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Editorial

Quo Vadis, Teragnosis?☆

It wouldn't be correct to say that theragnosis, or the use of molecules bound to radioactive isotopes for diagnosis and treatment, is a new therapeutic tool for treating diseases in nuclear medicine. This concept has been used in nuclear medicine for more than 7 decades thanks to the pioneer work of a physician called Saul Hertz and the physicist Arthur Roberts who used radioactive iodine (131I) in the Massachusetts General Hospital in the United States to treat patients with hyperthyroidism.[1] However, the term theragnostics was likely coined decades later by J. Funkhouser.[2]

Theragnosis is not exclusive to nuclear medicine since the concept refers to any combination of diagnostic and therapeutic modalities and for any disease. One of the well-established focuses of theragnostics is, for example, the selection of patients with breast cancer who are candidates for a specific treatment with antibodies against the human epidermal growth factor receptor 2 (i.e., trastuzumab) using immunohistochemical staining for these receptors.[3]

However, it is clear that we should take advantage of the momentum. This is the new golden era in nuclear medicine, which could also be called the renacimiento rebirth- o - revival -o-renaissance,[4] if I could be so bold.

Investment into new nuclear medicine equipment and especially in the development and approval of new radiopharmaceuticals for theragnostic purposes is facilitating the advancement of our specialty.

Peptide receptor radionuclide therapy (PRRT) with somatostatin analogs has been used for two decades in the treatment of well differentiated neuroendocrine tumors (NET) that express the receptors of somatostatin. The promising results of the phase III NETTER-1 clinical trial[5,6] in patients with small bowel NETs treated with lutetium-177 (^{177}Lu) have undoubtedly helped promote the concept of theragnostics. PRRT in this group of patients improves the quality of life of these patients, as well as the rate of objective response and survival. The results of the first analysis of this clinical trial[5] led to approval of the use of [^{177}Lu]Lu-oxodotreotide ([^{177}Lu]Lu-dodecanetetraacetic acid - tyrosine-3-octreotate [DOTA-TATE]) by the European Medicines Agency (EMA) in 2017.

Despite these good results, there is still debate as to its utility in other tumors such as pancreatic NET (pNET), paragangliomas, and pheochromocytomas, among many others. The controversy lies in the scarce scientific evidence published to date. Although the use of this type of treatment in many national and also international centers has been expanded to other tumors or indications, largely based on the guidelines of different scientific societies,[7–9] there are few phase III clinical trials involving PRRT. One of the most interesting study including this treatment, albeit in phase II, is the OCLURANDOM study (NCT02230176) evaluating the antitumoral efficacy of PRRT in unresectable pNET. In the Annual Congress of the European Society of Medical Oncology (ESMO 2022) held in Paris a few weeks ago, Baudin et al. presented the results of the first analysis in 84 patients in which patients were randomized (1:1) to receive either [^{177}Lu]Lu-DOTA-TATE or treatment with a multikinase inhibitor known as sunitinib. The primary endpoint evaluated was progression-free survival at 12 months. The first data have shown light on what was already considered in different retrospective or multicenter studies in the literature but which needed to be demonstrated in a clinical trial. The primary endpoint was achieved in 80% of the PRRT group (90% confidence interval [CI]: 67.5-89.9) versus 42% in the sunitinib group (90% CI: 29.1-55.5), thereby being a positive study for PRRT.

There are currently several active phase III trials that could broaden the indications of this type of treatment in NET. The NETTER-2 (NCT03972488) clinical trial is evaluating progression-free survival in patients with NET, but with greater tumor aggressiveness (grades 2 and 3), treated with [^{177}Lu]Lu-DOTA-TATE combined with somatostatin analogs (octreotide) versus another group receiving only high doses of octreotide (60 mg). Another interesting study called COMPETE (NCT03049189) is comparing more than 300 patients with NET of gastroenteric or pancreatic origin with Ki67 $\leq$ 20% randomized into two parallel groups (1:1): the experimental arm with [^{177}Lu]Lu-DOTA-TOC ([^{177}Lu]Lu-edotreotide) versus the control group treated with everolimus, a mechanistic target of rapamycin (mTOR) inhibitor. Lastly, COMPOSE (NCT04919226) is another clinical trial which only began recruiting a few months ago. This multicenter study will evaluate the efficacy, safety, progression-free survival and overall survival of PRRT with [^{177}Lu]Lu-DOTA-TOC as the first or second line of treatment compared with the best standard treatment available (CAPTEM, everolimus or FOLFOX) in patients with well differentiated grade 2 or 3 gastroenteric or pancreatic NET. A relevant data of note in the last study is the possibility of administering up to 6 cycles of PRRT at a standard dose (7.5 GBq/cycle) versus the 4 cycles administered in other phase III studies.

There are other interesting phase I/II trials which are of special interest for evaluating the therapeutic efficacy of PRRT using different posology, method of calculating the dose and even its intervals and, of course, combinations with other treatments (NCT04375267, NCT02736448, NCT04194125, NCT03454763, NCT02754297, NCT04385992).

One of the most relevant initiatives promoted by the Spanish Society of Nuclear Medicine and Molecular Imaging (SEMNIM in Spanish) and endorsed by the Spanish Society of Endocrinology and Nutrition (SEEN in Spanish) has been the creation of a national registry of patients treated with ^{177}Lu called SEPTRALU (NCT04949282). The aim of this study is to amalgamate the clinical experience of the Spanish centers treating patients with PRRT to evaluate the efficacy, tolerance and safety of the medication in clinical practice and establish the profiles of patients and tumors treated and the results in each type of patient and tumor. The latest results were presented in the Annual Congress of the European Society of Nuclear Medicine and Molecular Imaging (EANM 2022) with the registry of 533 patients collected in 23 Spanish hospitals.[10]

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Another revolution that has recently emerged in the field of theragnosis is the use of radiopharmaceuticals for the diagnosis and treatment of prostate cancer. Compared to neuroendocrine neoplasias, patients with metastatic castration-resistant prostate cancer (mCRPC) have a bad prognosis and may present rapid tumoral progression and a greater probability of symptomatic disease.

One of the most relevant molecules localized in the tumor cells of patients with prostate cancer is the prostate-specific membrane antigen (PSMA). This consists in a type II transmembrane glycoprotein that internalizes in the cells and is overexpressed in most prostate tumors.[11] Immunohistochemistry studies have shown that the expression of PSMA is also increased in patients with dedifferentiated metastatic tumors or mCRPC. This has led to PSMA becoming a target for the development of radiopharmaceuticals for both diagnosis and treatment.

Advances in the development of positron emission tomography (PET) radiopharmaceuticals labeled with PSMA ligands were achieved with the formulation of [^{68}Ga]Ga-PSMA-11. This radiopharmaceutical demonstrated utility not only in the initial staging but also the detection of relapse of prostate cancer, presenting a sensitivity greater than that of [^{18}F]F-choline PET/computerized tomography (CT), a radiopharmaceutical that continues to be used today.[12] Recently, new radiopharmaceuticals directed at the same molecule have been developed but with a longer half-life than those derived from ^{68}Gallium.

The development of PSMA compounds labeled with ^{18} Fluorodeoxyglucose (^{18}F) has led to a significant change of paradigm in the availability of PET radiopharmaceuticals for prostate cancer. This is mainly due to the greater availability of the radioisotope ^{18}F, produced with a cyclotron, in comparison with ^{68}Ga which is eluted from a generator. In 2011, the second generation of PSMA ligands labeled with ^{18}F, [^{18}F]F-DCFPyL were introduced, becoming a promising alternative to [^{68}Ga]Ga-PSMA-11.

From the therapeutic perspective, the ligand most used is PSMA-617 labeled with ^{177}Lu, known as PSMA radioligand therapy (PRLT). While the NETTER-1 clinical trials was a fundamental study in well differentiated neuroendocrine neoplasias, the VISION (NCT03511664) trial is fundamental in prostate cancer.

The VISION study was a randomized phase III study including 831 patients with mCRPC with a median follow-up of 20.9 months. The experimental arm with [^{177}Lu]Lu-PSMA-617 (7.4 GBq every 6 weeks $\times$ 6 cycles) combined with standard of care (SOC) treatment was compared with SOC alone and revealed a significant improvement in overall survival and a significantly longer progression-free survival with the experimental treatment compared to the control group.[13] These results showing the benefits of treatment with PRLT in prostate cancer were reinforced by their presentation in the last Congress of the American Society of Clinical Oncology (ASCO 2022) in June 2022[14–16] and in the ESMO congress in September 2022.[17–21]

At present, the results of other phase I/II clinical trials are available, such as the LuPSMA prospective, phase II trial with a single arm and single center, which analyzed 40 patients treated with [^{177}Lu]Lu-PSMA-617.[22] In this trial, 57% of the patients presented a 50% or greater reduction in the prostate-specific antigen (PSA). In addition, 82% of the patients presented objective lymph node or extra-lymph node response.

Recently, in ASCO 2022, the results of another phase II clinical trial called TheraP (NCT03392428) carried out in Australian centers were presented. The objective of this study was to determine the activity and safety of [^{177}Lu]Lu-PSMA-617 versus standard treatment with cabazitaxel (1:1), which is a antineoplastic chemotherapy drug derived from taxanes. Two hundred patients with mCRPC were analyzed, showing that the study arm treated with the radiopharmaceutical obtained a greater than 50% reduction in PSA values compared to baseline in 66% of the cases versus 37% with chemotherapy. In addition, the experimental group demonstrated a 12-month progression-free survival of 19% versus 3% in the control group and objective response of 49% versus 24%, respectively [23].

Lastly, today there are some very interesting phase III clinical trials, such as PSMAddition (NCT04720157) or PSMAfore (NCT04689828), that could expand the indications of this type of treatment with PRLT in patients with prostate cancer.

In addition to these treatments in these diseases, the perspectives of the development and availability of radiopharmaceuticals with therapeutic intent or even with their theragnostic equal (the same ligand that can be bound to a radionuclide for diagnosis and to others for therapeutic use) are very promising.

To demonstrate this, in October 2022 a search in ClinicalTrials.gov, the most complete repository of the registry of clinical trials and phase I/II/III studies, was made under the search terms of ŕadionuclide therapy,́ ŕadioisotope therapy,́ ŕadioligand therapy,́ ŕadiopharmaceutical therapyänd ẗheragnosticsänd “ongoing recruitment”, “still without recruitment” and “active but without recruitment”. The search found 70 studies, the vast majority of which originated in the United States[27] and Europe.[28] Fifty-three studies used ^{177}Lu as the radioactive isotope while 9 used some alpha particle emitter (^{225}Ac, ^{224}Ra or ^{212}Pb), and many were phase I or II trials. Among these, the objective of 22 studies was neuroendocrine neoplasias, 23 were studies of prostate cancer and the remaining were on other tumors such as neuroblastomas, differentiated thyroid carcinoma, lung neoplasia, or malignant head and neck tumors. Some studies involved solid tumors of different origins using the fibroblast activation protein (FAPI) as ligands in sarcomas or other types of tumors, such as adenocarcinomas or NeoB in tumors overexpressing gastrin-releasing peptide receptors, as may occur in breast cancer, non-small cell lung carcinoma, glioblastoma multiforme or gastrointestinal stromal tumors.

The current situation is exciting not only from a scientific point of view but overall, considering the possibility of having new therapeutic tools for oncological patients.

One of the challenges we are facing is the way to treat these patients and the current capacity available in our setting. We already have a great deal of experience in the treatment of thyroid cancer with ^{131}I, which requires special installations to guarantee the minimal length of stay, especially from the point of view of radiological protection. We know that ^{131}I decays with a half-life of 8.02 days by β- and γ emitters. An important part of the ^{131}I administered to patients is eliminated via the urinary tract, making its storage in special containers for several weeks necessary. In addition, mainly due to its γ emission of relatively elevated energy, radioprotection of the patient's environment is obligatory, requiring a stay within a radioactive installation during the time recommended by the guidelines of the scientific societies and the Forum for Radiological Protection in Health Care endorsed by the Nuclear Safety Counsel, the Spanish Society of Radiological Protection and the Spanish Society of Medical Physics.[24–26]

However, as mentioned previously, the current treatments are more aimed at the use of more manageable isotopes from the point of view of radiological protection, although also with diagnostic quality (returning to the concept of theragnosis). ^{177}Lu, which is also a β- and γ emitter, has a half-life that is lower than that of ^{131}I (6.7 days vs. 8.02 days, respectively) and a lower proportion of γ emission (208 KeV and 11% vs. 364 KeV and 81% for ^{131}I). To understand the restrictions necessary when treating a patient with one isotope or another, not only the type and proportion of radiation emitted is important but also the elimination of the isotope, mainly by the urinary tract.

Different dosimetry studies published on treatments involving [^{177}Lu]Lu-DOTA-TATE and [^{177}Lu]Lu-PSMA-617 have demon-

strated that treatment is possible in an outpatient setting, requiring a minimum stay of 6-8 hours after the injection of the radiopharmaceutical in duly authorized nuclear medicine installations.[27–30] Nonetheless, the regulatory bodies of each country establish the legal limits with respect to both the dose and the activity excreted, which vary among European countries, with, for example, greater restrictions in Germany, Austria and Italy.[31]

This has led to the possibility of outpatient management in this type of treatment with ^{177}Lu, provided that the clinical management and not exclusively radiological management allows this. Nonetheless, this implies many things. In fact, in our medical community, this aspect is currently generating an intense and interesting debate.

We are likely going through a change of paradigm in the specialty of nuclear medicine. Perhaps we need a reconversion and/or investment in our installations, a commitment to different types of rooms based on the needs and type of radiopharmaceuticals used. For example, in addition to the classical admission rooms in which patients with thyroid cancer are treated with ^{131}I or pheochromocytoma with [^{131}I]I-MIBG, we need other rooms or treatment boxes based on the concept of the Day Hospital [32] with the requisite of the necessary radiological protection. Many international centers have already developed this type of outpatient rooms.

Both the EAMN and the American Society of Nuclear Medicine and Molecular Imaging (SNMMI) have recently published guidelines to facilitate the creation or reconversion of nuclear medicine services into theragnostic centers of excellence[33,34] with the aim of preparing for the demand of oncological patients and facilitating understanding among the physicians requesting these treatments, society and other interested parts, such as health care institutions, governmental entities and the pharmaceutical industry for establishing theragnosis centers of excellence.

Lastly, and no less important, is the need for training in the management of these diseases and their symptoms. Today, patients are submitted to a wide range of therapies against cancer, often under the care of a multidisciplinary team of specialists frequently including medical oncologists, surgeons, interventionist radiologists and radiotherapeutic oncologists. Nuclear medicine has played an important role on this team in the diagnostic setting thanks to scintigraphic or PET/CT studies, as well as in therapeutic decision making in patients with thyroid diseases. However, as the new radiopharmaceutical therapies become increasingly more common, the composition of these multidisciplinary teams will expand and new roles will be adopted. Nuclear medicine, should, therefore, be a key and integral part of these teams.

If nuclear medicine is to become involved and be a leader in this type of treatments and within a multidisciplinary concept, we must be willing to advance and be prepared at not only the level of infrastructure but overall in decision making in multidisciplinary committees as well as in the clinical management of the complexities of oncological patients. Specific training may be necessary for professionals devoted to therapy in nuclear medicine. Indeed, different nuclear medicine societies are already promoting this type of training in the form of fellowships or specific certifications.[35]

In conclusion, advancements in technological equipment, the development of new molecules with their theragnostic equal and the approval of treatments such as [^{177}Lu]Lu-DOTA-TATE for NET and [^{177}Lu]Lu-PSMA-617 for mCPRC are leading nuclear medicine into a new golden era which we must take advantage of. The interest in therapies with radionuclides has increased enormously. The foreseen increase in demand for these treatments as well as the need for greater investment in infrastructure and duly qualified professional personnel will be both a challenge and an opportunity for the health care systems.

The era of theragnostics provides a great opportunity for improving patient care and it is clear that theragnostics will become an important pillar in the personalized treatment of cancer. We still have an unimaginable and exciting road ahead from which our specialty will reap the rewards. It is time to ask where theragnosis is going in nuclear medicine:

Quo Vadis, theragnosis.

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José L. Vercher-Conejero
Servicio de Medicina Nuclear - Unidad PET, Hospital Universitario de Bellvitge – IDIBELL, Barcelona, Spain
E-mail address: jlvercher@hotmail.com

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