Critical Reviews in Oncology / Hematology 138 (2019) 29–37

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Neuroendocrine differentiation in castration resistant prostate cancer. Nuclear medicine radiopharmaceuticals and imaging techniques: A narrative review

Sharjeel Usmani[a], Marina Orevi[b], Antonella Stefanelli[c], Alberto Zaniboni[d], Ofer Nathan Gofrit[e], Claudio Bnà[f], Sonia Illuminati[f], Giulia Lojacono[c], Silvia Noventa[d], Giordano Savelli[c,*]

[a] Department of Nuclear Medicine, Kuwait Cancer Control Center Al Sabah Medical District, 70653, Kuwait
[b] Nuclear Medicine Division, Kiryat Hadassah, POB 12000, Jerusalem 91120, Israel
[c] Nuclear Medicine Division, Fondazione Poliambulanza Istituto Ospedaliero, via L. Bissolati, 57, 25124 Brescia, Italy
[d] Department of Medical Oncology, Fondazione Poliambulanza Istituto Ospedaliero, via L. Bissolati, 57, 25124 Brescia, Italy
[e] Urology Division, Kiryat Hadassah, POB 12000, Jerusalem 91120, Israel
[f] Radiology Division, Fondazione Poliambulanza Istituto Ospedaliero, via L. Bissolati, 57, 25124 Brescia, Italy

ARTICLE INFO

Keywords:
Castration-resistant prostate cancer
Androgen deprivation therapy
Neuroendocrine differentiation
Somatostatin receptors
Positron Emission Tomography
Somatostatin analogs

ABSTRACT

Background: Androgen Deprivation Therapy (ADT) is the primary treatment for patients suffering from relapsing or advanced prostate cancer (PC). Hormone therapy generally guarantees adequate clinical control of the disease for some years, even in those patients affected by widespread skeletal and soft tissue metastases. Despite ADT, however, most patients treated with hormones eventually progress to castration-resistant prostate cancer (CRPC), for which there are no effective treatments. This clinical reality is an open challenge to the oncologist because of those neoplasms which elaborate neuroendocrine differentiation (NED).

Methods: An online search of current and past literature on NED in CRPC was performed. Relevant articles dealing with the biological and pathological basis of NED, with nuclear medicine imaging in CRPC and somatostatin treatment in NED were analyzed.

Evidence from the literature: NED may arise in prostate cancer patients in the late stages of ADT. The onset of NED offers prognostic insight because it reflects a dramatic increase in the aggressive nature of the neoplasm. Several genetic, molecular, cytological and immunohistochemical markers are associated with this transformation. Among these, overexpression of somatostatin receptors, seen through Nuclear Medicine testing, is one of the most studied.

Conclusions: Preliminary studies show that the overexpression of somatostatin receptors related to NED in CRPC may easily be studied *in vivo* with PET/CT. This finding offers a potentially useful objective for targeted therapy in CRPC. If the overexpression of SSTRs is shown to afflict a significant segment of patients with CRPC, this will open further study of possible therapeutic options based on this marker.

1. Introduction

Prostate cancer (PC) is the second most frequently diagnosed cancer in men worldwide, with 1.1 million new cases estimated (2012). Prostate-specific antigen (PSA) screening improved the detection of early-stage cancer, which can be treated surgically. The full treatment plan for PC is based on the “three-legged stool” model. The first two legs are radical prostatectomy (most appropriate for patients with localized neoplasms), and adjuvant radiotherapy (if positive surgical margins or seminal vesicles involvement and Gleason Score greater than 8). The third leg is ADT, which is carried out reducing testosterone levels through surgery (bilateral orchiectomy) or administration of luteinizing hormone-releasing hormone (LHRH) and blocking the androgen receptor (AR) which is present on PC cells (ADT). ADT may be indicated, respectively, as initial therapy in addition to prostatectomy and radiation (intermediate, high or very high-risk patients), or adjuvant treatment (patients with metastatic diseases). Because of these clinical indications, a significative percentage of the patients affected by PC undergo ADT during the disease, and endocrine responsiveness still influences the care of PC today.

* Corresponding author.
E-mail address: giordano.savelli@poliambulanza.it (G. Savelli).

https://doi.org/10.1016/j.critrevonc.2019.03.005
Received 8 November 2018; Received in revised form 12 March 2019; Accepted 12 March 2019
1040-8428/

Whatever the clinical context of ADT administration, eventually cancer cells become refractory to the treatment and castration resistance develops. The mechanisms underlying castration resistance are still not fully understood. However, it is now generally accepted that the AR remains active (Montgomery et al., 2008; Mohler et al., 2011; Kobayashi et al., 2013; Watson et al., 2015), despite castrate levels of androgens, and that PC almost invariably leads to distant metastases. This conclusion has led to synthesize novel AR pathway inhibitors, such as enzalutamide and abiraterone, which improved the survival of patients affected by castration-resistant-prostate cancer (CRPC). However, despite these therapeutic successes, it is impossible to deny that CRPC remains an incurable disease and that the median survival of patients affected by metastatic CRPC is less than two years. There is a consensus that there is a great need for more effective treatments.Over the last two decades, there has been increasing interest in neuroendocrine differentiation (NED) which can be detected in CRPC. Researchers have focused on NED because of its prognostic value. There has been significant debate over the definition of NED, the possible markers and the clinical significance of NED onset in CRPC. Although the prognostic impact of NED in hormone-naïve PC is still controversial (Berruti et al., 2007), there is growing acceptance of the theory that the development of NED in CRPC is predictive of a worse prognosis (Deeble et al., 2007; Abrahamsson, 1999a, 1999b; Hansson and Abrahamsson, 2001; Puccetti et al., 2005; Ahlgren et al., 2000; Taplin et al., 2005; Krauss et al., 2011). While this interest in NED is based on negative considerations, the study of markers associated with NED may offer positive treatment targets. Among the molecular, immunohistochemical and biologic markers of NED, several studies have reported the overexpression of membrane receptors for somatostatin. This selective review will summarize the principal hypothesis concerning the mechanism of NED development in CRPC and the biological and clinical characteristics of CRPC with NED. We will report on the few existent imaging studies of SSTRs hoping to prompt further study of the presence of these receptors in CRPC with the aim of promoting large prospective diagnostic and then therapeutic studies.

Research criteria – We carried out an online search for current and past peer-reviewed literature on neuroendocrine differentiation in castration-resistant prostate cancer. The search terms were “castration-resistant prostate cancer,” “neuroendocrine differentiation”, “androgen deprivation therapy”, “somatostatin receptors”, “scintigraphy,” “Single Photon Emission Tomography”, “Positron Emission Tomography”. Studies concerning the detection of SSTRs in CRPC, even those with partial results, were considered. Due to the relative rarity of nuclear medicine studies concerning the overexpression of SSTRs in CRPC, single, occasional reports of SSTRs detection by nuclear medicine procedures were collected as well, to give a whole and comprehensive picture with the aim of encouraging the clinical research in this field.

2. Evidence from the literature

In the normal prostate gland, NE cells are usually distributed in the acini and ducts. Two main hypotheses concerning the mechanism of NED in CRPC have been proposed. The first of these two suggests that NE PC cells share the same origin with normal NE cells from neural crest and that they differentiate from common pluripotent stem cells. Some indications support the thesis mentioned above. Indeed, NE cells express CD44 and CD133, like cancer stem cells, which may show resistance to hormonal therapy and lead to tumor recurrence (Palapattu et al., 2009; Richardson et al., 2004; Foster et al., 2013).

The second and possible alternative hypothesis claims that NE cells in PC originate from neoplastic epithelial cells subjected to pathological conditions, like androgen ablation and cytokines production. These NE cells, therefore do not derive from normal NE cells, and should be defined as ‘NE-like PC cells’ (Yuan et al., 2007; Cerasuolo et al., 2015; Noble et al., 2018). To date, a growing body of evidence in the literature supports the idea that the onset of NED from conventional prostate cancer is associated with systemic treatments (Miyoshi et al., 2001; Tanaka et al., 2001; Beltran et al., 2012; Gilani et al., 2017; Wang et al., 2018; Nouri et al., 2017). This transformation arises because of lineage plasticity. In this condition of defined trans-differentiation, tumor cells try to escape from AR pathway inhibition, transforming them from AR-driven adenocarcinoma to treatment-related CRPC with NED (t-NEPC).

Trans-differentiation is a process in which one mature somatic cell transforms into another mature somatic cell without undergoing an intermediate pluripotent state or progenitor cell type (Graf and Enver, 2009; Hochedlinger and Plath, 2009). This change may be associated with some genomic alterations in oncogenes (aurora kinase A gene, N-myc proto-oncogene protein overexpression), aberrant tumor protein p53 signaling and loss of tumor suppressor Rb protein.

Therefore, with the ongoing development of more potent AR pathway inhibitors, the incidence of t-NEPC is expected to increase further.

Irrespective of the mechanism underlying its development, it is now obvious that NED both brings with it prognostic information (a deterioration of the clinical outcome) and, at the same time, it turns a problem in an opportunity. Indeed, therapy-induced NED with its trans-differentiation, shifts the therapeutic strategies appropriate for classic prostate adenocarcinoma, now refractory to hormonal treatments, to a substantially different one for this neoplastic disease. This change creates the chance to treat the patients with therapies which originally were not appropriate for the classic CRPC.

To determine the best treatment, we must consider which clinical markers are closely linked to NED. How can we detect them in CRPC? Also, which are the most useful NED markers and in which clinical scenario?

In clinical practice, doctors do not generally perform routine immunohistochemical tests of prostate cancer for NED markers. When requested, NED in CRPC has been studied by immunoreactivity to NE markers (chromogranin A, CgA, neuron-specific enolase, NSE, somatostatin, and 5-HT)7, (Tagawa, 2014). These techniques usually identify NE cells in nearly 10%–100% of PC tissues (Kamiya et al., 2008; Marcu et al., 2010).

CgA is generally considered as a main specific NE tumor marker and its tissue, and plasmatic detection may mirror the NE activity present in CRPC (Berruti et al., 2001a; Angelsen et al., 1997). Therefore, several studies on CRPC used serum CgA as a surrogate marker of NED (Niedworok et al., 2017; Fan et al., 2017; Dong et al., 2017; VON Hardenberg et al., 2017). However, several non-neoplastic conditions may alter serum CgA levels. Gastrointestinal (atrophic gastritis (Peracchi et al., 2005), liver cirrhosis, chronic hepatitis (Spadaro et al., 2005) pancreatitis (Malaguarnera et al., 2009) inflammatory bowel disease (Sciola et al., 2009), irritable bowel syndrome (Sidhu et al., 2009)), cardiovascular, pulmonary, rheumatologic, renal, and endocrine diseases may show CgA alteration. Moreover, proton-pump inhibitors cause increased CgA level. Thus, serum CgA levels must be considered with caution in many patients with co-morbidity.

Another well recognized immunohistochemical parameter of neuroendocrine tumors and neuroendocrine differentiation is the overexpression of somatostatin receptors (SSTRs). Somatostatin is a small, cyclic neuropeptide present in neurons and endocrine cells with an inhibiting activity on the secretion of many hormones. Somatostatin actions are mediated by five subtypes of SSTRs (numbered 1–5). The *in vivo* diagnosis and peptide receptor radionuclide therapy has made been possible by the production of synthetic analogs.

SSTRs nuclear medicine imaging has been widely used to study neuroendocrine tumors in the last three decades. The gamma-emitting radiopharmaceuticals to image SSTRs overexpression, labeled with both ^{111}In and ^{99m}Tc, target the neuroendocrine tumors. Since the outset, however, it was clear to the whole of the scientific community that SSTRs overexpression is not a unique feature of neuroendocrine tumors (Reubi et al., 1990; Reubi et al., 1992). Indeed, many different tumors may overexpress SSTRs.

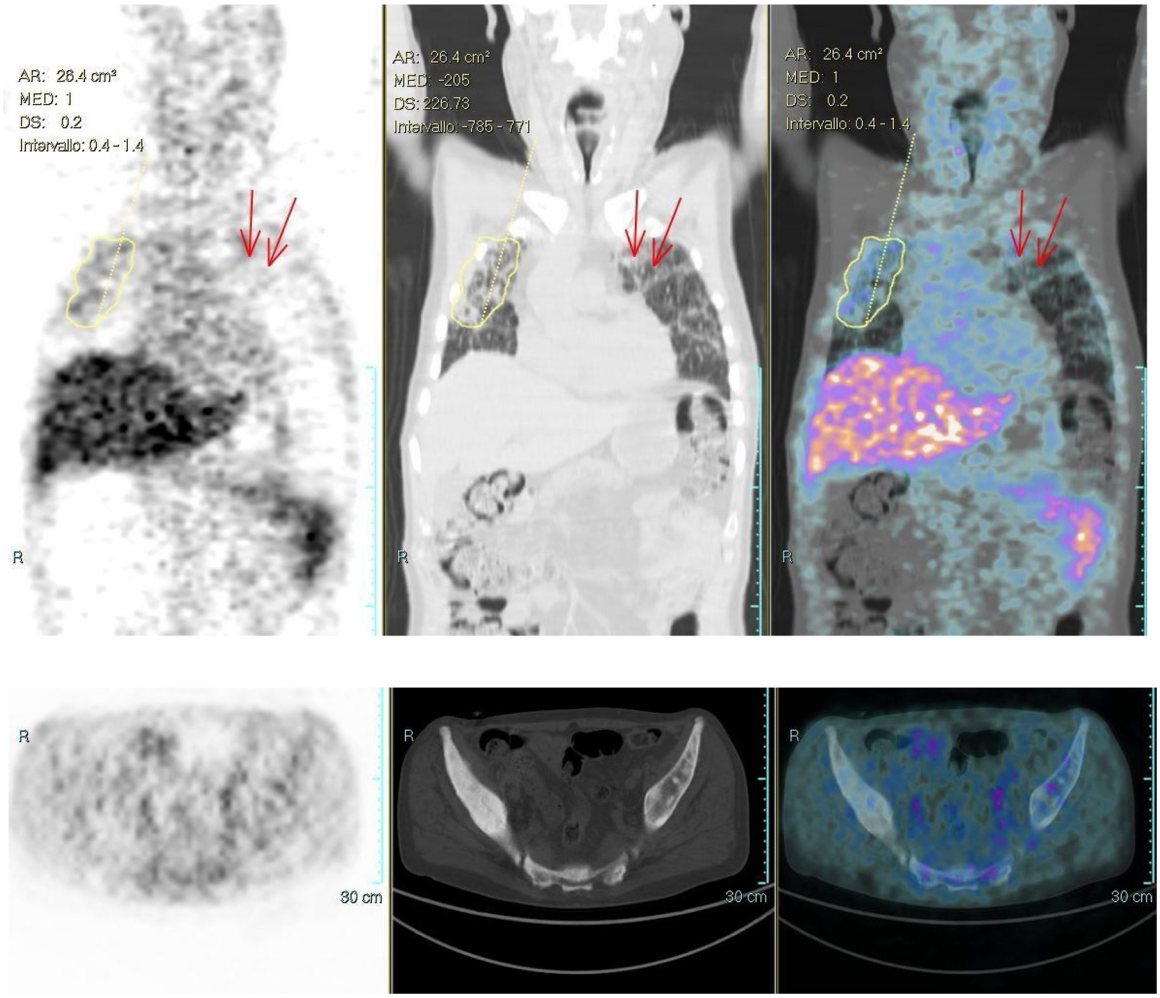

Fig. 1. (A) ^{68}Ga-DOTANOC PET/CT coronal view showing bilateral lung mild uptake (yellow circle area on the right, red arrows on the left). The final radiological diagnosis of lymphangitic carcinomatosis was reached by consensus, in accordance with the CT scan findings, and on the basis of clinical findings. (B) ^{68}Ga-DOTANOC PET/CT transaxial view is showing negligible uptake in the diffuse osteoblastic and mixed skeletal metastases (transaxial view). (For interpretation of the references to color in text, the reader is referred to the web version of the article).

The first human study of SSTRs overexpression studied 31 patients affected by CRPC with ^{111}In-pentetreotide scintigraphy (Nilsson et al., 1995). In this study, almost all (94%) of the CRPC patients affected by multiple metastases had at least one localization visualized by ^{111}In-pentetreotide, and nearly 40% of the metastases detected by bone scan were evidenced *in vivo* by SSTRS imaging. One of these patients with nearly 20% of the lesions positive to ^{111}In-pentetreotide scintigraphy was also treated with the somatostatin analog octreotide. This patient underwent an ^{11}C-methionine PET examination before and after three months of therapy to evaluate the response. The PET examination showed a reduction of approximately 80% of SUV of the target lesion and a symptomatic benefit. The Authors concluded with the hope that their results could be the basis for the *in vivo* characterization and for the development of new treatment strategy in CRPC.

Indeed, a later paper (Spieth et al., 2002) reports the detection of multiple SSTRs positive bone metastases in a CRPC patient. Following this result, octreotide was used to treat this patient, with some success. The Author concluded stressing the potential of somatostatin analogs as adjuvant treatments for prostate carcinoma.

Not all the researchers agreed that SSTRs overexpression by CRPC is predictive of a negative prognosis. Based on an ICH study in PC, Hennings suggested that SSTR-negative tumors have a worse prognosis compared with SSTR-positive ones (Hennigs et al., 2014). However, it must be emphasized that the specimens studied were from *naïve* patients, not treated with ADT, and therefore non-castration resistant.

Following the results of Nilsson et al. (1995), other researchers studied CRPC with ^{111}In-pentetreotide. Mencoboni et al. carried out the scintigraphy in 20 patients affected by CRPC, all with metastatic disease, treated with single-agent chemotherapy. ^{111}In-pentetreotide scintigraphy did not show metastases in 63% of patients, and only 11% of the bone metastases detected were positive at the examination (Mencobonii et al., 2006). Metastases were positive in only 37% of the patients. Thus, the Author concluded that chemotherapy probably might reduce SSTRs expression by CRPC. Once again, however, not all the typical characteristics of NED were present in the studied population, since the mean CgA values were 3.99 ng/ml, mainly within the normal values, thus raising the question if NED was present in a significant proportion of the studied population.

A contemporary study evaluated the power of ^{111}In-pentetreotide scintigraphy to show NED and to predict the response to SSTRs analog therapy in CRPC (Kalkner et al., 2006). Nevertheless, the conclusive results of this research were disappointing, since none of the parameters in the study (CgA levels and baseline ^{111}In-pentetreotide scintigraphy) were able to predict the outcome of the treatment. In one case, however, the parameters chosen to define NED differentiation in these patients, *i.e.* CgA levels at recruitment (mean CgA in the population 7.6 nmol/l, upper reference limit 4 nmol/l) and especially ^{111}In-pentetreotide scintigraphy (none of the patients studied with uptakes higher than the liver, thus clinically significant), were suggestive for a striking NED differentiation.

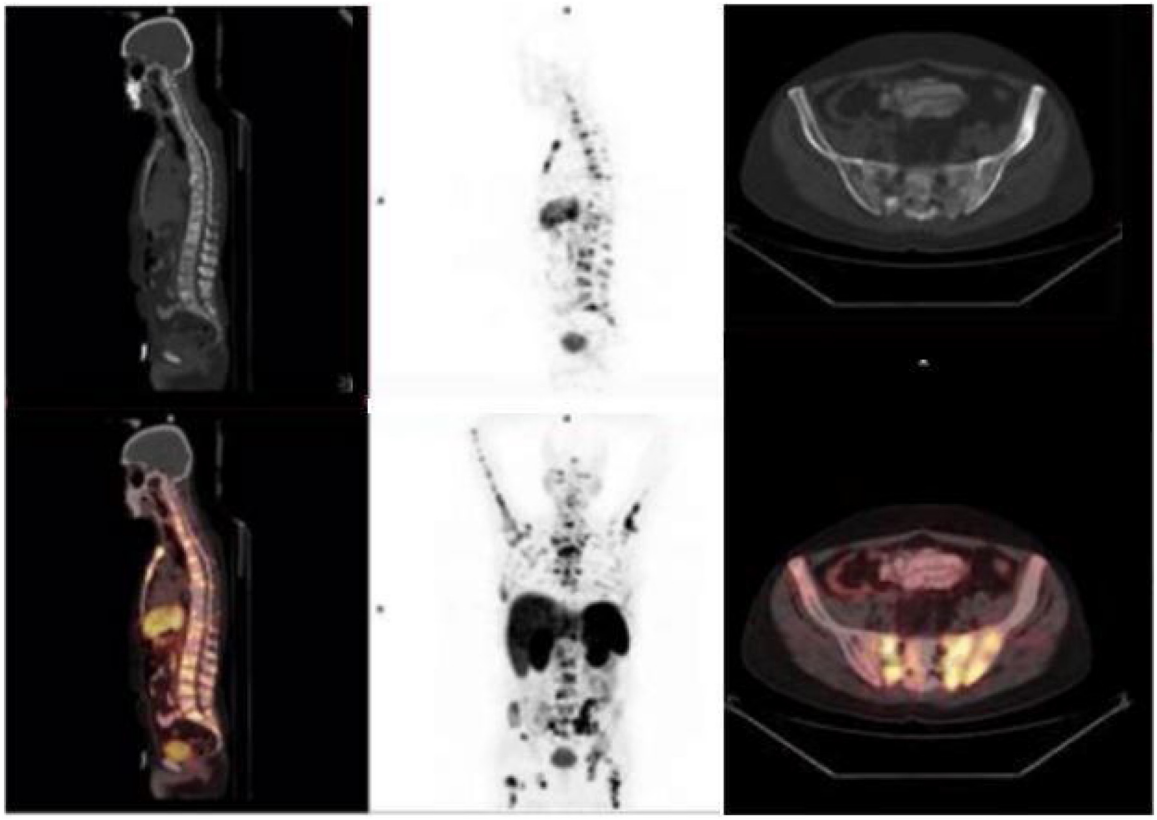

Fig. 2. Sagittal and transaxial (PET/CT mode, left and right panels) and coronal (PET only mode, middle panel) ^{68}Ga-DOTATATE PET/CT. Multiple foci of high skeletal uptake corresponding to the bone metastases are evident.

Thus, if we were to summarize the state of the art of SSTRs gamma-camera imaging in CRPC, we can state the following: currently there is not consensus on SSTRs gamma-camera imaging in CRPC because the results are quite contradictory. An explanation for this is that the recruitment criteria were not particularly homogeneous (serum raise of CgA is not necessarily synonymous with SSTRs overexpression). Also, despite some positive reports (Priftakis et al., 2015; Hope et al., 2015) gamma-cameras technology is somehow limited in the detection of the subtle structural and metabolic changes characteristic of the trans-differentiation.

Until the advent of clinical SSTRS PET/CT imaging, the combination of only partially verified NED parameters, unsuccessful outcomes of somatostatin treatments and the limits of technology shown in gamma-camera use, dampened enthusiasm about exploiting the potential of NED in CRPC therapy (Forrer et al., 2004; Hofmann et al., 2001 Dec; Wild et al., 2005; Lopci et al., 2008; Virgolini et al., 2010).

In 2010, a paper reported the results of a study carried out to assess the usefulness of ^{68}Ga-DOTA0, Tyr3-octreotide (^{68}Ga-DOTATOC), a positron emitter labeled somatostatin 2 and 5 receptor analog, in advanced prostate cancer with bone metastases. The basic idea was to define the SSTRs *status* of CRPC with ^{68}Ga–DOTATOC PET/CT to evaluate the possibility of a receptor-mediated therapy. Only 30% of focal metastases evidenced SSTRs overexpression on the reconstructed slices whereas two-thirds of patients with superscan showed somewhat increased tracer uptake (Luboldt et al., 2010). The Authors concluded that ^{68}Ga-DOTATOC may show the presence of SSTRs in CRPC but that the receptor concentration is so low that it is not useful for possible therapy. The final suggestion was to test a radiopharmaceutical with a different receptor affinity.

Five years later another report (EUDRA CT number 2010-021026-35 granted by Regione Lombardia) described the biodistribution and results of the PET/CT examination carried out after the administration of ^{68}Ga-DOTA,1-Nal$_3$-octreotide (^{68}Ga-DOTANOC), a compound with a slight difference from ^{68}Ga–DOTATOC in SSTRs affinity (DOTATOC binds to SSTRs 2 and 5 whereas DOTANOC binds to 2, 3 and 5) (Savelli et al., 2015). The recruitment criteria were patients with a rise in serum PSA or progression of the pre-existing disease and the appearance of new metastases despite ADT. Here, the ^{68}Ga-DOTANOC PET/CT evidenced, to some degree, SSTRs overexpression in two out the six patients studied. The Authors concluded that from this very preliminary and small cluster of patients, the positivity to PET/CT SSTRs examination is too weak to hypothesize a peptide receptor radionuclide therapy (PRRT). Fig. 1A shows the right lung biodistribution of ^{68}Ga-DOTANOC corresponding to diffuse lung metastases (yellow line irregular area) and subtle linear left lung uptake corresponding to neoplastic thickening (red arrows). Fig. 1B shows the faint uptake of the radiopharmaceutical by the massive pelvic bone metastasis. Indeed, the toxicity linked to PRRT (mainly renal) needs the high uptake of the target lesion to counterbalance its side effects, and this is not the case. However, the hypothesis to add somatostatin analogs to the usual therapeutic schedules as a complement to other pharmaceuticals should not be rejected especially considering its negligible toxicity.

The Nuclear Medicine study of SSTRs with the most striking results was reported in 2017 by Gofrit et al., ^{68}Ga-DOTA,Tyr(3)-octreotate (^{68}Ga-DOTATATE) PET/CT was used to study twelve patients affected by multiple metastases — previously treated with ADT. PSA rise or imaging studies defined disease progression. This radiopharmaceutical is a further evolution of somatostatin receptors analogs compounds used in Nuclear Medicine, characterized by a narrower affinity to the receptor sub-classes, *i.e.*, it binds only to SSTRs type 2 but with a 10-fold higher affinity compared to ^{68}Ga-DOTATOC. Fig. 2 shows the results of a ^{68}Ga-DOTANOC PET/CT in a patient with advanced CRPC. Multiple foci of moderately to high ^{68}Ga DOTATATE uptake are widely present in almost all the skeleton. Some of the lesions are lytic whereas others

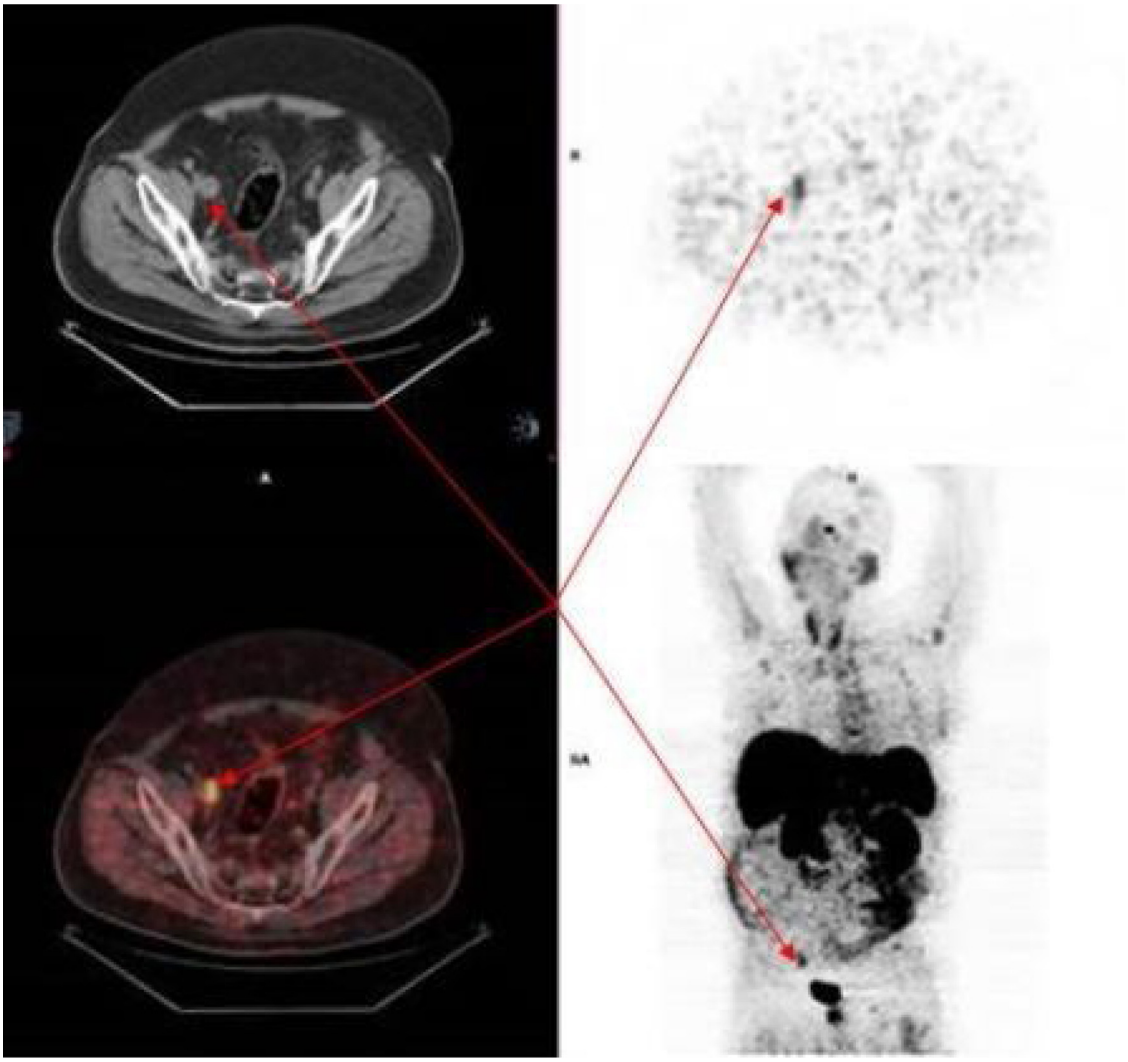

Fig. 3. ^{68}Ga-DOTATATE PET/CT. Red arrows highlight the external iliac nodal metastasis at the CT stand-alone view (left upper panel), PET only imaging (right upper panel) and eventually fused PET/CT image (left bottom panel) and maximum intensity projection (right bottom panel). (For interpretation of the references to color in text, the reader is referred to the web version of the article).

are sclerotic.

Fig. 3 represents the PET/CT findings of nodal metastasis (red arrows, transaxial view, and maximum intensity projection). It is a somewhat lower uptake of the radiopharmaceutical compared to the skeletal findings.

The authors concluded suggesting that NED is common in these patients and that the possible therapies exploiting SSTRs overexpression in CRPC should be explored.

3. Discussion

PC remains a major concern of public health. It is the most prevalent cancer in men and the second leading cause of male cancer deaths in the Western World, the sixth in China (Chen et al., 2016) and increasing in India (Jain et al., 2014). Only through the growth and aging of the global population, PC is expected to rise to 1.7 million new cases and 499,000 new deaths by 2030 worldwide (Ferlay et al., 2010). ADT is generally useful to treat the patients for some years. However, most patients treated with ADT progress to CRPC, for which there are no treatments as effective as ADT. Advanced prostate cancer is a disease that almost invariably progresses and is fatal. Abiraterone and enzalutamide, the new hormonal agents, classically used before chemotherapy, are somehow effective but not completely (Sartor and de Bono, 2018). The new bone-seeking alpha-emitting radiopharmaceutical ^{223}Ra-chloride improved the overall survival rate compared with the best standard of care (Parker et al., 2013; Kluetz et al., 2014). This result gives the hope of possible combination therapy with ^{223}Ra-chloride and abiraterone or enzalutamide. However, ongoing phase 3 randomized controlled trials (ERA-223: NCT02043678 and PEACE-3: NCT02194842) with ^{223}Ra-chloride administered in combination with abiraterone showed more fractures and deaths in the combination treatment arm (Parker et al., 2018). In summary, there would appear to be room for complementing and improving the treatment strategy for this clinical scenario.

NED in CRPC has been studied for many years. From the beginning, the stumbling block was the definition of NED in CRPC and, therefore the mechanism by which it develops. The first reports regarding a possible NED in CRPC came from the detection of tissue and blood markers such as chromogranin A and neuron-specific in CRPC 7 and led to the trials with somatostatin analogs (octreotide) to treat CRPC patient with high NED markers blood levels (Hashimoto et al., 2013; Vainas et al., 1997; D'Angelillo et al., 2014; Berruti et al., 2001b). However, the encouraging partial results did not lead to the use of somatostatin analogs be definitively recommended for clinical practice. The lack of clarity in recruitment criteria likely made the interpretation of the results more difficult and therefore less useful in clinical

Table 1
Summary of the SSTRS PET/CT imaging studies. They are reported the main clinical parameters of the patients at the time of examination, the radiopharmaceutical used for the study, the SUVmax.

Author n° pts.	PSA at test	Gleason score	Radioph.	Diffuse bone M+	Focal bone M+	Bone M+SUVmax	Nodes SUV max	Other SUVmax
Luboldt								
1	6	n.a.	DOTATOC		x	3,4		
2	6	n.a.	DOTATOC		x	3,8		5,9 P
3	31	n.a.	DOTATOC		x	2,4		
4	112	n.a.	DOTATOC	x		3,6		
5	1554	n.a.	DOTATOC		x	3,9		
6	4700	n.a.	DOTATOC		x	5,4		
7	n.a.	n.a.	DOTATOC		x	2,3		
8	7	n.a.	DOTATOC		x	5,4		
9	8	n.a.	DOTATOC		x	2,5		
10	40	n.a.	DOTATOC		x	3,7		
11	49	n.a.	DOTATOC		x	2,2		
12	121	n.a.	DOTATOC		x	5,4		
13	208	n.a.	DOTATOC	x		4,6		
14	214	n.a.	DOTATOC		x	5,1		
15	9400	n.a.	DOTATOC		x	5,5		
16	n.a.	n.a.	DOTATOC	x		0		
17	n.a.	n.a.	DOTATOC	x		7,1		
18	1830	n.a.	DOTATOC	x		0		
19	2224	n.a.	DOTATOC	x		3,9		
Gofrit								
1	213	5 + 4	DOTATATE	x		7, 6	11, 1	
2	500	4 + 5	DOTATATE	x		5, 1		
3	44	5 + 5	DOTATATE		x	4, 4	3, 7	
4	24	4 + 5	DOTATATE	x		2, 7		
5	2	4 + 4	DOTATATE	x		5, 8		
6	29	5 + 4	DOTATATE	x		3, 4	5, 6	
7	0, 2	5 + 5	DOTATATE		x	3, 3		
8	133	3 + 3	DOTATATE	x		14, 2		
9	9	4 + 3	DOTATATE	x		4, 11		
10	42	4 + 5	DOTATATE		x	3, 9		
11	0, 6	4 + 5	DOTATATE	x		5, 8		
12	42	4 + 3	DOTATATE	x		6, 5		8, 5
Savelli								
1	5	4 + 3	DOTANOC	x		0		2, 8 P
2	20	4 + 5	DOTANOC	x		0		
3	21	4 + 4	DOTANOC		x	0		
4	246	4 + 5	DOTANOC	x		0		
5	4	4 + 4	DOTANOC	x		3, 4		1.8 Lu
6	5	4 + 4	DOTANOC	x		0		
Usmani								
1	0,049	3 + 3	DOTANOC			n.a.	25,7	18,8 Li

Abbreviations: Lu, lung, Li, liver, P, prostate.

scenarios. Indeed, as stated before, the elevation of blood CgA levels may be induced by many non-oncological and non-CRPC related clinical and physiological conditions. Moreover, the therapeutic mechanism acts through the binding of somatostatin analogs and a reliable assessment of this condition cannot be attained by only measuring the circulating marker (Matei et al., 2012).

The first studies dealing with Nuclear Medicine imaging in the section of NED in CRPC yielded contradictory and not very encouraging results. These figures could originate from a bias in the recruitment and the limits of the gamma-camera technology. The detection of SSTRs overexpression by CRPC with NED improved with the move from gamma-camera to PET/CT technology and using 68Ga-labeled SSTRs radiotracers. Since then, the sensitivity in the detection of SSTRs reported in the literature has gradually improved and the paper by Gofrit et al. represents the best result to date. Table 1 summarizes the main results of studies with 68Ga-labeled SSTRs radiotracers together with PSA levels at test and SUV of the lesions. Table 1 summarizes the main results of studies with ^{68}Ga-labeled SSTRs radiotracers together with PSA levels at test and SUV of the lesions.

Why is it important to study “in vivo” NED in CRPC?

The reason to look for SSTRs overexpression in this cluster of patients is the consequence of the close link that intrinsically exists between the diagnosis and the treatment. Theranostics describes a new field of medicine which combines and integrates a specific targeted diagnostic test with an equally specific targeted therapy. Besides SSTRs, other molecular targets which have the potential to combine the diagnosis to therapy are under study in CRPC. Prostate-specific membrane antigen (PSMA) is probably the most studied of these, but other targets with theranostic potential, such as Gastrin Releasing Peptide Receptor and Human Copper Transporter 1 (CTR1), are under evaluation.

PSMA is a membrane glycoprotein highly expressed in PC cells. One of the characteristics of this antigen is that it is internalized once linked to anti-PSMA antibodies. Over the past three decades, nuclear medicine approaches to PSMA detection followed technological and radiopharmaceutical developments. The first compounds studied with traditional gamma-camera imaging were antibodies (Bermejo et al., 2003; Pandit-Taskar et al., 2008) or fragments of antibodies and had limited clinical results. The most significant advance was reached a few years later, with the identification of structural homology between N-acetylaspartylglutamate peptidase (NAAALDASE) and PSMA. Indeed, many enzymatic inhibitors directed against NAALDASE were already available. Thus, when the homology between PSMA and NAALDASE was clear, several compounds specific for PSMA starting from NAALDASE structure were labeled. The figures of merit of these radiopharmaceuticals may result in a change in the treatment strategy for

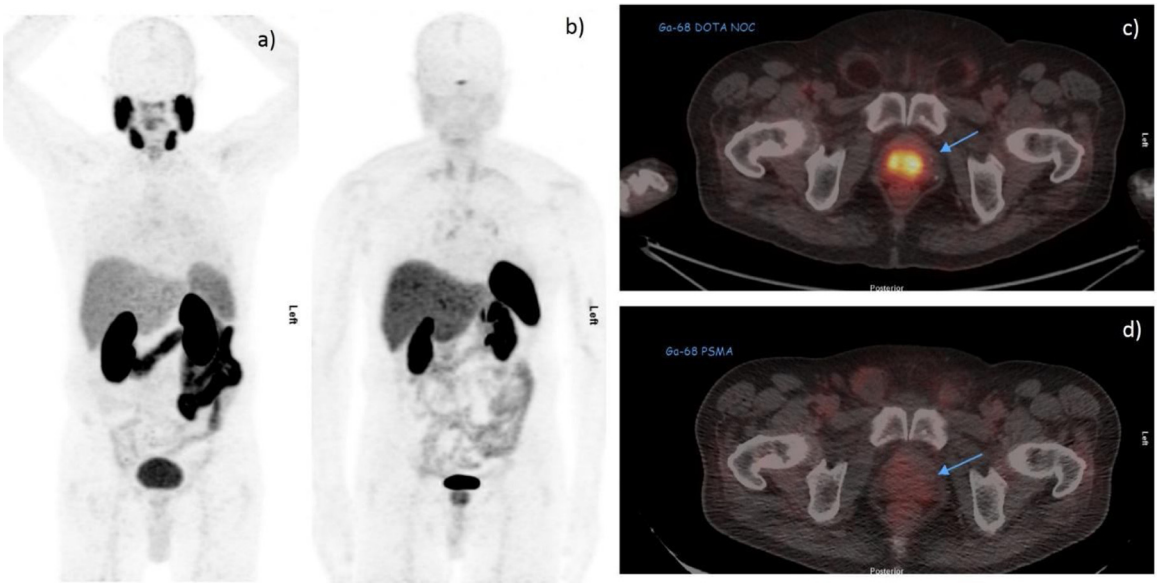

Fig. 4. A-72-year-old gentleman is a case of metastatic prostate cancer on androgen deprivation therapy. (a) ^{68}Ga-PSMA scan. (b) ^{68}Ga-DOTANOC study. (c) Fused ^{68}Ga-DOTANOC. The prostate gland is enlarged with focal calcification and demonstrates diffusely intense increased radiotracer localization with SUVmax of 9.4. (d) Mild tracer uptake of SUV max 2.2 is seen at enlarged prostate. Prostate biopsy was performed showing neuroendocrine differentiation.

more than two thirds of the patients (Albisinni et al., 2017; Bluemel et al., 2016; Calais et al., 2017; Dewes et al., 2016; Barbaud et al., 2018), and they have paved the way for the use of their analogs in phase I and II clinical trials (Emmett et al., 2019; Eppard et al., 2017; Giesel et al., 2016; Heinzel et al., 2019) with encouraging preliminary results.

Gastrin Releasing Peptide Receptor (GRPR) belongs to the family of bombesin neuropeptide and is overexpressed, *inter alia*, by prostate cancer cells. The clinical history of bombesin in nuclear medicine imaging shares some issues with PSMA development. The first trials using bombesin analogs labeled with gamma emitting compounds were promising, however, they did not result in successful clinical use (Wiele et al., 2000; Scopinaro et al., 2002; Cescato et al., 2008) but sowed the seeds for the following research labeled with positron emission compounds (Zhang et al., 2017; Maina et al., 2015). GRPR antagonists compounds proved to be more reliable than agonists to image primary prostate cancer, and metastases are under evaluation in ongoing clinical trials in the U.S. (NCT02559115, NCT03724253, NCT03604757) and the European Union (EudraCT Number: 2017-003432-37).

Copper is an essential element in humans. Once absorbed, copper is imported into the cells by Human Copper Transporter 1 (CTR1) (Peng et al., 2006) a 190-amino-acid protein with three transmembrane domains. CTR1 is overexpressed in metastatic CRPC (Righi et al., 2018) and thus may be imaged by $^{64}CuCl_3$, a positron emitting radiopharmaceutical. In addition to the production of a positron, which guarantees the PET/CT imaging, ^{64}Cu decays emitting both a β and Auger electrons, characterized by medium-to-high linear energy transfer, which are theoretically useful for radionuclide therapy.

Therefore, it is evident that pre-clinical and clinical research is moving toward the detection of new biological markers with different biochemical structure, effective mechanism and biological significance in CRPC. A futuristic clinical scenario is one in which it will be possible to study *in vivo* the receptors mosaic pattern of CRPC with different radiopharmaceuticals and, thus, to define the more appropriate treatment. Fig. 4 is an example of the receptor mismatch between PSMA and SSTRs which may be present in CRPC.

Coming back to SSTRs imaging, ^{68}Ga-DOTATATE PET/CT has shown to detect *in vivo* the overexpression of the receptors in CRPC with NED, to quantify their cellular density and to study the whole burden of the neoplastic foci which show enough uptake to be clinically relevant (Van Etten and Dehm, 2016 Apr). In summary, ^{68}Ga-DOTATATE PET/CT may select those CRCP patients in which there would be the logical base for treatment with somatostatin analogs.

The treatment could be carried out with non-radiolabeled or with radiolabeled SSTRs pharmaceutical analogs, as it is now state of the art for gastro-entero-pancreatic neuroendocrine tumors. To date, the Nuclear Medicine paraphernalia for peptide receptors radionuclide therapy includes the well-established β-emitters compounds (DOTATOC or DOTATATE labeled with ^{177}Lu or ^{90}Y). The future, more innovative and potentially powerful approach will possibly take advantage of the use of α-emitters which are still under pre-clinical and clinical investigation (Chan et al., 2017a; Chan et al., 2017b; Kratochwil et al., 2014; SSTR, in press).

To date, no strong clinical evidence concerning the effectiveness of SSTRs analogs in the treatment of CRPC is present. This paper aims to inspire further clinical research in this field.

4. Conclusions

Over the past two decades, the onset of NED in CRPC has been hypothesized and discussed, sought, found, lost and then recovered. Thus, the trend of the study of NED in CRPC follows and replicates the theory of eternal recurrence. We believe it is time for Nuclear Medicine procedures to be used to shed some light on the degree to which SSTRs and NED can play a role in CRPC treatment.

Conflict of interest

The authors stated no conflict of interest.

Funding

This study has no sponsors.

This research did not receive any specific grant from funding agencies in the public, commercial, or Not-for-profit sectors.

Acknowledgements

We thank Dr. Joseph Taddeo, MD for his comments that greatly improved the manuscript and for the review of the text, and Prof.

Francesca Poli, PHD, for the editing of the manuscript.

References

Abrahamsson, P.A., 1999a. Neuroendocrine differentiation in prostatic carcinoma. Prostate 39 (2), 135–148.

Abrahamsson, P.A., 1999b. Neuroendocrine cells in tumour growth of the prostate. Endocr. Relat. Cancer 6 (4), 503–519.

Ahlgren, G., Pedersen, K., Lundberg, S., Aus, G., Hugosson, J., Abrahamsson, P.A., 2000. Regressive changes and neuroendocrine differentiation in prostate cancer after neoadjuvant hormonal treatment. Prostate 42 (4), 274–279.

Albisinni, S., Artigas, C., Aoun, F., Biaou, I., Grosman, J., Gil, T., et al., 2017. Clinical impact of 68Ga-prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) in patients with prostate cancer with rising prostate-specific antigen after treatment with curative intent: Preliminary analysis o. BJU Int. 120 (2), 197–203. https://doi.org/10.1111/bju.13739.

Angelsen, A., Syversen, U., Haugen, O.A., Stridsberg, M., Mjølnerød, O.K., Waldum, H.L., 1997. Neuroendocrine differentiation in carcinomas of the prostate: do neuroendocrine serum markers reflect immunohistochemical findings? Prostate 30 (1), 1–6.

Barbaud, M., Frindel, M., Ferrer, L., Thiec, M.L., Rusu, D., Rauscher, A., et al., 2018. 68Ga-PSMA-11 PET-CT study in prostate cancer patients with biochemical recurrence and non-contributive 18F-Choline PET-CT: impact on therapeutic decision-making and biomarker changes. Prostate 79 (5), 454–461. https://doi.org/10.1002/pros.23751.

Beltran, H., Tagawa, S.T., Park, K., MacDonald, T., Milowsky, M.I., Mosquera, et al., 2012. Challenges in recognizing treatment-related neuroendocrine prostate cancer. J. Clin. Oncol. 30 (36), e386–e389. https://doi.org/10.1200/JCO.2011.41.5166.

Bermejo, C.E., Coursey, J., Basler, J., Austenfeld, M., Thompson, I., 2003. Histologic confirmation of lesions identified by Prostascint® scan following definitive treatment. Urol. Oncol. Semin. Orig. Investig. 21 (5), 349–352. https://doi.org/10.1016/s1078-1439(02)00253-3.

Berruti, A., Dogliotti, L., Mosca, A., Gorzegno, G., Bollito, E., Mari, M., et al., 2001a. Potential clinical value of circulating chromogranin A in patients with prostate carcinoma. Ann. Oncol. 12 (Suppl 2), S153–S157.

Berruti, A., Dogliotti, L., Mosca, A., Tarabuzzi, R., Torta, M., Mari, M., et al., 2001b. Effects of the somatostatin analog lanreotide on the circulating levels of chromogranin-A, prostate-specific antigen, and insulin-like growth factor-1 in advanced prostate cancer patients. Prostate 47 (3), 205–211. https://doi.org/10.1002/pros.1064.

Berruti, A., Mosca, A., Porpiglia, F., Bollito, E., Tucci, M., Vana, F., et al., 2007. Chromogranin A expression in patients with hormone naïve prostate cancer predicts the development of hormone refractory disease. J. Urol. 178 (3 Pt 1), 838–843. https://doi.org/10.1016/j.juro.2007.05.018. quiz 1129.

Bluemel, C., Linke, F., Herrmann, K., Simunovic, I., Eiber, M., Kestler, C., et al., 2016. Impact of 68Ga-PSMA PET/CT on salvage radiotherapy planning in patients with prostate cancer and persisting PSA values or biochemical relapse after prostatectomy. EJNMMI Res. 6 (1). https://doi.org/10.1186/s13550-016-0233-4.

Calais, J., Fendler, W.P., Eiber, M., Gartmann, J., Chu, F.I., Nickols, N.G., et al., 2017. Actual impact of 68Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. J. Nucl. Med. 59 (3), 434–441.

Cerasuolo, M., Paris, D., Iannotti, F.A., Melck, D., Verde, R., Mazzarella, E., et al., 2015. Neuroendocrine transdifferentiation in human prostate cancer cells: an integrated approach. Cancer Res. 75 (15), 2975–2986. https://doi.org/10.1158/0008-5472.CAN-14.

Cescato, R., Maina, T., Nock, B., Nikolopoulou, A., Charalambidis, D., Piccand, V., Reubi, J.C., 2008. Bombesin receptor antagonists may be preferable to agonists for tumor targeting. J. Nucl. Med. 49 (2), 318–326. https://doi.org/10.2967/jnumed.107.045054.

Chan, H.S., de Blois, E., Konijnenberg, M.W., Morgenstern, A., Bruchertseifer, F., Norenberg, J.P., et al., 2017a. Optimizing labeling conditions of (213)Bi-DOTATATE for preclinical applications of peptide receptor targeted alpha therapy. EJNMMI Radiopharm. Chem. 1 (1), 9. https://doi.org/10.1186/s41181-016-0014-4.

Chan, H.S., Blois, E.D., Morgenstern, A., Bruchertseifer, F., Jong, M.D., Breeman, W., Konijnenberg, M., 2017b. In Vitro comparison of 213Bi- and 177Lu-radiation for peptide receptor radionuclide therapy. PLOS One 12 (7). https://doi.org/10.1371/journal.pone.0181473.

Chen, W., Zheng, R., Baade, P.D., Zhang, S., Zeng, H., Bray, F., et al., 2016. Cancer statistics in China, 2015. CA Cancer J. Clin. 66 (2), 115–132. https://doi.org/10.3322/caac.21338.

D'Angelillo, R.M., Greco, C., Fiore, M., Ippolito, E., Eolo Trodella, L., Iurato, A., et al., 2014. Somatostatin analogs and disease control in castration-resistant prostate cancer: different biological behavior? Case series and review of the literature. Tumori J. 100 (3), 249–253. https://doi.org/10.1700/1578.17192.

Deeble, P.D., Cox, M.E., Frierson, H.F., Sikes, R.A., Palmer, J.B., Davidson, et al., 2007. Androgen-independent growth and tumorigenesis of prostate cancer cells are enhanced by the presence of PKA-differentiated neuroendocrine cells. Cancer Res. 67 (8), 3663–3672. https://doi.org/10.1158/0008-5472.CAN-06-2616.

Dewes, S., Schiller, K., Sauter, K., Eiber, M., Maurer, T., Schwaiger, M., et al., 2016. Integration of 68Ga-PSMA-PET imaging in planning of primary definitive radiotherapy in prostate cancer: a retrospective study. Radiat. Oncol. 11 (1). https://doi.org/10.1186/s13014-016-0646-2.

Dong, B., Fan, L., Wang, Y., Chi, C., Ma, X., Wang, R., et al., 2017. Influence of abiraterone acetate on neuroendocrine differentiation in chemotherapy-naive metastatic castration-resistant prostate cancer. Prostate 77 (13), 1373–1380. https://doi.org/10.1002/pros.23397.

Emmett, L., Crumbaker, M., Ho, B., Willowson, K., Eu, P., Ratnayake, L., et al., 2019. Results of a prospective phase 2 pilot trial of 177Lu–PSMA-617 therapy for metastatic castration-resistant prostate cancer including imaging predictors of treatment response and patterns of progression. Clin. Genitourin. Cancer 17 (1), 15–22. https://doi.org/10.1016/j.clgc.2018.09.014.

Eppard, E., Fuente, A.D., Benešová, M., Khawar, A., Bundschuh, R.A., Gärtner, F.C., et al., 2017. Clinical translation and first in-human use of [44Sc]Sc-PSMA-617 for PET imaging of metastasized castrate-resistant prostate cancer. Theranostics 7 (18), 4359–4369. https://doi.org/10.7150/thno.20586.

Fan, L., Wang, Y., Chi, C., Pan, J., Xun, S., Xin, Z., et al., 2017. Chromogranin A and neurone-specific enolase variations during the first 3 months of abiraterone therapy predict outcomes in patients with metastatic castration-resistant prostate cancer. BJU Int. 120 (2), 226–232. https://doi.org/10.1111/bju.13781.

Ferlay, J., Shin, H.R., Bray, F., International Agency for Research on Cancer; Lyon, France, 2010. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10.

Forrer, F., Uusijärvi, H., Waldherr, C., Cremonesi, M., Bernhardt, P., Mueller-Brand, J., et al., 2004. A comparison of (111)In-DOTATOC and (111)In-DOTATATE: biodistribution and dosimetry in the same patients with metastatic neuroendocrine tumours. Eur. J. Nucl. Med. Mol. Imaging 31 (9), 1257–1262. https://doi.org/10.1007/s00259-004-1553-6.

Foster, B.A., Gangavarapu, K.J., Mathew, G., Azabdaftari, G., Morrison, C.D., Miller, A., Huss, W.J., 2013. Human prostate side population cells demonstrate stem cell properties in recombination with urogenital sinus mesenchyme. PLoS One 8 (1), e55062. https://doi.org/10.1371/journal.pone.0055062.

Giesel, F.L., Cardinale, J., Schäfer, M., Neels, O., Benešová, M., Mier, W., et al., 2016. 18F-Labelled PSMA-1007 shows similarity in structure, biodistribution and tumour uptake to the theragnostic compound PSMA-617. Eur. J. Nucl. Med. Mol. Imaging 43 (10), 1929–1930. https://doi.org/10.1007/s00259-016-3447-9.

Gilani, S., Guo, C.C., Li-Ning, E.M., Pettaway, C., Troncoso, P., 2017. Transformation of prostatic adenocarcinoma to well-differentiated neuroendocrine tumor after hormonal treatment. Hum. Pathol. 64, 186–190. https://doi.org/10.1016/j.humpath.2017.01.006.

Graf, T., Enver, T., 2009. Forcing cells to change lineages. Nature 462 (7273), 587–594.

Hansson, J., Abrahamsson, P.A., 2001. Neuroendocrine pathogenesis in adenocarcinoma of the prostate. Ann. Oncol. 12 (Suppl 2), S145–S152.

Hashimoto, K., Masumori, N., Tanaka, T., Maeda, T., Kobayashi, K., Kitamura, H., et al., 2013. Zoledronic acid but not somatostatin analogs exerts anti-tumor effects in a model of murine prostatic neuroendocrine carcinoma of the development of castration-resistant prostate cancer. Prostate 73 (5), 500–511. https://doi.org/10.1002/pros.22590.

Heinzel, A., Boghos, D., Mottaghy, F.M., Gaertner, F., Essler, M., Mallek, D.V., et al., 2019. 68Ga-PSMA PET/CT for monitoring response to 177Lu-PSMA-617 radioligand therapy in patients with metastatic castration-resistant prostate cancer. Eur. J. Nucl. Med. Mol. Imaging. https://doi.org/10.1007/s00259-019-4258-6.

Hennigs, J.K., Müller, J., Adam, M., Spin, J.M., Riedel, E., Graefen, M., et al., 2014. Loss of somatostatin receptor subtype 2 in prostate cancer is linked to an aggressive cancer phenotype, high tumor cell proliferation and predicts early metastatic and biochemical relapse. PLoS One 9 (7), e100469. https://doi.org/10.1371/journal.pone.0100469.

Hochedlinger, K., Plath, K., 2009. Epigenetic reprogramming and induced pluripotency. Development 136 (4), 509–523. https://doi.org/10.1242/dev.020867.

Hofmann, M., Maecke, H., Börner, R., Weckesser, E., Schöffski, P., Oei, L., et al., 2001 Dec Dec. Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur. J. Nucl. Med. 28 (12), 1751–1757 (Epub 2001 Oct 31).

Hope, T.A., Aggarwal, R., Simko, J.P., VanBrocklin, H.F., Ryan, C.J., 2015. Somatostatin imaging of neuroendocrine-differentiated prostate cancer. Clin. Nucl. Med. 40 (6), 540–541. https://doi.org/10.1097/RLU.0000000000000776.

Jain, S., Saxena, S., Kumar, A., 2014. Epidemiology of prostate cancer in India. Meta Gene 2, 596–605. https://doi.org/10.1016/j.mgene.2014.07.007.

Kalkner, K.M., Acosta, S., Thorsson, O., Frederiksen, H., Nilsson, A., Gustavsson, B., et al., 2006. Octreotide scintigraphy and Chromogranin A do not predict clinical response in patients with octreotide acetate-treated hormone-refractory prostate cancer. Prostate Cancer Prostatic Dis. 9 (1), 92–98. https://doi.org/10.1038/sj.pcan.4500843.

Kamiya, N., Suzuki, H., Kawamura, K., Imamoto, T., Naya, Y., Tochigi, N., et al., 2008. Neuroendocrine differentiation in stage D2 prostate cancers. Int. J. Urol. 15 (5), 423–428. https://doi.org/10.1111/j.1442-2042.2008.02015.x.

Kluetz, P.G., Pierce, W., Maher, V.E., Zhang, H., Tang, S., Song, P., et al., 2014. Radium Ra 223 dichloride injection: U.S. Food and Drug Administration drug approval summary. Clin. Cancer Res. 20 (1), 9–14. https://doi.org/10.1158/1078-0432.CCR-13-2665.

Kobayashi, T., Inoue, T., Kamba, T., Ogawa, O., 2013. Experimental evidence of persistent androgen-receptor-dependency in castration-resistant prostate cancer. Int. J. Mol. Sci. 14 (8), 15615–15635. https://doi.org/10.3390/ijms140815615.

Kratochwil, C., Giesel, F.L., Bruchertseifer, F., Mier, W., Apostolidis, C., Boll, R., et al., 2014. 213Bi-DOTATOC receptor-targeted alpha-radionuclide therapy induces remission in neuroendocrine tumours refractory to beta radiation: a first-in-human experience. Eur. J. Nucl. Med. Mol. Imaging 41 (11), 2106–2119. https://doi.org/10.1007/s00259-014-2857-9.

Krauss, D.J., Hayek, S., Amin, M., Ye, H., Kestin, L.L., Zadora, S., …, Martinez, A.A., 2011. Prognostic significance of neuroendocrine differentiation in patients with Gleason score 8-10 prostate cancer treated with primary radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 81 (3), e119–e125. https://doi.org/10.1016/j.ijrobp.2010.12.064.. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21596486.

Lopci, E., Nanni, C., Rampin, L., Rubello, D., Fanti, S., 2008. Clinical applications of 68Ga-DOTANOC in neuroendocrine tumours. Minerva Endocrinol. 33 (3), 277–281.
Luboldt, W., Zöphel, K., Wunderlich, G., Abramyuk, A., Luboldt, H.J., Kotzerke, J., 2010. Visualization of somatostatin receptors in prostate cancer and its bone metastases with Ga-68-DOTATOC PET/CT. Mol. Imaging Biol. 12 (1), 78–84. https://doi.org/10.1007/s11307-009-0230-3.
Maina, T., Bergsma, H., Kulkarni, H.R., Mueller, D., Charalambidis, D., Krenning, E.P., et al., 2015. Preclinical and first clinical experience with the gastrin-releasing peptide receptor-antagonist [68Ga]SB3 and PET/CT. Eur. J. Nucl. Med. Mol. Imaging 43 (5), 964–973. https://doi.org/10.1007/s00259-015-3232-1.
Malaguarnera, M., Cristaldi, E., Cammalleri, L., Colonna, V., Lipari, H., Capici, A., et al., 2009. Elevated chromogranin A (CgA) serum levels in the patients with advanced pancreatic cancer. Arch. Gerontol. Geriatr. 48 (2), 213–217. https://doi.org/10.1016/j.archger.2008.01.014.
Marcu, M., Radu, E., Sajin, M., 2010. Neuroendocrine differentiation in prostate adenocarcinoma biopsies and its correlation to histological grading. Curr. Health Sci. J. 36 (1), 37–42.
Matei, D.V., Renne, G., Pimentel, M., Sandri, M.T., Zorzino, L., Botteri, E., et al., 2012. Neuroendocrine differentiation in castration-resistant prostate cancer: a systematic diagnostic attempt. Clin. Genitourin. Cancer 10 (3), 164–173. https://doi.org/10.1016/j.clgc.2011.12.004.
Mencobonii, M., Tredici, S., Rebella, L., Bergaglio, M., Galbusera, V., Manzara, A., et al., 2006. Effect of chemotherapy on somatostatin receptor detection with octreotide scintigraphy in hormone-refractory prostate cancer patients. Anticancer Res. 26 (3B), 2233–2235.
Miyoshi, Y., Uemura, H., Kitami, K., Satomi, Y., Kubota, Y., Hosaka, M., 2001. Neuroendocrine differentiated small cell carcinoma presenting as recurrent prostate cancer after androgen deprivation therapy. BJU Int. 88 (9), 982–983. https://doi.org/10.1046/j.1464-4096.2001.00936.
Mohler, J.L., Titus, M.A., Bai, S., Kennerley, B.J., Lih, F.B., Tomer, K.B., et al., 2011. Activation of the androgen receptor by intratumoral bioconversion of androstanediol to dihydrotestosterone in prostate cancer. Cancer Res. 71 (4), 1486–1496. https://doi.org/10.1158/0008-5472.CAN-10-1343.
Montgomery, R.B., Mostaghel, E.A., Vessella, R., Hess, D.L., Kalhorn, T.F., Higano, C.S., et al., 2008. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res. 68 (11), 4447–4454. https://doi.org/10.1158/0008-5472.CAN-08-0249.
Niedworok, C., Tschirdewahn, S., Reis, H., Lehmann, N., Szücs, M., Nyirády, et al., 2017. Serum chromogranin A as a complementary marker for the prediction of prostate cancer-specific survival. Pathol. Oncol. Res. 23 (3), 643–650. https://doi.org/10.1007/s12253-016-0171-5.
Nilsson, S., Reubi, J.C., Kalkner, K.M., Laissue, J.A., Horisberger, U., Olerud, C., Westlin, J.E., 1995. Metastatic hormone-refractory prostatic adenocarcinoma expresses somatostatin receptors and is visualized in vivo by [111In]-labeled DTPA-D-[Phe1]-octreotide scintigraphy. Cancer Res. 55 (23 Suppl), 5805s–5810s.
Noble, A.R., Maitland, N.J., Berney, D.M., Rumsby, M.G., 2018. Phospholipase D inhibitors reduce human prostate cancer cell proliferation and colony formation. Br. J. Cancer 118 (2), 189–199. https://doi.org/10.1038/bjc.2017.391.
Nouri, M., Caradec, J., Lubik, A.A., Li, N., Hollier, B.G., Takhar, M., et al., 2017. Therapy-induced developmental reprogramming of prostate cancer cells and acquired therapy resistance. Oncotarget 8 (12), 18949–18967. https://doi.org/10.18632/oncotarget.14850.
Palapattu, G.S., Wu, C., Silvers, C.R., Martin, H.B., Williams, K., Salamone, L., et al., 2009. Selective expression of CD44, a putative prostate cancer stem cell marker, in neuroendocrine tumor cells of human prostate cancer. Prostate 69 (7), 787–798. https://doi.org/10.1002/pros.20928.
Pandit-Taskar, N., Odonoghue, J.A., Morris, M.J., Wills, E.A., Schwartz, L.H., Gonen, M., et al., 2008. Antibody mass escalation study in patients with castration-resistant prostate cancer using 111In-J591: lesion detectability and dosimetric projections for 90Y radioimmunotherapy. J. Nucl. Med. 49 (7), 1066–1074. https://doi.org/10.2967/jnumed.107.049502.
Parker, C., Nilsson, S., Heinrich, D., Helle, S.I., O'Sullivan, J.M., Fosså, S.D., Investigators, A., et al., 2013. Alpha emitter radium-223 and survival in metastatic prostate cancer. N. Engl. J. Med. 369 (3), 213–223. https://doi.org/10.1056/NEJMoa1213755.
Parker, C., Heidenreich, A., Nilsson, S., Shore, N., 2018. Current approaches to incorporation of radium-223 in clinical practice. Prostate Cancer Prostatic Dis. 21 (1), 37–47. https://doi.org/10.1038/s41391-017-0020-y.
Peng, F., Lu, X., Janisse, J., Muzik, O., Shields, A.F., 2006. PET of human prostate cancer xenografts in mice with increased uptake of 64CuCl2. J. Nucl. Med. 47, 1649–1652.
Peracchi, M., Gebbia, C., Basilisco, G., Quatrini, M., Tarantino, C., Vescarelli, C., et al., 2005. Plasma chromogranin A in patients with autoimmune chronic atrophic gastritis, enterochromaffin-like cell lesions and gastric carcinoids. Eur. J. Endocrinol. 152 (3), 443–448.
Priftakis, D., Kritikos, N., Stavrinides, S., Kleanthous, S., Baziotis, N., 2015. Neuroendocrine differentiation in castration-resistant prostate cancer: a case report. Mol. Clin. Oncol. 3 (6), 1392–1394. https://doi.org/10.3892/mco.2015.645.
Puccetti, L., Supuran, C.T., Fasolo, P.P., Conti, E., Sebastiani, G., Lacquaniti, S., et al., 2005. Skewing towards neuroendocrine phenotype in high grade or high stage androgen-responsive primary prostate cancer. Eur. Urol. 48 (2), 215–221. https://doi.org/10.1016/j.eururo.2005.03.018. (Discussion 221-213).
Reubi, J.C., Kvols, L., Krenning, E., Lamberts, S.W., 1990. Distribution of somatostatin receptors in normal and tumor tissue. Metabolism 39 (9 Suppl 2), 78–81.
Reubi, J.C., Krenning, E., Lamberts, S.W., Kvols, L., 1992. In vitro detection of somatostatin receptors in human tumors. Metabolism 41 (9 Suppl 2), 104–110.
Richardson, G.D., Robson, C.N., Lang, S.H., Neal, D.E., Maitland, N.J., Collins, A.T., 2004. CD133, a novel marker for human prostatic epithelial stem cells. J. Cell Sci. 117 (Pt 16), 3539–3545. https://doi.org/10.1242/jcs.01222.. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15226377.
Righi, S., Ugolini, M., Bottoni, G., Puntoni, M., Iacozzi, M., Paparo, F., et al., 2018. Biokinetic and dosimetric aspects of 64CuCl2 in human prostate cancer: Possible theranostic implications. EJNMMI Res. 8 (1). https://doi.org/10.1186/s13550-018-0373-9.
Sartor, O., de Bono, J.S., 2018. Metastatic prostate cancer. N. Engl. J. Med. 378 (7), 645–657. https://doi.org/10.1056/NEJMra1701695.
Savelli, G., Muni, A., Falchi, R., Zaniboni, A., Barbieri, R., Valmadre, G., et al., 2015. Somatostatin receptors over-expression in castration resistant prostate cancer detected by PET/CT: preliminary report of in six patients. Ann. Transl. Med. 3 (10), 145. https://doi.org/10.3978/j.issn.2305-5839.2015.06.10.
Sciola, V., Massironi, S., Conte, D., Caprioli, F., Ferrero, S., Ciafardini, C., et al., 2009. Plasma chromogranin a in patients with inflammatory bowel disease. Inflamm. Bowel Dis. 15 (6), 867–871.
Scopinaro, F., Varvarigou, A., Ussof, W., Vincentis, G.D., Archimandritis, S., Evangelatos, G., et al., 2002. Breast cancer takes up 99mTc bombesin. A preliminary report. Tumori J. 88 (3). https://doi.org/10.1177/030089160208800331.
Sidhu, R., McAlindon, M.E., Leeds, J.S., Skilling, J., Sanders, D.S., 2009. The role of serum chromogranin A in diarrhoea predominant irritable bowel syndrome. J. Gastrointestin. Liver Dis. 18 (1), 23–26.
Spadaro, A., Ajello, A., Morace, C., Zirilli, A., D'arrigo, G., Luigiano, C., et al., 2005. Serum chromogranin-A in hepatocellular carcinoma: diagnostic utility and limits. World J. Gastroenterol. 11 (13), 1987–1990.
Spieth, M.E., Lin, Y.G., Nguyen, T.T., 2002. Diagnosing and treating small-cell carcinomas of prostatic origin. Clin. Nucl. Med. 27 (1), 11–17.
Tagawa, S.T., 2014. Neuroendocrine prostate cancer after hormonal therapy: knowing is half the battle. J. Clin. Oncol. 32 (30), 3360–3364. https://doi.org/10.1200/JCO.2014.57.5100.
Tanaka, M., Suzuki, Y., Takaoka, K., Suzuki, N., Murakami, S., Matsuzaki, O., Shimazaki, J., 2001. Progression of prostate cancer to neuroendocrine cell tumor. Int. J. Urol. 8 (8), 431–436. https://doi.org/10.1046/j.1442-2042.2001.00347. (Discussion 437).
Taplin, M.E., George, D.J., Halabi, S., Sanford, B., Febbo, P.G., Hennessy, et al., 2005. Prognostic significance of plasma chromogranin a levels in patients with hormone-refractory prostate cancer treated in Cancer and Leukemia Group B 9480 study. Urology 66 (2), 386–391. https://doi.org/10.1016/j.urology.2005.03.040.
Vainas, G., Pasaitou, V., Galaktidou, G., Maris, K., Christodoulou, K., Constantinidis, C., Kortsaris, A.H., 1997. The role of somatostatin analogues in complete antiandrogen treatment in patients with prostatic carcinoma. J. Exp. Clin. Cancer Res. 16 (1), 119–126.
Van Etten, J.L., Dehm, S.M., 2016 Apr. Clonal origin and spread of metastatic prostate cancer. Endocr. Relat. Cancer 23 (4), R207–R217. https://doi.org/10.1530/ERC-16-0049.
Virgolini, I., Ambrosini, V., Bomanji, J.B., Baum, R.P., Fanti, S., Gabriel, M., et al., 2010. Procedure guidelines for PET/CT tumour imaging with 68Ga-DOTA-conjugated peptides: 68Ga-DOTA-TOC, 68Ga-DOTA-NOC, 68Ga-DOTA-TATE. Eur. J. Nucl. Med. Mol. Imaging 37 (10), 2004–2010. https://doi.org/10.1007/s00259-010-1512-3.
VON Hardenberg, J., Schwartz, M., Werner, T., Fuxius, S., Müller, M., Frangenheim, T., et al., 2017. Prospective evaluation of neuromediator dynamics in castration-resistant prostate cancer patients during docetaxel. Anticancer Res. 37 (9), 5117–5124. https://doi.org/10.21873/anticanres.11931.
Wang, C., Peng, G., Huang, H., Liu, F., Kong, D.P., Dong, K.Q., et al., 2018. Blocking the feedback loop between neuroendocrine differentiation and macrophages improves the therapeutic effects of enzalutamide (MDV3100) on prostate cancer. Clin. Cancer Res. 24 (3), 708–723. https://doi.org/10.1158/1078-0432.CCR-17-2446.
Watson, P.A., Arora, V.K., Sawyers, C.L., 2015. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat. Rev. Cancer 15 (12), 701–711. https://doi.org/10.1038/nrc4016.
Wiele, C.V., Dumont, F., Broecke, R.V., Oosterlinck, W., Cocquyt, V., Serreyn, R., et al., 2000. Technetium-99m RP527, a GRP analogue for visualisation of GRP receptor-expressing malignancies: a feasibility study. Eur. J. Nucl. Med. 27 (11), 1694–1699. https://doi.org/10.1007/s002590000355.
Wild, D., Mäcke, H.R., Waser, B., Reubi, J.C., Ginj, M., Rasch, H., et al., 2005. 68Ga-DOTANOC: a first compound for PET imaging with high affinity for somatostatin receptor subtypes 2 and 5. Eur. J. Nucl. Med. Mol. Imaging 32 (6), 724. https://doi.org/10.1007/s00259-004-1697-4.
Yuan, T.C., Veeramani, S., Lin, M.F., 2007. Neuroendocrine-like prostate cancer cells: neuroendocrine transdifferentiation of prostate adenocarcinoma cells. Endocr. Relat. Cancer 14 (3), 531–547. https://doi.org/10.1677/ERC-07-0061.
Zhang, J., Niu, G., Fan, X., Lang, L., Hou, G., Chen, L., et al., 2017. PET using a GRPR antagonist 68ga-RM26 in healthy volunteers and prostate cancer patients. J. Nucl. Med. 59 (6), 922–928. https://doi.org/10.2967/jnumed.117.198929.