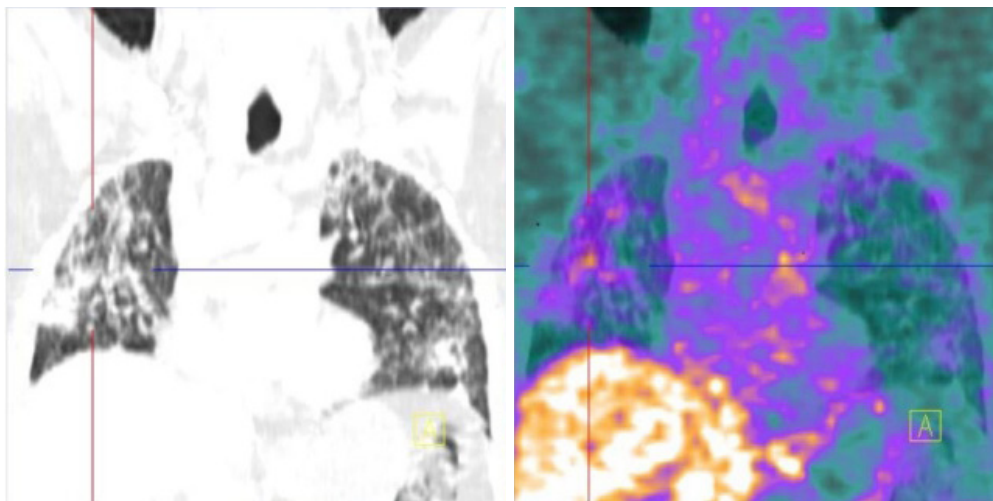
**Table 1** Main clinical characteristics of the patients enrolled in our study at diagnosis

Patients	Age	Gleason Score	PSA	M+	Surgery	EBRT	Adjuvant therapy
1	47	4+3	870	Bone	Yes	No	ADT, bisphosphonate
2	61	4+5	2.3	None	No	Yes	None
3	61	4+4	5.9	None	No	Yes	ADT, bisphosphonate
4	71	4+5	24	Bone	No	No	ADT, bisphosphonate
5	59	4+4	3.4	Bone	No	No	ADT, bisphosphonate
6	55	4+4	407	Bone	No	No	ADT, bisphosphonate

PSA, prostate-specific antigen; M+, synchronous metastases; EBRT, external-beam radiation therapy; ADT, androgen deprivation therapy.

Patients	Age	Recruitment criterion	PSA (ng/mL)	CgA (ng/mL)	<sup>68</sup> Ga-DOTANOC uptake
1	49	Multiple bone metastases	5	289	Bone
2	61	Multiple bone metastases	20	13	Negative
3	61	Raising PSA	21	NA	Negative
4	71	Multiple bone metastases	246	NA	Negative
5	59	Bone metastases + lung lymphangitis	4	1, 5	Bone, lung
6	55	Multiple bone metastases	5	2,400	Negative

PSA, prostate-specific antigen; CgA, chromogranin A.



**Figure 1** Coronal view of a <sup>68</sup>Ga-DOTANOC PET/CT scan of patient 5. Irregular shaped areas of mild increase uptake are clearly visible in both lungs corresponding to septal thickening due to lymphangitic spread of the disease (localizer).

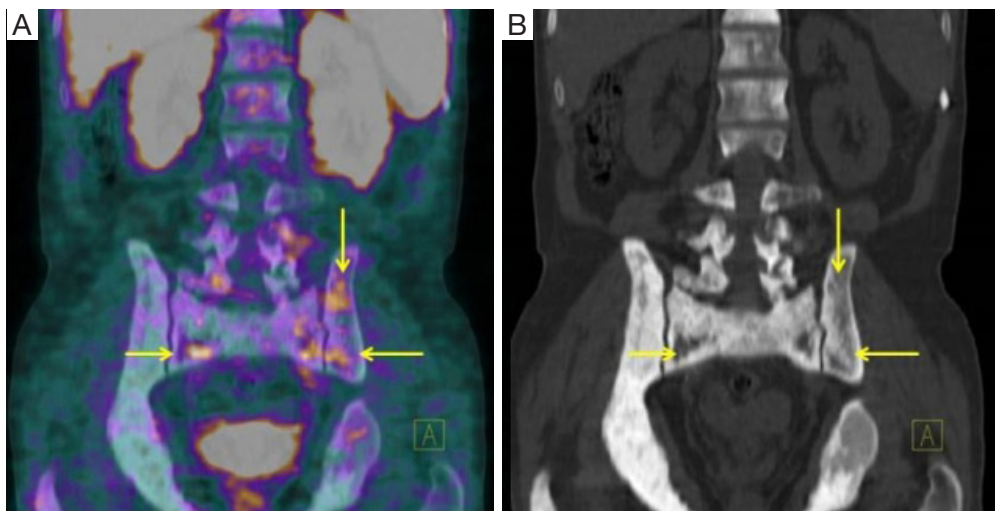
lymphangitic carcinomatosis at CT scan.

<sup>68</sup>Ga-DOTANOC PET/CT was positive in two patients. In patient 5 some areas of uptake were detected in both lungs in areas of irregular septal thickening, consistent with the lymphangitic spread (*Figure 1*) and in bone metastases previously evidenced by CT scan.

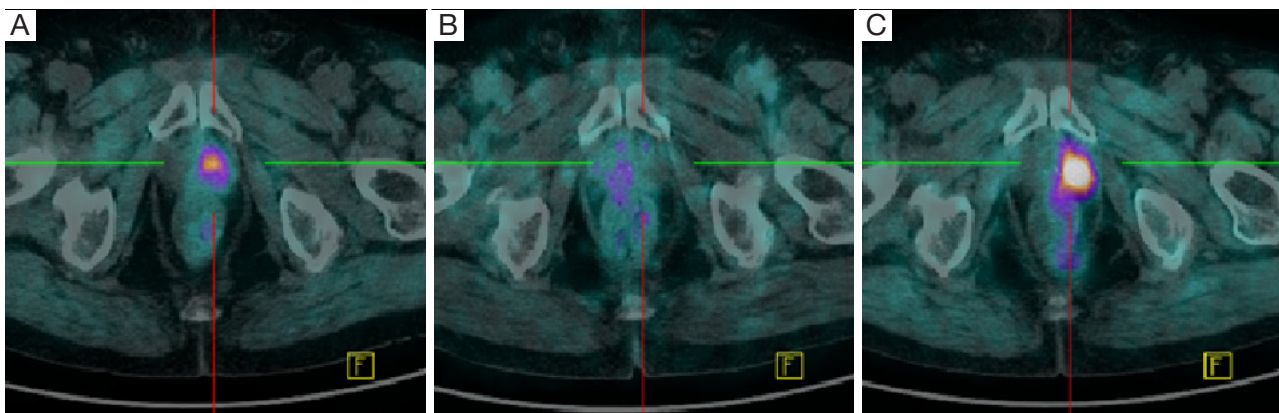
The second patient positive to <sup>68</sup>Ga-DOTANOC PET/CT (patient 1) had multiple bone metastases detected at the diagnosis carried out one year before. The examination showed multiple areas of radiopharmaceutical's uptake (*Figure 2*).

*Figure 3* shows the negative pattern of <sup>68</sup>Ga-DOTANOC uptake in patient 3, and compared it with the findings of <sup>18</sup>F-Choline PET/CT. This patient was the only patient without already known parenchymal metastases at the enrollment. His recent pathological anamnesis clued of a hormonal recurrence. <sup>18</sup>F-Choline PET/CT carried

out to restage him detected a focal uptake in the left side of the prostate (*Figure 3A*). However, this finding was not considered diagnostic due to the occasional and unpredictable uptake of the radiopharmaceutical in non prostatectomized patients. Thus, the nodule was not studied by biopsy and a wait and see strategy was decided. Two months later the patient was recruited due to the continuous raise of PSA in spite of ADT. <sup>68</sup>Ga-DOTANOC PET/CT did not disclose any uptake in the whole of body. More in detail, no specific uptake in the area corresponding to the previous <sup>18</sup>F-Choline PET/CT was detected (*Figure 3B*). One more time, a wait and see strategy was adopted. The <sup>18</sup>F-Choline PET/CT carried out four months later, confirmed and reinforced the finding of the first similar examination showing an increased uptake in the left side of the prostate gland (*Figure 3C*). This final evidence was considered suffices for the diagnosis, no biopsy was decided



**Figure 2** Coronal view of a  $^{68}\text{Ga}$ -DOTANOC PET/CT scan in patient 1. Areas of increase uptake (yellow arrows) are clearly visible on fused PET/CT (A) in the sacrum and left iliac wing, corresponding to skeletal spread with a prevalently lytic component on co-registered CT (B). The high uptake of the kidneys is illustrative of the SUV scale which needs to be stressed to highlight the low SSTRs expression of the metastases.



**Figure 3** Transaxial prostate view of a  $^{18}\text{F}$ -Choline (A, at diagnosis),  $^{68}\text{Ga}$ -DOTANOC (B), and  $^{18}\text{F}$ -Choline (C, at follow up) PET/CT (patient 3). The follow-up  $^{18}\text{F}$ -Choline PET/CT shows an increase of the uptake compared to the same examination carried out at diagnosis, confirming the site of relapse. No uptake is present in  $^{68}\text{Ga}$ -DOTANOC PET/CT.

and the patient started abiraterone acetate treatment. Therefore, in this case  $^{68}\text{Ga}$ -DOTANOC PET/CT did not disclosed SSTRs in the relapse.

## Discussion

The presence of SSTR in PC is still not completely understood. Some studies suggests that SSTR2 are overexpressed in CRPC (11,12) whereas others disagree with this finding (13-15). These contradictory results

perhaps reflect the pattern of receptor expression, which are probably different in the primary compared to the metastatic disease.

The main incentive to study and quantify SSTRs in CRPC is to evaluate the possibility to use them as a therapeutic target with somatostatin analogs. Therefore, we did not pursue a diagnostic objective i.e., we did not look for metastases. Indeed, their presence was one of the inclusion criteria of our trial. In this regard, the terms true positive or false positive lose their emphasis. Indeed, of the

pivotal point of our examination shifted from the detection of possible, but still not proved, metastases (typical of the “pure” diagnostic approach) towards the description of the receptorial panel of the widespread secondary. In conclusion, the question to answer with  $^{68}\text{Ga}$ -DOTANOC is: do these neoplasms overexpress SSTRs? And in how many of the metastases show significant SSTRs expression? Could this information be worth for therapeutic purposes?

Some researchers treated patients affected by CRPC on the base of serum CgA level taken as a surrogate marker of SSTRs expressions. However, serum CgA elevation is not a synonymous of this biological behavior (16-18). A possible comment is this approach, “blind” to the effective expression of the receptors, may partly explain the poor response to somatostatin analogs.

Nuclear Medicine procedures with gamma emitting radiopharmaceuticals have been occasionally employed in the past to detect SSTR overexpression in PC (19,20). In the last few years, newer PET/CT radiopharmaceuticals have been synthesized. These are  $^{68}\text{Ga}$ -DOTATOC,  $^{68}\text{Ga}$ -DOTANOC and  $^{68}\text{Ga}$ -DOTATATE, three almost similar compounds with only slight differences in chemical structure and receptor's affinity. In 2010, the first study to evidence SSTRs overexpression in CRPC with  $^{68}\text{Ga}$ -DOTATOC, revealed a weak uptake of the metastases. The researcher concluded suggesting the use of a radiopharmaceutical with different affinity for SSTRs (21).  $^{68}\text{Ga}$ -DOTANOC differs with  $^{68}\text{Ga}$ -DOTATOC in the amino acidic sequences. This change results in different receptors affinity, i.e.,  $^{68}\text{Ga}$ -DOTANOC binds to SSTR types 2, 3 and 5, whereas  $^{68}\text{Ga}$ -DOTATOC lacks of affinity for SSTR3. Thus, if some neoplasms overexpress SSTR3 in a significant quota, they may be imaged with  $^{68}\text{Ga}$ -DOTANOC but not by  $^{68}\text{Ga}$ -DOTATOC.

Our case series showed  $^{68}\text{Ga}$ -DOTANOC uptake in two patients with skeletal and in lung metastases. The possible criticism is that the real correspondence between SSTRs expression evidenced by  $^{68}\text{Ga}$ -DOTANOC and real presence of SSTRs on cell surface may be reached only with tissue samples. In our opinion, however, the clinical, radiologic and biochemical scenario of our patients give strong evidences about the metastatic nature of skeletal and pulmonary changes. Moreover, the proposal to biopsy a suspected skeletal metastasis in a plural-treated patient in sharp clinical, laboratory and radiological disease progression should be criticized from the ethical point of view. Indeed, a biopsy to test SSTRs expression could be justified only if it results in a

variation of the treatment, which is the aim of our study. The same criticism could hamper the definition of a control population. Our regulatory rules are intransigent in avoiding unnecessary radiation exposure in patients and healthy population. However, the experience of  $^{68}\text{Ga}$ -DOTANOC biodistribution in patients affected by in neuroendocrine tumors provided us useful information to define that skeletal and lung uptakes were abnormal. It goes without saying that the study of organs involved in  $^{68}\text{Ga}$ -DOTANOC clearance (liver, kidneys) or physiologic uptake (spleen) is not possible. On the other hand, these anatomic districts are not preferential sites of CRPC metastatization. Finally, it must be stressed that unlike  $^{18}\text{F}$ -FDG,  $^{68}\text{Ga}$ -DOTANOC is not a “metabolic” tracer. Thus, its uptake is far more dependent by SSTRs overexpression than by the blood flow.

Unfortunately,  $^{68}\text{Ga}$ -DOTANOC uptake in CRPC (SUV mean 1.57) is scant if compared to neuroendocrine tumors. Probably this finding comes from they are not naïve neuroendocrine neoplasms thus process to express receptors is not fully accomplished.

We are unable to assess the prognostic significance of SSTRs overexpression. Surely, the paucity of their number hampers the use of similar radiolabeled compounds for treatment, as it comes for neuroendocrine tumors. Indeed, this kind of treatment calls for a higher tumor to background ratio to balance renal and hematological toxicity. Nevertheless, the clinical relevance of SSTRs overexpression should not be unacknowledged, particularly in those patients in which a significant amount of receptor is detected. The hypothesis to add somatostatin analogs to the usual therapeutic schedules as a complement to other pharmaceuticals could be considered especially in light of its low toxicity. The hart of the cultural leap is to start thinking this examination like a bridge between the diagnosis and therapy. In this setting,  $^{68}\text{Ga}$ -DOTANOC PET/CT may play a pivotal role.

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