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Nuclear Medicine Theranostics: Perspective from Pakistan

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Abstract
Nuclear medicine has been offering diagnostic and therapeutic solution since the introduction of radioactive iodine for thyroid diseases since decades. However, the concept of theranostics has given a new found impetus to the use of pairs of radiopharmaceuticals for diagnosis and treatment. Presented here is a perspective on theranostics from Pakistan.

Keywords Theranostics · Ga68 · Lu177 · DOTATATE · Hybrid imaging · Pakistan

Theranostics is an innovative aspect of nuclear medicine which targets the different disease states by applying a specific targeted therapy based on precise diagnostic tests. This approach is personalized to the patient for treating the disease state. This methodology moves away from a conventional medicine platform to a tailored and meticulous practices. The theranostics model encompasses bridging of the nanochemistry with diagnostic and therapeutic applications to engender a single agent to expedite the correct diagnosis, targeted drug delivery, and precise treatment response monitoring. Nuclear medicine has been all about diagnostic and therapeutic possibilities since its inception. With the recent advancement in the nuclear medicine in the form of theranostics, efforts are in progress to escalate the novel field applications in Pakistan in line with rest of the world [1].

Radioactive iodine (I-131) is in use since 1940s to diagnose and treat benign and malignant thyroid diseases [2]. It is extensively available in the nuclear medicine departments across the globe and also in Pakistan due to relatively simplified production and abundant supply. Other therapeutic applications of radioiodine (I^{131}) like mIBG, Lipiodal embolization have not had a similar impact due to limited indications, dwindling success rate, and infrequent availability [3, 4]. Radionuclide treatment methodologies for the management of bone pain secondary to metastases (i.e., strontium Sr^{89}, samarium Sm^{153}, radium Ra^{223}) had been introduced a long time ago; however, their availability in the larger part of the world is highly variable and largely limited by the immense cost involved in a palliative treatment [4]. Radio immunotherapy for lymphoma withI^{131} and Y^{90} labeled (ibritumomab tiuxetan) emerged in the market over one and half decade ago, however with limited therapeutic and market impact globally [5].

In the twenty-first century, the therapeutic applications of radionuclides have resurged with a new name all together as "theranostics." This resurrection is made at the back of a new paradigm in imaging with hybrid SPECT and PET scanners. PET tracers, i.e., (Flouride-18, Gallium-68) labeled somatostatin analogs and prostate-specific membrane antigens (PSMA) have higher affinity than the SPECT-based tracers labeled with indium-111 (In^{111}) or technetium (Tc^{99m}) [6]. Peptide receptor radionuclide therapy (PRRT) with high energy β (beta) emitters such as lutetium-177 (Lu-177) and yttrium-90 (Y-90) lead the way along with actinium-225 as (Alpha) emitter [4, 7]. Rhenium 188 is another promising generator produced radionuclide with significant patronage from WARMTH to make a sustainable breakthrough as a therapeutic radionuclide [8].

In Pakistan, nuclear medicine services are delivered under the Pakistan Nuclear Regulatory Authority (PNRA) that, in turn, is guided by the principles laid down by the International Atomic Energy Agency (IAEA). There are 51 nuclear medicine setups, public and private sector included, with varying degree of

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services in the country. Pakistan Atomic Energy Commission (PAEC) is the largest single contributor with 18 centers spread across the length and breadth of the country, including some remote cities. In terms of radionuclide therapy radioiodine for outpatient treatment of hyperthyroidism is more widely available across Pakistan. Inpatient facilities for delivering high-dose are limited, but given the spread of centers across the country, a large extent of the country's landscape is covered. It goes with saying that provisions fall short of the needs of the over 200 million population and various options are always under evaluation to work around it [9, 10].

The first PET-CT service in Pakistan was introduced in the private sector at the charity-based Shaukat Khanum Memorial Cancer Hospital and Research Centre in Lahore in 2009. At present 6 PET/CT centers are operational, 2 in Lahore (north to center country), 4 in Karachi (south country) backed by 5 hospital-based cyclotron (Lahore 2, Karachi 3). In the next 2 to 6 months, first PET/CT with onsite cyclotron is expected to commission in Rawalpindi (north country) along with a scanner in Peshawar (north country) and Lahore taking the total tally to 9 scanners. A fourth cyclotron is expected to be operational in Karachi in the same period. All cyclotrons are used for F-18 labeled FDG as it remains the work horse of PET imaging. The optimal half-life, simple chemistry, and tons of experience and literature makes it ideal to make a successful enterprise. Short-lived radiotracers like are C-11, N-13, and O-15 are not being produced or used anywhere in the country. At present, there is no registry for the utilization of PET-CT across Pakistan; however, institutional clinical experience is increasingly shared on national and international meeting and published in literature [11–15].

Growth of PET-CT in low- to middle- income countries including Pakistan have been hampered by requirement of onsite or nearby cyclotron facility for supply of FDG. The first 2 PET-CT centers that started working in 2009–11 in Lahore relied on installing their own cyclotrons for regular supply of FDG. With the passage of time, new regulations regarding production and safe transport (within the same city or other provinces) have been formulated and implemented; ensuring regularized supply of F18-FDG to the distant PET-CT centers.

Globally PET-CT and nuclear medicine procedures are expected to raise many folds mainly due to increased incidences of target disease such as cancer and cardiovascular diseases though most cases may be prevented through early detection and treatment. Nuclear medicine has a significant role in this context. According to the GLOBOCAN 2012, the globally prevalence of cancer patients was 14.1 million and by 2025, approximately 19.3 million new cases are expected to be detected per annum.

In 2013, the International Atomic Energy Agency (IAEA) along with the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) issued a joint practical guidance on PRRT [16]. This joint effort was based on review of experience and data acquired over 15 years, initiated in Europe. The groundbreaking results of the famous NETTER-1 Phase III Trial of Lu-177 DOTATATE for midgut neuro-endocrine tumors made it to the multidisciplinary conferences and tumor boards and caused the much desired stir among the oncologists [17, 18]. The FDA approval of Ga-68 DOTATATE in 2016 for imaging followed by Lu-177 DOTATATE for therapy in 2018 has been perceived as a paradigm shift in the large US market with favourable effect internationally. Theranostics for prostate cancer also appear promising in phase II trials, pressing the case for phase III trials [19–21].

Ge-68/Ga-68 generator has opened new avenues for PET/CT to grow as modality. In countries with low to middle income, a generator-based PET radiopharmaceuticals obviates the need for investment in a cyclotron at the outset. With the large populations residing in Asia and particularly in South Asia that houses 25% of world population, this is all round great news. It is no surprise that Ge-68/Ga-68 generators have gained market share over last 5 years at a rapid rate owing to its unsurpassable attributes including long shelf life of 10 months, reasonably long half-life of approximately 70 min for Ga-68 and module-based chemistry that allows automation. Many Ga-68-based radiopharmaceuticals are under research and undergoing trials including bone seeking agents, specific tumor receptors binding agents for breast and pancreas cancers; antibodies that may be used for imaging of leukemia and lymphomas.

Pakistan's first theranostic laboratory had been established at INMOL hospital (PAEC) in November 2017, in Lahore with support from IAEA. INMOL's theranostics so far have focused on the use of Ga68-Lu177 for metastatic neuroendocrine and prostate cancers. Since this pioneering effort a tertiary care urology center in Karachi (i.e., Sindh Institute of Urology and Transplant) has also introduced diagnostic Ga68 service in the last year. Multiple other specialist centers, in the private and public sector, are also contemplating to formally introduce the combination of Ga68 and Lu177 services in near future.

An interesting aspect of Lu177-based radionuclide therapies is that while PET imaging can be performed at the limited centers in big cities; the therapy itself can be delivered in a peripheral nuclear medicine department with the necessary logistics and trained manpower for handling the commercially available automatic synthesizers, Ga68 generators, and provision for gamma camera imaging. This idea is gaining ground and can add significant impetus to the efforts to expand radionuclide therapy and nuclear medicine all together.

Progression in biotechnology and related scientific fields has gained the ability to combine therapeutic and diagnostic capabilities into one single agent (nanomaterials) that will have multifaceted diagnostic and therapeutic implications on healthcare system. However, a major limitation in this process is going to be the economic constraints for personalized treatment. The evidence is still evolving for the usefulness of Lu177 like radionuclide therapies and expectation is that an increase in use of theranostics may bring down treatment costs. However, demand for large scale production of new therapeutic radiopharmaceuticals will also pose challenges of radioative waste and its disposal [22]. An emphasis on building tactical partnerships with global players in the pharma and diagnostics sectors may be the way forward for Pakistani research institutes in this space. At the moment, Pakistan does not have comprehensive data on molecular nature of disease(s) among the Pakistani population. Nevertheless, combining the three major diseases including diabetes, heart disease, and cancer, molecular theranostics market should value anywhere between US $300–500 billion in the next 5 years, looking at the global and regional trends. The outlook for nuclear medicine theranostics looks good in Pakistan much like the region and rest of the world. The challenges of high cost, availability of best quality products, and trained manpower are also not much different just as is the expectation that this time radionuclide therapeutics are here to stay and expand. Training programs for physicians, scientists, technologists, and engineers are in place; however, these need to be revisited and geared up to the needs of the twenty-first century theranostics [23, 24].

Series of theranostics world congresses since 2011 have played a significant role in galvanizing the stake holders so far. Now, it is time that it also serves as the platform for cooperation for progression and uniform access to nuclear medicine provisions for all the patients in need, across the globe.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures quoted in the review articles involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent Informed content data exists for the quoted procedures in this review article.

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