# Theranostics: Are We at a Turning Point for Nuclear Medicine?

# Teranóstico: Estamos num Ponto de Viragem para a Medicina Nuclear?

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## Introduction

The advent of theranostics (formed by merging the words therapeutics and diagnostics) is a significant event in the era of precision medicine because it allows us to understand the distribution of specific administered medications in the body, enhancing the possibility of preselecting patients who may benefit from such therapies.

In Nuclear Medicine, in particular, this concept is not new. For several decades, therapeutic interventions have been carried out, for example, targeting differentiated thyroid carcinoma with Iodine-131. This isotope not only emits negative beta radiation (cytotoxic) but also gamma radiation (which allows imaging to assess the locations where the radiopharmaceutical is taken up). Other examples include the therapy of neuroblastomas or metastatic pheochromocytomas/paragangliomas with Iodine-131-metaiodobenzylguanidine, therapy for hepatic metastases with Yttrium-90 or Holmium-166 microspheres, and, in recent years, therapies for well-differentiated neuroendocrine tumors with Lutetium-177-DOTATE or metastatic prostate adenocarcinoma with Lutetium-177-PSMA.

Radiopharmaceuticals, due to their radiation emission, not only have a distinct mechanism of action from other drugs, but also present a set of challenges and opportunities in their clinical use that are worth mentioning.

## Challenges

### Radiation handling

The need for dedicated facilities and personnel to handle radioactive isotopes and administer them safely to patients requiring therapy. In addition to potential clinical side effects, these patients must follow procedures to protect themselves and others from the ionizing radiation they emit over an extended period, which can last for several days to weeks.

### Expected field growth

The adaptation of Nuclear Medicine services in Portugal and globally must keep pace with the increasing demand for these therapies, which has been growing and could change the

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paradigm of this specialty. In particular, it is worth mentioning that Lutetium-177-PSMA (the "new kid on the block", in 2021 coming out with its first phase III clinical trial proving benefit) is indicated for a much wider amount of patients, when compared to the other previously mentioned radiopharmaceuticals.

## Opportunities

### Pre-therapeutic patient selection

A radiopharmaceutical typically has at least two essential components: a radiation-emitting isotope and a ligand that guides it in the patient's body to the appropriate uptake site. By maintaining a similar ligand but using different radioactive isotopes, it is possible, initially, to perform a diagnostic/staging exam with a gamma radiation emitter. This exam confirms that the disease in question has an affinity for the ligand, not only in a local sample but throughout the entire body, non-invasively and with a reduced dose of radiation exposure. At a later time, therapy can be performed with the same ligand but associated with a beta (or alpha) emitter isotope, which has a cytotoxic effect on target cells and thus is potentially therapeutic.

### Confirmation of administration and instant imaging

Many beta or alpha emitters also have gamma emission, allowing imaging immediately after therapy (*e.g.*, scintigraphy). These exams determine the distribution of the radiopharmaceutical throughout the body, providing immediate insight into any issues that may have arisen during its administration (*e.g.*, subcutaneous extravasation). These exams also provide some knowledge about the extent of the disease, albeit with a lesser resolution than their usual diagnostic counterparts.

### Dosimetry

Dosimetry involves calculations that allow understanding the distribution of a specific radiopharmaceutical in the body, obtaining concrete values of radiation exposure dose in various organs and irradiated lesions. Knowing these doses provides reliable and quantified knowledge of the radiopharmaceutical's distribution in the body, allowing the opportunity to adjust the activity for each patient. This may allow the maximization off the radiation exposure dose to neoplastic lesions within the safety window (AHASA principle - as high as safely administrable) or the minimization of the dose of radiation exposure to healthy organs within the therapeutic window (ALARA principle - as low as reasonably achievable).

## The Present

Although theranostics in Nuclear Medicine has been around for several decades, there has been a renewed and growing interest in recent years, given the advent of therapies targeting prostate carcinoma. While most techniques are directed at rare neoplastic diseases, often in the last line of treatment, therapies targeting prostate carcinoma have the potential to be used more frequently and earlier in the disease,[1] making a more significant impact on their need and notoriety. For example, in the last 7 years, in 4 of them, the European Association of Nuclear Medicine (EANM) awarded the Marie Curie prize (for the best research work) at its annual congress to studies related to theranostics in the field of prostate carcinoma.[2] Globally, it is estimated that Nuclear Medicine, like other specialties, will grow over the years, but disproportionately, with significantly more growth in the therapeutic field compared to the diagnostic/staging field.[3]

Among the various radiopharmaceuticals directed at treating prostate carcinoma, Lutetium-177-PSMA is the one that has recently proven to be more relevant. On the one hand, it deals with negative beta and low-energy gamma radiation, which are easy to handle in Nuclear Medicine. On the other hand, its binding to PSMA has shown favorable clinical results, particularly with increased survival in patients with metastatic prostate carcinoma, as demonstrated in the VISION or TheraP trials.[4,5] The Marketing Authorization by INFARMED dates back to December 2022,[6] and its commercialization in Portugal began in July 2023, with the first administrations already taking place in both the National Health Service and in the private context.

## In the Future

Artificial intelligence (AI) and machine learning algorithms are playing an increasingly vital role in theranostics. These technologies aid in the interpretation of complex imaging data, enhance the accuracy of radiopharmaceutical distribution mapping, and optimize patient-specific treatment planning. The integration of AI can potentially lead to more efficient and effective theranostic strategies, thereby improving patient outcomes.

Practically speaking, despite having a potentially significant number of indications, theranostics requires Nuclear Medicine facilities that may not be adequately sized for the time being. It is crucial for Nuclear Medicine services in Portugal and globally to redesign themselves, grow, and establish solid communication with other specialties involved in the process, making this a turning point in the course of this medical specialty. Only then will it be possible to improve healthcare for patients who can benefit from various theranostic modalities, effectively using these radiopharmaceuticals. This starts with the capable use of Lutetium-177-PSMA and probably will evolve into others that may show significant benefits in the meantime. While theranostics shows great promise, its global accessibility remains a challenge. Ensuring equitable access to these advanced treatments, particularly in low-resource settings, is crucial.

The future of theranostics in Nuclear Medicine relies heavily on interdisciplinary collaboration. This includes close coordination between nuclear medicine specialists, oncologists, radiologists, pharmacists, medical physicists and others. Such collaboration ensures a comprehensive approach to patient care, from diagnosis and treatment planning to follow-up and management of side effects.

## Conclusion

Theranostics represents a paradigm shift in the treatment of cancers, including prostate carcinoma. As we continue to witness advancements in this field, it is essential to address the challenges of accessibility and interdisciplinary collaboration. With these efforts, theranostics can potentially redefine the landscape of cancer treatment, making it more personalized, effective, and patient-centered.


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