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THERAGNOSTICS: SEE WHAT YOU TREAT AND TREAT WHAT YOU SEE

*Alessio Marino Md, °Aniello Iacomino Md, PhD, * Davide Manni Md , *Vincenzo Cuccurullo Md, PhD

* Università della Campania "Luigi Vanvitelli" - Napoli, Italia
° Dipartimento di Scienze Umane, Università Guglielmo Marconi – Roma, Italia

a.marino94@gmail.com

Abstract

Theragnostics is not a new conception, even if nowadays it is gaining more and more importance in clinical practice and interest among researchers, thanks to their great results obtained in oncologic (especially in neuroendocrine tumors) and non-oncologic fields, too. A theragnostic approach is synthesizable in "see what you treat and treat what you see", in other words a strategy that has the goal to be in between diagnostics and therapy. Theragnostics is founded on functional and biological characteristics of diseases, on which is based radiopharmaceuticals' development, there is to say very specific drugs able to bind a precise target and labeled to a particular radionuclide, that is specifically chosen depending on its diagnostic or therapeutic purpose. In this paper, the Authors will focus the attention on several current and promising future application of theragnostics in several clinical scenarios, starting from neuroendocrine tumors (one of the most active sectors in this field), differentiated thyroid carcinoma, neuroblastoma and pheochromocytoma/paraganglioma, castration-resistant prostatic cancer, liver neoplastic lesions (metastases and/or hepatocellular carcinoma) through SIRT/TARE locoregional techniques.

Keywords: *Theragnostics, theranostics, neuroendocrine tumors, pheochromocytoma, paraganglioma*

INTRODUCTION

"*Kaizen*"(改善) is a Japanese expression that, simply, means "change for the better, continuous improvement". This is at the base of science and progress in general, so we can affirm that the same attitude is typical of medicine. In this context, "improvements" have far greater consequences, because getting better in diagnosing and treating diseases implies a step up in healthcare and population's health.

This concept is particularly coherent with **theragnostics**, a branch of nuclear medicine that, since its birth, has always shown this behavior. (1)

But what exactly theragnostics is (also referred to as "theranostics")?

The idea that gives origin to this practice is quite simple and genial at the same time: given a certain molecular target that is characteristic of a precise disease (independently if it is an oncologic or non-oncologic one), is it possible to use a specific drug to both diagnose and treat it? Today, even if results are not, the answer is affirmative.

Let's begin from the word itself: "theragnostics". Even by only reading or pronouncing it, the term immediately recalls two separate words, that have been fused together: "therapy" and "diagnostics". In fact, the main goal of this nuclear medicine branch is exactly this: by the employment of specific drugs, called radiopharmaceuticals, it is possible to firstly diagnose the presence of a precise condition, then treat it with other radiodrugs. In synthesis, if we want to summarize this concept in a "mantra", the latter would be: "*see what you treat and treat what you see*".

Theragnostics originates in the Forties, so this is not a new conception at all, but during last decades the interest in this research field has grown up very rapidly, because of its potential applications, from oncological diseases (e.g. neuroendocrine neoplasms) till non-oncological conditions (e.g. sarcoidosis or Grave's ophthalmopathy). (2)

The first example of a theragnostic approach in nuclear medicine is represented by thyroid diseases, in particular iodine-capturing tumors. Dr. Hertz, in 1941, was the first physician that thought and succeeded in the utilization of radioiodine in former tumors' treatment, with encouraging results. (3)

For these reasons, the theragnostic approach is so much fascinating thanks to its hidden potential, even if it is exploiting more and more, nowadays. (4)

Beside thyroid applications, theragnostics is a pivotal strategy in neuroendocrine tumors (also known as NENs or NETs), but further application are affirming in clinical practice, as we will describe later: hepatic and prostatic cancers are only some examples, because, as aforementioned, there are also several benign conditions that enjoy this kind of approach, such as sarcoidosis, thyroid associated ophthalmopathy (in Basedow-Graves thyreopathy), rheumatoid arthritis, histiocytosis and, finally, idiopathic pulmonary fibrosis. (5)

In this paper, we are going to describe current theragnostic approaches in several diseases, mainly oncologic ones, starting from neuroendocrine tumors, then debating about differentiate thyroid tumors, pheochromocytomas/paragangliomas and neuroblastomas, castration-resistant prostate cancers and, in conclusion, hepatic tumors.

PRINCIPLES OF THERAGNOSTICS

What makes theranostics very exciting is the way it works: it makes advantage of functional and molecular characteristics of diseases, targeting specific molecules/receptors that are expressed by certain cells in order to bind them (through radiopharmaceuticals) and, firstly, localizing them: in this way, the first moment of the path is realized, in other words the diagnostic phase. Thanks to the correct radiodrug combined to nuclear medicine

machineries (such as scintigraphy, SPECT or PET), wherever the target of the pharmaceutical is present, it will be bound and localized, thanks to the emission of a signal (represented by radiations that the machinery is able to intercept). (6-11)

Later, the therapeutic phase: once it has been demonstrated the presence of molecular targets and evidence of disease are clear, it is possible to define the patient as "suitable" for the next step. In fact, using the same radiopharmaceutical, it is possible to convert the latter in order to give it a therapeutic action simply by substituting its radionuclide. This step outlines the so-called **PRRT**, i.e. Peptide Receptor Radionuclide Therapy. (12-17)

Different radionuclides cover different roles, because they are not equal to each other from a physical perspective: depending on the radiation they are able to emit, they can be employed in diagnostic or therapeutic procedures. (18) More precisely, α- or β^--emitting radionuclides constitute the radioactive component of diagnostic radiopharmaceuticals (also definable "radiotracers"), while isotopes emitting γ-rays or β^+ particles are perfect for therapeutic purposes. (19)

We can affirm that the prodigious nature of theragnostics lies into radiopharmaceuticals and their mechanisms of action, which is based on functional/molecular characteristics of targeted cells. So, the question is spontaneous: what exactly are radiopharmaceuticals?

This kind of drugs is constituted by several components, each one with a specific role. Mainly, we can synthetize its composition as following:

- A **binding molecule** (or, simply, a ligand): this component is a molecule able to bind other molecules that are expressed on targeted cells. To better explain that, let's refer to neuroendocrine tumors (NETs): these neoplasms, in majority of cases, overexpress a particular membrane receptor called SSTR (or somatostatin receptor). Using radiopharmaceuticals constituted by radiolabeled SSAs (somatostatin analogues, i.e. peptides that mimic somatostatin's structure and activity) is it possible to allow them to bind SSTRs, in order to interact with the cell, with the purpose of internalizing the drug itself and allowing its accumulation inside the cell (meaning that it collects radiations, too).
- A **radionuclide**: as aforementioned, they can be α-, β^+-, β^-- or γ-emitters, everyone with its physical characteristics, like half-life, and they are all suitable for specific purposes (diagnostic or therapeutic ones). At this point, we can observe the prodigy happen: if we have a certain molecule that is able to bind a molecular target, reporting its presence in a specific malady condition, we can use this ligand in combination with different isotopes in order to diagnose or treat a disease: the best example is represented, again, by tumors like NETs. In these cases, the employment of a β^+-emitting radionuclide (like ^{68}**Ga**) coupled with SSAs allows the individuation of neoplastic cells expressing SSTRs. Later, once the patient has been studied and staged, it would be suitable for a treatment based on radionuclide-labeled molecules that could kill those cells using the same mechanism adopted during the diagnostic phase: in fact, today, we can use ^{177}**Lu**-labeled SSAs to specifically target SSTR-overexpressing NETs' cells (this isotope of lutetium is a β^- emitter). In conclusion, using the exact same molecule labelled with different radionuclides in different clinical phases, it is possible to realize a theragnostic approach to a specific disease. (20)
- A **bifunctional chelator** (BFC): a chelator is a molecule that acts as a bridge between the ligand and the radionuclide, simply making a connection with them. The choice of a chelator is crucial in terms of pharmacokinetics, because it can deeply influence it. At this purpose, sometimes an additional molecule is intercalated into the drug's structure, it is called "**spacer**": it is usually employed with the purpose of modifying pharmacokinetic aspects of the

drug. Having the purpose to propose a BFC example, we need to go back to SSAs employed in NETs: the most utilized chelator in this context is DOTA (we will talk about it more in-depth later), realizing a connection between the radionuclide and the SSA itself. This is the way "DOTA-peptides" (where "peptides" stays for somatostatin analogues, in this case) are structured and they represent, today, the first choice in theragnostics applied to NETs, in combination with ^{68}Ga and ^{177}Lu. (21)

PRRT requires the injection of radiopharmaceuticals. The administration of the drug can occur in different modalities, more precisely through an intravenous or locoregional injection. The first approach is currently the most utilized. (22)

First things first, prepare the patient to receive the pharmaceutical. Once its administration has been performed, the drug distributes among the entire body. Every area or structure that shows the molecules that can be bound by the radiotracer will be depicted, thanks to the interaction between the former and the specific receptor the drug is designed for, usually it is represented by a membrane receptor overexpressed (or typically expressed) by targeted cells. The formation of the radiotracer-receptor complex activates a molecular pathway that ends with the internalization of the former (through an endocytosis process): thus, this phenomenon allows the entrance of the drug (and subsequently of radionuclides, source of radiations) inside the cell, implying its cytoplasmatic accumulation. The event is at the base of structural cell damage, due to the radiations themselves, causing irreversible DNA breaks and other sort of integrity losses, bringing to cellular death.

In conclusion, there is an important concept that needs explanation: the internalization process is, today, a pivotal concept in the therapeutic field, since its actuation allows the collection of sufficient amount of intracellular radiations in order to cause cell death; regarding diagnostic purposes, instead, the internalization process is not so fundamental and the reason is quite simple: once the radiotracer binds its target, the former still acts as a signal source till its connection persists, even outside the cell itself, because in this situation the only task of the drug is to allow the localization of targeted cells and this happens independently by its internalization. (23)

Following, we will discuss more in-depth about single diseases, with the intention to outline an overview on current theragnostic approaches available.

NETs AND PRRT

Neuroendocrine tumors (NETs) represent one of the most important examples in theragnostic field, because most of the researchers' efforts have been concentrated in this context, especially in order to define an efficient therapeutic approach in metastatic/advanced conditions, which could not contemplate surgery as a definitive treatment (that represents the main therapeutic strategy in well differentiated and non-metastatic patients). (24)

GEP-NENs (GastroEnteroPancreatic NENs) are by far the most frequent entities: in particular, pancreatic localization is also the most frequent location. From an anatomopathological point of view, they are distinguished in "functional" and "non-functional" tumors, depending on their hormone secretion capability: in this context, functional PNETs (Pancreatic NETs) are able to secrete insulin, gastrin, glucagon, serotonin, VIP (Vasoactive Intestinal Peptide), ACTH (AdrenoCorticoTropic Hormone), somatostatin; high blood levels of these peptides are crucial in determining the related clinical picture, configuring a typical endocrine syndrome. (25)

One of the most important characteristics of NETs is the overexpression of somatostatin receptors (SSTRs): the discovery of these biological aspect has completely revolutionized the diagnostic and therapeutic approach of these diseases, allowing the realization of a theragnostic approach. (26) SSTRs are 7-domain transmembrane receptors, also

known as GPCR (G-Protein Coupled Receptors). Five different subtypes of SSTRs have been identified (SSTR-1, SSTR-2, SSTR-3, SSTR-4, SSTR-5);(27) researchers have defined their unique characteristics, especially in terms of ligand binding affinity and internalization of the ligand-receptor complexes (through an endocytic process), so it is important to stress the conception that they are not equale to each other. (28) In NETs, SSTR-2 is the subtype most frequently overexpressed (even if there are some exceptions, like insulinomas and high-graded neoplasia that show the "escape phenomenon", which consists in the lack of expression of these receptors on their membrane surface). (29)

SSTRs are physiologically bound by somatostatin, activating the receptor. (30) When this bond takes place, several effects are mediated in terms of cellular biological and metabolic activity, thanks to pleiotropic effects regulated by the receptor itself: it is able to inhibit cell's hormone secretion, gastrointestinal motility and cellular growth, too. (31)

Today, SSTRs cover a pivotal role in theragnostics because they are used as targets for radiopharmaceuticals, both in diagnostics and therapy, but there is more: thanks to the inhibiting actions of somatostatin receptors (when activated), their pleiotropic regulative effects are also utilized to control both clinical signs and symptoms, in addition to the tumor growth. All these results have been reached thanks to the development of a particular class of drugs, called SSAs (Somatostatin Analogues): these peptides mimic both the structure and the biological activity of somatostatin, even being different from a molecular point of view. (32-34) They present several pharmacokinetic differences that make them a better choice in terms of half-life, whereas they preserve the agonistic action towards SSTRs. SSAs are employed in therapeutic strategies both as "cold" and "radiolabeled" drugs. (35)

In the first case, they simply have to act as long-acting ligands in respect to SSTRs, triggering their inhibiting effects on neoplastic cells, controlling tumor growth and hormone secretion (especially in functional lesions).

Radiolabeled SSAs, instead, represent the core of theranostics applied to NETs: using the same ligand (i.e. the peptide that acts as a somatostatin agonist) that targets the same molecule (SSTRs), it is possible to realize a diagnostic investigation or a therapeutic act, simply choosing the most adequate radionuclide, depending on the purpose of the medical act desired. The first SSA ever widely employed in clinical applications was octreotide, both as cold and radiolabeled drug, but also other molecules have been proposed: lanreotide, as an example, is another largely used "cold SSA".

Focusing on nuclear diagnostics, ^{111}In-DTPA-octreotide (also known as ^{111}In-pentetreotride or OctreoScan® or OCT) has been largely used in combination with scintigraphy (i.e. SRS or Somatostatin Receptor Scintigraphy). This radiopharmaceutical shows a high affinity towards SSTR-2 (and a lower one with SSTR-3/-5, whereas other SSTR subtypes are not bound at all). OctreoScan®-based SRS has been largely employed as a diagnostic investigation in order to demonstrate SSTRs' overexpression in suspect lesions, making possible the subsequent utilization of cold SSAs and PRRT. (36-37)

Later, other radiopharmaceuticals have been introduced, representing today the gold standard in diagnostics of well-differentiated NETs: ^{68}Ga-DOTA-SSAs, consisting in DOTA-TATE (^{68}Ga-DOTA-Tyr3-octreotate), DOTA-TOC (^{68}Ga-DOTA-Tyr3-octreotide) and DOTA-NOC (^{68}Ga-DOTA,1-Nal3-octreotide). They allowed a significant progress in diagnostic accuracy, especially in combination with hybrid techniques (PET/CT and SPECT/CT), meaning they provided a great improvement in both sensitivity and specificity. (38-46) After the identification of receptor expression, these drugs have been adequately modified in order to act as therapeutic drugs: the substitution of ^{68}Ga with ^{90}Y or ^{177}Lu makes the radiocompound suitable for PRRT. At this purpose, we can report **Lutathera®** (**^{177}Lu-DOTA-TATE**) as the first radiopharmaceutical approved by both FDA (Food and Drug Administration, in America, in January 2018) and EMA (European Medicines Agency, in 2017) in peptide receptor

radionuclide therapy of progressive GEP-NETs: its administration is fractioned into 4 cycles with 7.4 GBq of fixed activity, with an interval of 8 weeks between each cycle. The approval of this drug represents the result of more than 20 years of studies and researchers' efforts in the demonstration of good outcomes regarding PRRT as an efficient therapeutic strategy in NENs. (47-50)

Currently, NENs' PRRT makes advantage of two radionuclides, mainly: ^{90}Y and ^{177}Lu, even if other experimentations have been led in the past, but with unsatisfactory results. (51)

^{90}Y-DOTA-TOC was an early-adopted radiopharmaceutical employed in clinical practice. ^{90}Y has been chosen for its physical characteristics, such as E_{max}: 2.27 MeV, max range of 11 mm, a half-life of 64 hours. The drug bases its action on the SSA DOTA-TOC to selectively bind targeted cells, allowing the subsequent internalization of the radiopharmaceutical through the stimulation and activation of SSTR-2; there is more: a "cross-fire effect" has been described, meaning that the radiocompound showed the capability to target both targeted neoplastic cells in addition to neighboring malignant tissue. ^{90}Y-DOTA-TOC is administered via an intravenous injection and its main side effect (that represents also its main limit) is nephrotoxicity, due to renal parenchymal retention, that is a phenomenon able to cause chronic renal insufficiency as a consequence of prolonged tissue irradiation: this condition limits the administrable dose to 25-27 Gy, as a threshold. In contrast, several advantages have been enlightened with the co-administration of positively-charged amino acids, together with the radiopharmaceutical: outcomes provided by several studies have shown how this practice can reduce renal parenchymal damage. (52,53)

^{177}Lu-DOTA-TATE is a more recent radiopharmaceutical employed in PRRT, making advantage of ^{177}Lu physical characteristics, a β- and γ-emitting radionuclide (thanks to the latter characteristic, it allows also post-therapy dosimetric studies): E_{max}: 0.49 MeV, maximum range of 2 mm and a half-life of 6.7 days).

This radiocompound has been compared to ^{90}Y-DOTA-TOC, reporting stimulating results in NET therapy, especially thanks to their tolerable toxicity profiles. (54,55)

It is important to report hematotoxicity (1% of cases neutropenia, 2% thrombocytopenia, 9% lymphopenia) of grade 3 and 4, according to CTCAE, i.e. Common Terminology Criteria for Adverse Events, together with not severe renal toxicity, even if it was described anyway; furthermore, this initial impaired renal function did not impact PFS. Another important aspect was represented by QoL (Quality of Life) findings: PRRT group recorded a longer period of time before the appearance of deterioration phenomena, such as global health status worsening, mental stress related to disease and symptoms (like diarrhea).

IODINE THERAPY IN DIFFERENTIATED THYROID CARCINOMA

From an historical point of view, the application of radiolabeled drugs in diagnostic and therapeutic strategies was adopted for the first time in the management of thyroid diseases, in particular thyroid neoplasms.

Thyroid carcinomas are distinguished in several types, basing on their histological aspect: there are differentiated tumors (papillary and follicular carcinomas, that are also the most frequent variants, arising especially in women, showing two different incidence peaks, one around 20-30 years and another in older patients) and undifferentiated ones (anaplastic carcinoma of the thyroid, more often diagnosed in older patients, representing the most malignant variant); just as a side note, there are also other types of neoplasms that can arise in this endocrine glans: medullar thyroid cancer (a neuroendocrine tumor), thyroid lymphomas and metastases. (56)

Surgery represents the first-choice treatment, because in this way it is possible to remove a portion of the gland or the entire thyroid (partial or

total thyroidectomy), depending on the best risk/benefit ratio of a specific patient and the specific type of lesion. Nevertheless, surgery not always results in an appropriate radical outcome, meaning that some residual neoplastic tissue could be left involuntarily in place. (57)

Basing on the rationale that thyroid gland internalizes iodine in order to synthetize its hormones (T_3, or triiodothyronine, and T_4, or tetraiodothyronine or thyroxine), a treatment that utilizes radioactive iodine as a therapeutic option took place, also known as **RAI** (i.e. RadioActive Iodine therapy), configuring the first (and oldest) example of theragnostic approach with cancer.(58)

As ATA (American Thyroid Association) reports, RAI with ^{131}I configures a valid adjuvant therapeutic strategy in intermediate- and high-risk patients, to whom this treatment is usually recommended for.

So, we can affirm that the theragnostic approach, in differentiated thyroid carcinomas, is represented by the combined employment of ^{123}I in diagnostics, in order to find neoplastic residuals into the thyroid bed (after surgery), thus to define patients as eligible for ^{131}I therapy, able to kill residual neoplastic cells. (59)

An interesting debate regards the conception of radioactive iodine "fixed-dose", an empirical approach that ends with the possibility to underestimate or overestimate the best dose for the patient, leading to the assumption that a "personalized dosimetry" represents a far better strategy in order to maximize benefits (especially the delivery of radiation to the targeted tissue) and minimize side effects (such as the irradiation of non-targeted tissues), in addition to make a cost-effective choice in terms of drug utilization. (60) The choice between these alternatives as the best treatment choice is still in debate.(61)

MIBG IN NEUROBLASTOMA AND PHEOCHROMOCYTOMA/ PARAGANGLIOMA

Neuroblastoma (NB) is a neoplasia originating from primordial sympathoadrenal cells of neural crest, able to arise from every location among sympathetic system, especially sympathetic paraganglia and adrenal medulla (which can be considered as a peculiar sympathetic ganglion secreting adrenaline and noradrenaline into the blood stream). It is also the most frequent solid tumor in children, even if is considerable as a rare disease (one case on 8000 live births), distinguished in low, intermediate and high-risk lesions depending on their peculiar biological and clinical characteristics, as defined by COG (Children's Oncology Group). It is responsible of 13% of pediatric deaths related to malignant neoplasms, maintaining its prognosis poor despite progress reached into its therapeutic approach.

Otherwise, pheochromocytoma and paraganglioma are neoplasms originating from chromaffin cells, localized especially in paraganglia and adrenal medulla (so, the difference with neuroblastoma lies mainly in the type of cell that undergoes to neoplastic transformation). These neoplasms are far more common in adult patients, plus hereditary conditions, like Multiple Endocrine Neoplasia (MEN) type 2A and 2B. (62)

In this context, theragnostics is a very useful approach: it bases on the employment of MIBG (MetaIodoBenzylGuanidine), that is a norepinephrine analogue, meaning it can be internalized by sympathetic nervous cells, thanks to its catecholamine-mimicking behavior. Labeling MIBG to a radionuclide, in particular iodine isotopes (^{123}I and ^{131}I), allows it to act as a diagnostic or therapeutic radiopharmaceutical.

First ^{131}I-MIBG was employed in scintigraphy applied to benign and malignant lesions in adrenal medulla, soon enlightening its usefulness in pheochromocytoma, a neoplasm that, as neuroblastoma and paraganglioma, metabolizes catecholamines, allowing its visualization. Later the involvement of ^{123}I-MIBG provided even better results in scintigraphy, largely used in both diagnosis and follow-up of patients. The subsequent introduction of hybrid techniques (SPECT/CT) made further progress in localization of lesions, allowing the collection of more detailed and accurate information in about 39% of cases investigated with scintigraphy only. (63)

Theragnostics in neuroblastoma takes advantage of ^{123}I as a diagnostic tool and ^{131}I in radionuclide therapy. It is important to enlighten that ^{123}I and ^{131}I have superimposable performance in imaging, but ^{123}I is not able to outline cerebellar uptake, whereas ^{131}I does. Furthermore, ^{131}I-MIBG (alone or in combination with other drugs) is utilized to treat or down-size neuroblastomas (relapsed or chemorefractory lesions), providing a response rate of 20-40%, in children; in addition, it is employed in the treatment of pheochromocytoma and paraganglioma, in adults.

Moreover, the *in vivo* demonstration of radioiodine uptake with ^{123}I is crucial for the subsequent treatment with ^{131}I-MIBG. At this regard, a very stimulating approach is represented by ^{124}I-MIBG in combination with PET/CT, thanks to its nature of positron-emitting radionuclide; in addition, it could also be very useful in terms of calculating patients' dosimetry respecting the criteria of MIRD (Medical Internal Dosimetry), establishing the maximum dose the patient is able to bear basing on body weight. (64)

CASTRATION RESISTANT PROSTATE CANCER

The most frequent tumor in men is represented by prostate cancer (PC), even if it is not the first cause of death related to neoplastic disease in the world, instead the latter is represented by lung cancer (determining about 24% of deaths in men affected by neoplasms in the world).

An old adage, very common among physicians of the last century, recites "men die *with* cancer tumor, but *not because of* cancer tumor". This conception stresses the idea that this neoplasm tends to be slowly progressive, even if there are some cases that make the therapy very complicated, due to their spread in the organism and/or treatment-resistant behavior.

Prostate cancer is mainly an adenocarcinoma, usually arising in the peripheric zone of prostate (lateral lobes) there is to say the richest portion of the gland in adenomeres.

The progression of the disease, as aforementioned, is usually slow, requiring even ten years between its onset and the appearance of clinically evident signs and symptoms, due to local and distant infiltration. The neoplasm tends to metastasize through a hematogenic and lymphatic dissemination, mainly reaching lungs, liver and bones (typically determining osteoaddensant lesions), in addition to other extraprostatic sites. Diagnosis is made through PSA evaluation, digital rectal examination, transrectal ultrasonography, multiparametric MRI and biopsy (for definitive diagnosis). (65)

Therapy of PC strictly depends on patient's staging, as it typically happens with neoplastic diseases. Surgery is obviously the most efficient strategy in localized cases (the cancer is limited only to the prostate, neither involving the capsule), represented by laparoscopic radical prostatectomy; therefore, it is not always feasible, such as in locally advanced and metastatic patients. Radiotherapy (and brachytherapy, a particular radiation-based technique) is another effective treatment, reserved for more advanced cases (locally advanced diseases and localized PC patients judged as "unfit" for surgery). Recent advances in surgery have led to robotic techniques, representing the most advanced procedure in terms of precision, efficacy, post-operative course and low complication incidence: the latter opens also new futuristic scenarios of "telemedicine", allowing the surgeon to perform the intervention even if he is in a completely different place in respect of the structure hosting the robot. In metastatic patients, surgery is an absolute counterindication, so a medical treatment is required: androgen-deprivation therapy (ADT) is the first line approach (i.e. LHRH analogues), such as buserelin, goserelin and leuprolide, realizing a chemical castration in order to stop the production of the hormones that represent the neoplastic hormonal stimulation to proliferate. Unfortunately, there is the possibility that these cancers do not respond to this first line strategy, configuring the state of "castration resistant prostatic cancer" (CRPC): this condition leads to alternative therapeutic options, substituting androgen-deprivation drugs with hormonal therapy,

represented by abiraterone, enzalutamide; eventually, chemotherapy is considerable (i.e. docetaxel) if the former do not provide a significant outcome. (65)

But how theragnostics takes place in prostate cancer context?

The first application of nuclear medicine techniques in diagnostic procedures related to PC was represented by **^{111}In-capromab pendetide** (ProstaScint®), a radiolabeled monoclonal antibody (MoAb) that targets the intracellular portion of a prostatic cell's specific membrane molecule, there is to say PSMA (Prostatic-Specific Membrane Antigene). The main utilization of this radiopharmaceutical is represented in patients displaying neoplastic recurrences after surgery or radiotherapy, which usually show an increase of PSA levels (meaning the neoplasm widely restarts proliferating).

Researchers naturally continued the theragnostic approach realizing the MoAb **^{90}Y-CYT-356**, another radiopharmaceutical targeting the same molecule of capromab, there is to say the intracellular epitope of PSMA, this time conjugated with a β^--emitting radionuclide.

As a last note, the use of monoclonal antibodies showed a certain immunogenicity inclination, so the sum of all these disadvantages ended in considering MoAb-based radiopharmaceutical inadequate with the utilization purpose in therapy and imaging, although they displayed encouraging results in the latte field.

The real change arrived with **^{68}Ga-PSMA-HBED-CC** (also known as PSMA-11), a drug that belongs to PSMA inhibitors, capable to bind, this time, the *extracellular portion* of the prostatic-specific membrane antigen expressed on neoplastic cells, outlining new potentials regarding this class of radiopharmaceuticals applied to CRPC. Today, even if other similar radiodrugs have been synthetized, **^{68}Ga-PSMA-11** is still the most diffused one in its category, especially in PET/CT imaging. (66)

Since CRPC has shown to be an aggressive neoplasm, alternative treatments have been elaborated in metastatic conditions, when neither androgen deprivation therapy nor chemotherapy, hormonal treatment or the more recent sipuleucel-T (cellular therapy) work. Speaking of symptomatic bone metastatic lesions, **^{223}Ra-dichloride** (Xofigo®) is a radiopharmaceutical designed for this therapeutic purpose, but its application is very limited, since it is effective only with this exact type of lesion's localization, making it useless in patients with visceral metastases.

The turning point has been represented by **^{177}Lu-PSMA-617**, constituting the so-called RLT (RadioLigand Therapy), allowing significant improvements in CRPC patients. (67)

To realize the theragnostic approach, it is necessary to demonstrate that the neoplasm would be responsive to therapeutic radiopharmaceuticals through a previous investigation utilizing diagnostic ones: this is the reason why ^{68}Ga-PSMA uptake is evaluated with PET/CT in order to candidate the patient to RLT with ^{177}Lu-PSMA-617; once this response is observed, the patient can be enrolled to the subsequent therapeutic phase.

In conclusion, also prostate cancer, nowadays, is taking advantage of theragnostic approaches, even if it is not standardized yet, since more studied are needed in order to totally define their influences and changes in clinical and prognostic aspects, especially in CRPC. (68)

RADIOEMBOLIZATION OF HEPATIC TUMORS

Liver is one of the most involved organs in metastatic processes, especially by metastatic neoplasms originating from gastrointestinal tract, since the venous drainage of these viscera reaches the portal vein, allowing metastatic neoplastic cells reaching hepatic sinusoids and here they start proliferating in order to create new solid lesions.

Liver metastases represent also the most frequent type of malignant neoplastic lesions in the liver itself and, as it happens with HCC (HepatoCellular Carcinoma), they are usually irrorated by new branches originating from hepatic artery through neoplastic neo-angiogenesis. At this regard, it is important to remember the double vascularization of the entire organ, represented by the hepatic artery itself (responsible of about 20% of

blood supply) together with portal vein (about 80% of hepatic blood supply). So, malignancies tend to be vascularized by hepatic artery, while healthy parenchyma is supplied by portal vasculature.

Thanks to this characteristic vascularization, two techniques have been developed to act as locoregional approaches to primary and secondary neoplastic lesions: **SIRT** (Selective Internal Radiation Therapy) and **TARE** (TransArterial RadioEmbolization). (69)

The theragnostic approach applied to SIRT/TARE is realized through two main phases: firstly, a preventive angiography is performed, aimed to study the anatomy of mesenteric system and hepatic arterial vasculature, using ^{99M}Tc-MAAs (^{99M}Tc-MacroAggregated Albumin); secondarily, a different radionuclide is involved, i.e. microspheres containing ^{90}Y.

^{99M}Tc-MAAs are radiolabeled albumin macroaggregated that are directly injected into a selective branch of hepatic artery, with the purpose to depict a suspicious lesion among hepatic parenchyma. Several evidences have shown the role of ^{99M}Tc-MAAs as a predictive biomarker, since it has been judged as a valid surrogate marker of ^{90}Y-microspheres; in this way it is possible to evaluate the distribution of the radiotracer into liver, lungs and gastrointestinal tract without irradiating the patient with β^- particles (that would be inappropriate at this step). This approach is made possible thanks to physic-chemical characteristic of radiolabeled albumin macroaggregates, even if they are not identical to resin/glass microspheres(70)

Once the lesion demonstrates to be responsive to albumin macroaggregates, it is time to pass to the next phase: at this point, it is possible to address radioactive isotopes straight to the lesion (utilizing its same arterial vascularization) with SIRT/TARE: this step bases on the locoregional administration of **^{90}Y-embedded microspheres**. ^{90}Y, an already presented β^--emitting radionuclide, is incorporated into microspheres made of *resin* (SIR-Sheres®) or *glass* (TheraSphere®), then they are injected into a catheter previously placed into a selective hepatic artery branch, in order to allow them to reach the lesion; as a side note, they present slightly different activity and physical/mechanical properties, but their clinical efficacy (as trials have demonstrated) is very similar. (71)

Recently, another type of microsphere has been elaborated: **^{166}Ho-PLLA-MS** [^{166}Ho embedded into poly(l-lactic acid) microspheres]. The peculiar physical characteristic of ^{166}Ho is its β^--and γ-rays-emitting properties (respectively 1.77 MeV and 80.57 keV), making this radionuclide very suitable for a theragnostic approach, since its β^--particle emissions are useful in a therapeutic perspective, whereas its γ-rays-emissions are very useful for imaging, in particular for scintigraphy and for dosimetry, too. But that is not all: this isotope also displays paramagnetic characteristic, meaning these microspheres are also eligible for application with magnetic resonance imaging (MRI), even for dosimetry. This new type of microspheres is the object of study of two main trials: (72)

- *HEPAR*, a phase I study that involves 15 patients affected by liver metastases and treated with TARE using ^{166}Ho-PLLA-MS, establishing that the maximum tolerated dose for the whole liver is 60 Gy; otherwise, several important adverse effects tend to show up: thrombocytopenia (grade 4 according to CTCAE), leucopenia (grade 3), hypoalbuminemia (grade 3), abdominal pain (grade 3).
- *HEPAR PLUS*, a phase II study trial with the purpose to legitimate ^{166}Ho-PLLA-MS in clinical practice and its usefulness, through the evaluation of tumor partial or complete response to the treatment, according to RECIST 1.1, not neglecting adverse effects and toxicity. Additionally, this study considers the administration of ^{166}Ho-RE within 20 weeks after the last PRRT cycle (constituted by 7.4 GBq of ^{177}Lu-DOTA-TATE) to the included patients.

NEW FRONTIERS IN THERAGNOSTICS

Since the field of radiopharmacy is continuing evolving, it is estimated that, in next years, results will be even more significant regarding nuclear medicine progresses. Following, there will be

presented some new radiopharmaceuticals and approaches.

^{64}Cu is a radionuclide that is finding application in some neoplastic disorders, such as prostate cancer and melanoma, because these tumors overexpress CTR-1 (human Copper Transporter 1). The latter is a transmembrane protein able to internalize copper into the cell, since copper is a pivotal element in several cellular activities, i.e. cell differentiation, growth and metabolism. ^{64}Cu is produced through a cyclotron, characterized by a half-life of 12.7 hours and positronic- and β-particles emission, a feature that makes it appropriate for a theragnostic employment: all these aspects brought to the synthesis of $^{64}CuCl_2$, acting as a substrate for CTR-1, a radiopharmaceutical currently under investigation in some trials assessing its efficiency in prostatic cancer and melanoma. (73)

Targeted alpha therapy (TAT) is a nuclear medicine radiotherapy technique that takes advantage of the effects created by α-particles emitted by specific radionuclides, in order to irreversibly damage targeted cells (usually neoplastic ones), causing their death: α-particles are able to produce severe chromosomal damage, DNA double-strand breaks, oxygen-independent tumor cell destruction. Additionally, they can represent an alternative to β$^-$-emission resistance showed by certain neoplastic lesions, even if α-emitters provide a shorter range of radiation range (tissue penetration) compared to the former.

By the moment of writing this paper, **^{223}Ra-dichloride** is the only clinically approved radiopharmaceutical capable of α-emission.

In neuroendocrine neoplasms, **^{213}Bi-DOTA-TOC** displays promising results in patients who resulted resistant to PRRT based on ^{177}Lu-DOTA-TATE.

In castration-resistant prostatic cancer, patients in which therapy with ^{177}Lu-PSMA-617 fails are investigated to define the advantages of radioligand therapy based on **^{225}Ac-PSMA-617**. (74)

EGFR (Epidermal Growth Factor Receptor) is a particularly interesting molecule in oncologic field. Since its overexpression has been described in several epithelial neoplasms, such as lung and breast cancer, this receptor has been at the center of researchers' attention: several inhibiting monoclonal antibodies have been synthetized, then they have been radiolabeled in order to realize **^{64}Cu-DOTA-cetuximab** and **^{111}In-DOTA-cetuximab**. Their employment in nuclear imaging, such as in combination with PET and SPECT, represents a crucial investigation technique aimed to demonstrate *in vivo* overexpression of EGFR itself in lesions. Unfortunately, the biochemical nature of these radiodrugs constitutes one of their most important drawbacks, especially considering their immunogenicity.

Subsequently, the introduction of aptamers represents the attempt to go beyond the former MoAbs' limitations. **Aptamers** are single-stranded oligonucleotides of DNA/RNA, obtained through SELEX® technology (i.e. Systematic Evolution of Ligands produced through EXponential enrichment). The major advantages are represented by low immunogenicity (fixing one of the major disadvantages of radiolabeled MoAbs) together with high target specificity. Currently, aptamers seem to be a promising theragnostic strategy, although other studies are needed to better test their possible applications and clinical advantages, but specifically regarding EGFR, recently has been developed **^{18}F-RNA aptamer**: this radiopharmaceutical has been tested in mice models affected by tumors expressing different EGFR densities, reporting highly specific targeting capabilities. (75)

CONCLUSIONS

The main goal of theragnostics is the capability of combining diagnostics and therapy utilizing the exact same molecule or, alternatively, two very similar molecules, able to bind the same target: simply changing the labeled radionuclide (or the administered dose of the radiopharmaceutical without substitute its isotope), the molecule (or the molecules) acquire very specific purposes (i.e. diagnostic or therapeutic tools). This field is

outlining a more and more consistent "personalized medicine" conception, finally focusing on the individual, on the patient, rather than on the disease itself.

Furthermore, theragnostics has the opportunity to put nuclear medicine in deep connection with oncology, internal medicine and other branches, in order to help earlier and more precise individuation of diseases to better clinically manage patients, potentially revolutionize several fields.

Even if further studies are needed in order to properly legitimate some new theragnostic strategies into clinical practice, the path is traced, leading also towards a new and innovative approach to medicine, with the main goal of improving people's quality of life.

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