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Theranostics in the Arab World; Achievements & Challenges

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Abstract

In nuclear medicine, theranostics (combining therapy and diagnostics in one platform) is made possible through the utilization of radiopharmaceuticals for both therapeutic and diagnostic purposes by targeting one specific tumor receptor or certain molecular pathway.

To make radiopharmaceuticals biologically relevant compounds, receptor ligands must be labeled with radionuclides. The possible applications are multifold and include: in vivo visualization of tumor biology; diagnosis and tumor staging; therapy planning and treatment of specific tumors.

The application of theranostics results in giving the right treatment to the right patient at the right time, which is expected to improve therapeutic efficacy and increase overall compliance to therapy. For example, theranostics can be used to determine the heterogeneity of cancer lesions, which is one of the most difficult aspects of therapeutic success, allow the identification of patients who will benefit from therapy, avoid unnecessary conventional therapies, and implement salvage treatments for those who need them.

The use of theranostics has seen unprecedented value for cancer patients in the last decade. Several radiopharmaceuticals are currently in use in clinical practice (e.g., [68Ga/177Lu] DOTATATE), while dozens more are still in the preclinical stages.

The goal of this review article is to cover the current and future status of nuclear theranostics, particularly in the Arab world, with a focus on expanding the discipline beyond neuroendocrine tumors, castration-resistant prostate cancers, and differentiated thyroid cancers. Furthermore, representatives from different Arab countries were invited to describe their recent understanding and contributions to drive innovation in this evolving field.

Keywords: Nuclear Medicine; Theranostics; Arab World, Therapy; Diagnosis.

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Introduction

Theranostics is a hybrid term that was first introduced in 2002, reflecting the fusion of two words: therapy and diagnostics [1]. Despite the fact that this term is relatively new, the concept is not, as it has been revisited and used extensively in recent decades [2].

The main principle of theranostics is to improve therapy response and decrease tissue toxicity by combining diagnostic and therapeutic techniques targeting the same molecular levels, allowing for a better overall outcome and survival.

Nuclear medicine diagnostics were made possible through incorporating radioactive isotopes into specific molecules, resulting in a suitable radiotracer that is capable of assessing both biologic and pathophysiologic features [3]. Therapeutic advances in nuclear medicine follow the same principle, opting to apply radiation to the diseased tissue at a cellular level by virtue of particular chemical and/or biological affinity.

The diagnostic or therapeutic capabilities of each radiotracer are mainly dependent on the type of radiation emitted, whether it be electromagnetic radiation (which is of diagnostic value) or particulate radiation (which is of therapeutic value) [as shown in Figure1 and Figure2]. Particulate radiation is subdivided into two main forms (alpha and beta particles). Both particles share cytotoxic properties, exerting high energy transfer to tissue sufficient enough to cause cellular damage at the DNA level. When compared to beta particles, alpha particles have much higher mass and energy. Some radioisotopes, such as ^{177}Lu can exhibit two different forms of radiation (i.e., both particulate and electromagnetic), making simultaneous treatment and imaging possible.

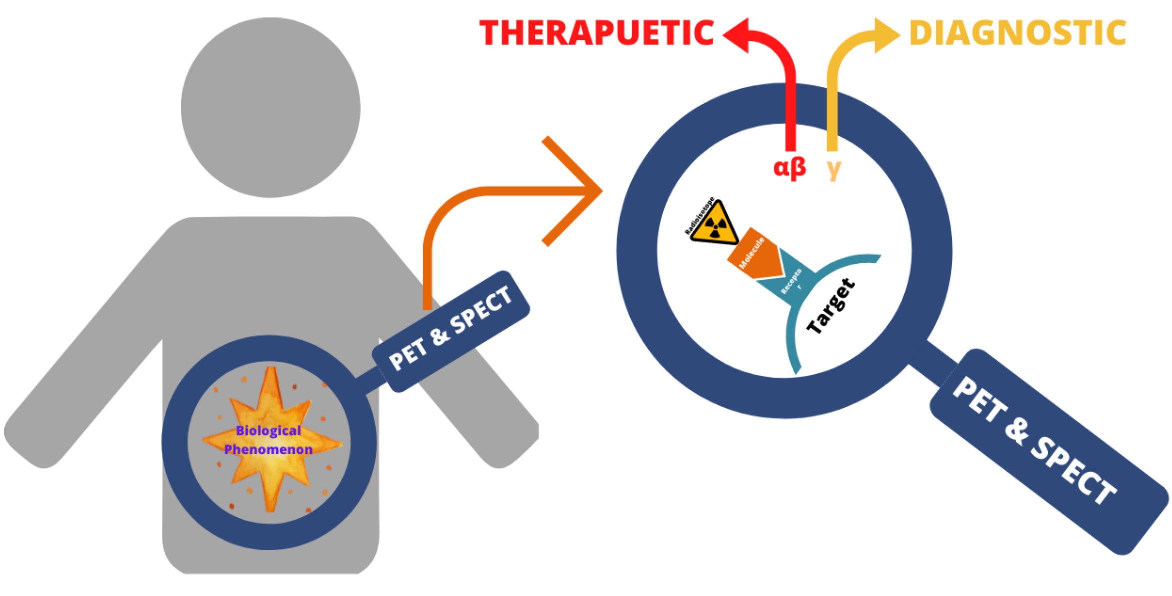

Fig1 - Diagram demonstrating an overview of Nuclear Theranostics

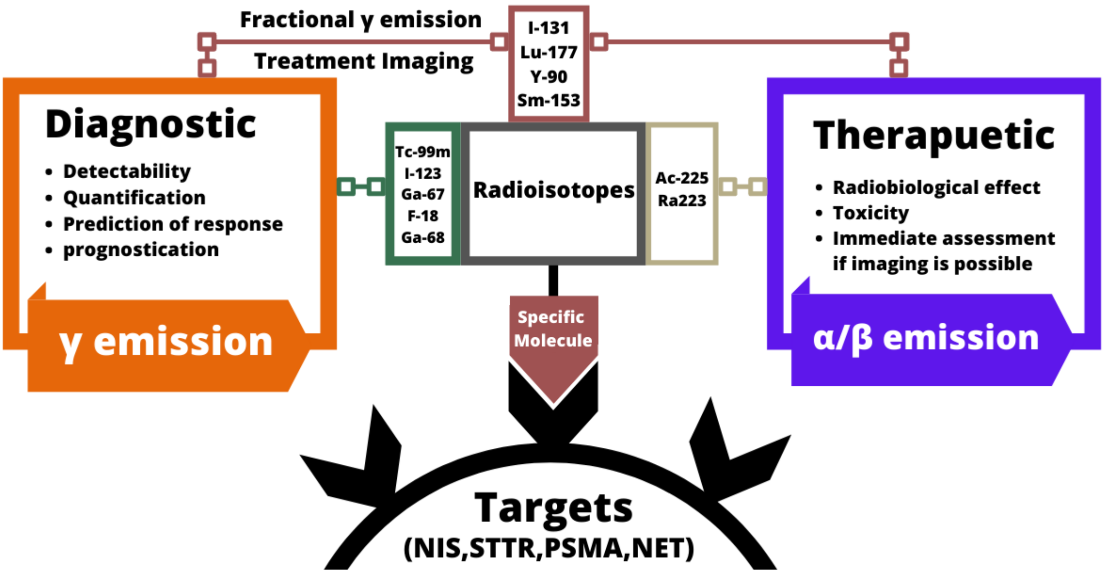

Fig2 - Diagram summarizing the theranostic approach in nuclear medicine

Diagnostic and therapeutic radiopharmaceuticals that share the same molecular target are called theranostic pairs and are widely used in nuclear medicine practice [as shown in Table 1].

Table 1 -Theranostic Pairs Commonly Used in Clinical Nuclear Medicine Practice

Diagnostic Agent(s)	Therapeutic Agent(s)	Target	Implementation
^{123}I or ^{131}I	^{131}I	NIS	Differentiated Thyroid Cancer Hyperthyroidism
^{123}I-MIBG	^{131}I-MIBG	NET	Neuroblastoma Pheochromocytoma Paraganglioma MTC
^{68}Ga DOTATOC ^{68}Ga DOTATATE	^{177}Lu DOTATOC ^{177}Lu DOTATATE	Somatostatin receptor	Neuroendocrine Tumors
^{18}F-sodium fluoride	^{223}Ra	Bone hydroxyapatite	Prostate cancer with bone metastasis
^{68}Ga-PSMA, 18F-PSMA	^{177}Lu-PSMA, ^{225}Ac-PSMA	PSMA	Prostate cancer

NIS: Sodium iodide Symporter; MIBG: metaiodobenzylguanidine; NET: Norepinephrine transporter; MTC: Medullary thyroid cancer; PSMA: Prostate specific membrane antigen.

During the past 70 years, radioactive iodine in various forms has been widely used to diagnose(^{123}I) and treat (^{131}I) thyroid cancers[4,5]. Upon the introduction of radioactive iodine, metastatic thyroid cancer was transformed from a disease with a poor prognosis to a disease with an excellent survival rate of about 85%[6]. Nowadays, radiotheranostics are undergoing a transition to be more incorporated into cancer therapy. The main aims of radiotheranostics have been to stabilize end-stage disease that is resistant to other treatments and to improve the overall quality of life. As shown in the latest clinical trials, this opens the door for patients with differentiated thyroid cancers and untreatable prostate cancer, as well as neuroendocrine tumors, to achieve a better prognosis.

Furthermore, advancements in molecular biology, radiochemistry, and imaging technology, particularly the emergence of hybrid imaging modalities like SPECT/CT, PET/CT, and PET/MRI, provide the foundation for new theranostics while also improving the quality of traditional procedures.

Method

In this review article, representatives from different Arab countries describe the clinical applications of various radiopharmaceuticals in the field of interest, sharing their knowledge and contributions in regards to the utilization of radioactive iodine in differentiated thyroid cancer and radiolabeled metaiodobenzylguanidine (MIBG) in neuroblastoma, while also demonstrating the clinical impact of peptide receptor radionuclide therapy (PRRT) in the management of neuroendocrine tumors. Furthermore, the clinical value of the rapidly evolving advanced theranostic modalities such as radioligand therapy with^{177} Lu-prostate specific membrane antigen (PSMA) and targeted alpha therapy in castration-resistant prostate cancer will be highlighted, making it easier to identify and distribute the key knowledge and opinions and providing insight into the future application trend in this field.

Results and Discussion

Theranostics Applications in Jordan

Cancer is the second most common cause of death in Jordan after cardiovascular disease [7]. According to a 2018 epidemiological study, the overall incidence of cancer cases among Jordanians increased by 60% over the previous decade (2000–2013) because of increased life expectancy and increased exposure to risk factors, with smoking being a major concerning factor in the country [8].

Over the past decade, cancer care in Jordan has witnessed remarkable improvement through access to advanced diagnostics and therapeutics as well as the development and establishment of advanced cancer centers within the country [7]. King Hussein Cancer Center (KHCC) is the leading regional cancer center in terms of providing comprehensive and high-standard cancer care to Jordanian citizens as well as Arabs in neighboring countries.

In Jordan, clinical application of radioactive iodine started back in 1984 in the clinical diagnosis and workup of patients with differentiated thyroid cancer. As a prototype in the field, radioactive iodine- and sodium iodide symporter (NIS)-based theranostics have been used for the treatment of patients with differentiated thyroid cancer (DTC) for more than 40 years, even before coining the term "theranostics". Approximately 600 patients with DTC are treated every year with ^{131}I in Jordan with subsequent follow-up using diagnostic ^{131}I whole-body scans [9-11]. The largest five public medical centers in Jordan, in addition to some private centers use diagnostic and therapeutic ^{131}I doses in the assessment and treatment of DTC and hyperthyroidism.

The use of PET/CT with radiolabeled somatostatin receptor analogs (^{68}Ga DOTA-peptide) in the diagnosis of NETs began at KHCC in 2013, shortly after the first Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generator was installed [12]. This molecular diagnostic imaging technique is currently regarded as the gold standard for staging, stratifying for therapies, evaluating therapy response, and restaging most NETs [12]. In high-risk neuroblastoma patients, PET/CT scan results were compared to other standard modalities [13]. Promising results were obtained when using ^{68}Ga DOTATAOC PET/CT and FDG PET/CT [13]. To date, more than 400 scans have been completed with several reported cases [14-15]. A success that opens the door for other types of peptide PET imaging and peptide-based radionuclide targeted treatment to be enrolled. On the other hand, PRRT has been established at KHCC since 2014 through the use of ^{177}Lu DOTA-TATE based on published data showing impressive results in terms of disease stabilization [16]. ^{177}Lu PRRT is a new and promising treatment for NET, especially for those with grades 1 and 2 who are inoperable and have failed to respond to somatostatin analogues. It can be utilized as a neoadjuvant treatment in patients with inoperable NETs, as well as adjuvant therapy following surgery [17].

The KHCC was also a pioneer in establishing a theranostics approach for prostate cancer in 2015. Under the supervision of Al-Ibraheem et al., innovative approaches were made to introduce ^{68}Ga PSMA PET/CT in the primary staging of patients with high-risk prostate cancer (PCa). The main aim was to explore the ^{68}Ga PSMA PET/CT overall impact on high-risk prostate cancer patients' management plans and to compare this new promising modality to the standard imaging modality (CT, magnetic resonance imaging (MRI), and bone scans). This study was one of the earliest studies to address this important aspect [18]. It was concluded that 68Ga PSMA PET/CT outperforms CT, magnetic resonance imaging (MRI), and bone scintigraphy in terms of primary staging of high-risk prostate cancer patients, and that 68Ga PSMA PET/CT appears to be an invaluable imaging modality in the assessment of primary high-risk prostate cancer patients, particularly if CT or MRI scans and bone scintigraphy show equivocal findings [18].

In 2017, ^{177}Lu PSMA-617 was first introduced in the KHCC nuclear medicine department. Excellent results in terms of partial biochemical response, quality of life improvement, and a low toxicity profile were obtained in patients with progressive metastatic castration-resistant prostate cancer [19] [as shown in Figure 3], who had previously been heavily treated and had exhausted all other available treatment options [12]. In light of these results, it has been decided by the genitourinary multi-disciplinary clinic at KHCC to integrate this nuclear medicine treatment into the institutional guidelines for eligible patients who have a history of metastatic castrate-resistant prostate (mCRP) cancer [12]. Following this decision, a group of KHCC patients received ^{177}Lu PSMA-617 therapy and were followed up periodically to monitor both the efficacy and safety of this therapy. An analysis of the results in 23 patients to examine the biochemical response, quality of life, as well as the toxicity profile demonstrated overall promising outcomes for ^{177}Lu PSMA-617 therapy in our cohort at KHCC [19].

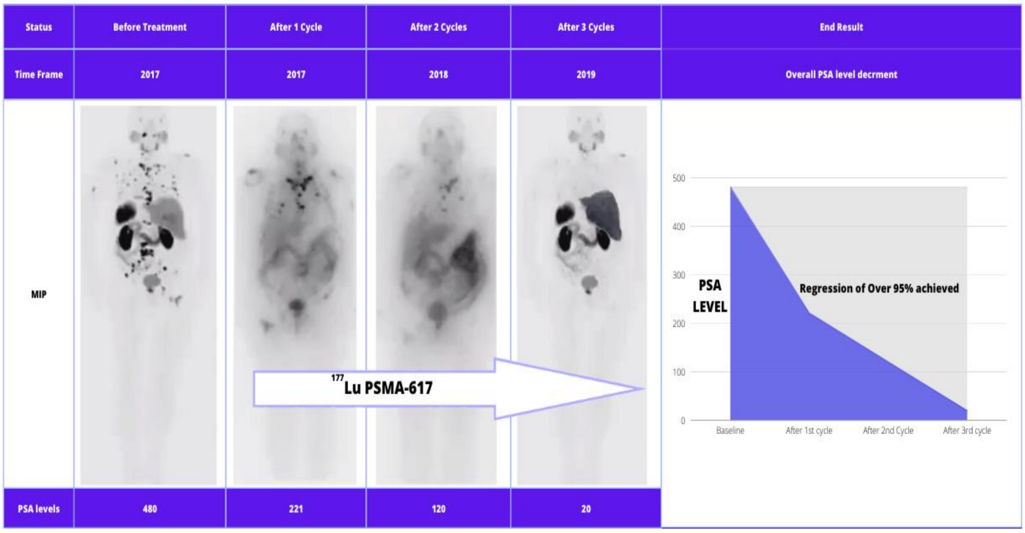

Fig3 - Serial Coronal maximum intensity projection (MIP) images for a patient receiving 3 cycles of Lu-177-PSMA Therapy demonstrating a substantial reduction in tumor burden on the MIP images as well as PSA level after each treatment cycle.

In 2021, further investigations were made to assess the impact of ^{68}Ga PSMA PET/CT on staging and planning of definitive radiation therapy, which was published by Al-Ibraheem et al [20]. A sample size of 336 men was evaluated by ^{68}Ga PSMA PET/CT to explore the potential impact of ^{68}Ga PSMA PET/CT on radiotherapy planning, including both radiation dose and definition of target volumes [20]. It was concluded that ^{68}Ga PSMA PET/CT has better accuracy in detecting prostate cancer sites when compared to conventional imaging modalities. Thus, about 30% of patients' staging and management plans were changed guiding them to better treatment and outcomes [20].

In the setting of biochemical relapse and restaging of prostate cancer, ^{68}Ga PSMA PET/CT is increasingly replacing traditional imaging modalities at KHCC. It is also becoming more widely used in the staging of high-risk prostate cancer because it is more accurate and can help achieve the best treatment options for a given patient. However, the impact on survival of an earlier initiation of therapy based on PSMA-targeted imaging is not yet established, and that is why further research is being conducted to confirm efficacy as well as enhance safety and outcomes at earlier stages of the disease.

Another explored aspect in the field of theranostics is the use of metaiodobenzylguanidine (MIBG). During the last decade, KHCC physicians have been utilizing ^{123}I MIBG in the diagnosis of NET while stratifying for treatment with ^{131}I MIBG, which has been implemented following the European guidelines [21]. In addition to KHCC, ^{68}Ga/^{177}Lu-DOTATATE and ^{68}Ga PSMA theranostics are performed at the King Hussein Medical Center in Amman, Jordan.

Participation in Multicentric Prospective Trials

In a field where prospective trails play a vital role in determining the capability of theranostic impact on both detection and management, Arab World representatives from both Jordan and Lebanon participated in a large-scale prospective trail to assess the impact of ^{68}Ga PSMA PET/CT in the detection of early relapsed prostate cancer after radical therapy [22]. As a matter of fact, this study is by far the largest prospective trial to be conducted, evaluating 1004 patients from 4 different continents (Africa, America, Asia, and Europe). Despite being a relatively novel modality, this study proves the reliability as well as feasibility of 68Ga PSMA PET/CT in achieving similar accuracy results among all the four continents while helping other physicians seek the best treatment options possible [22].

Theranostics Applications in the UAE

The United Arab Emirates (UAE) comprises seven emirates. Dubai is the most populous emirate, with 35.6% of the total UAE population. The capital city, the Emirate of Abu Dhabi, is the second most populous city, hosting about 31.2% of the total population, meaning that over two-thirds of the UAE population live in either Abu Dhabi or Dubai. As a result, healthcare facilities such as nuclear medicine and molecular imaging are concentrated in these two cities.

There are multiple major governmental healthcare providers in the UAE out of Dubai Health Authority (DHA) in Dubai and the Ministry of Health and Prevention (MOH) in Abu Dhabi. Together with private healthcare sectors, these providers are offering nuclear medicine and molecular imaging with radionuclide therapy services for the UAE population in different Emirates.

The Dubai nuclear medicine and molecular imaging center is operated under DHA and currently functions as the largest nuclear medicine facility in the UAE with a full range of diagnostic, therapeutic, and theranostics services in one place.

In the UAE, nuclear medicine and radiology centers are licensed under the Federal Authority of Nuclear Regulation-FANR. There are about 15 nuclear medicine setups in the UAE, public and private, with varying degrees of services in the country.

Cardiovascular diseases are the leading cause of death in the UAE, accounting for 28% of all deaths. Other major causes include congenital anomalies, cancer, road accidents, and injuries.

Cancer is the third leading cause of death in the UAE and, according to the World Health Organization statistics in 2020, the total number of deaths in the UAE due to cancer was estimated at 1896 cases. There are multiple oncology centers within the UAE, both private and public, covering the population of Dubai and other emirates.

In terms of theranostics, radioactive iodine application for outpatient treatment of hyperthyroidism is widely used in the UAE. However, because inpatient facilities for treating well-differentiated thyroid cancer with high-dose radiation are limited, the Dubai Nuclear Medicine and molecular imaging Center serves a large number of patients from the UAE and the region.

Radioactive iodine (^{131}I) application in DHA started in the early 80s for the diagnosis and treatment of benign and malignant thyroid diseases. Other therapeutic applications of radioiodine (^{131}I) like MIBG have limited indications and do not exceed 1-2 cases per year, while ^{123}I has been recently utilized for diagnostic scans during the last 4 years.

At present, about 9 PET/CT centers are operational in the UAE. The first PET/CT in the private sector was introduced in mid-2000 in Dubai with a private cyclotron for the production of FDG. A few other centers started with PET/CT in the Emirate of Abu Dhabi with limited services using mainly FDG for diagnostic scans.

The first public PET/CT facility was established in 2017 under the leadership of Dr. Batool Al Balooshi at the Dubai Nuclear Medicine and Molecular Imaging Center in DHA.

Shortly after the establishment of PET/CT in early 2018, the first theranostics settings, including a self-shielded Ga-68 generator, an automated synthesizer, and quality control tools, were established in DHA at the Dubai nuclear medicine and molecular imaging center. This year also witnessed the establishment of ^{68}Ga PSMA PET/CT and ^{68}Ga DOTATOC PET/CT scans for the staging and restaging of prostate cancer and neuroendocrine tumors, respectively. A few other private nuclear medicine centers provided 68Ga-based radiotracer scans for a short time, but service continuity was not guaranteed due to regulatory and other constraints. Patients with prostate cancer and patients with NETs are referred to DHA for Ga-68 scans and theranostics.

The first therapy with ^{177}Lu PSMA-617 was introduced in early 2018 according to EANM and IAEA guidelines for theranostics and with the approval of a multidisciplinary committee at DHA including oncologists, urologists, and nuclear medicine physicians under the supervision of Dr. Batool Albalooshi. As per the collected data and results, ^{177}Lu PSMA-617 therapy showed good response in the majority of patients, with some remaining in remission and a significant decline in PSA levels. Overall resolution of bone metastases, which was noticed in all patients, resulted in a better quality of life.

Consequently, because of the large number of patients who were enrolled for ^{68}Ga PSMA PET/CT and Tc^{99m} PSMA SPECT/CT at DHA, a retrospective study was conducted and was published for direct comparison of Tc^{99m} PSMA SPECT/CT and ^{68}Ga PSMA PET/CT in prostate cancer [23]. The published study has opened horizons for those nuclear medicine facilities without PET/CT to enroll patients for staging and restaging of prostate cancer and eventually for theranostics and scanning with SPECT/CT [23]. Besides publication, a series of international conferences and symposiums in theranostics and molecular imaging, which were conducted in Dubai with input from local and international experts, have played a significant role in the awareness of other medical specialists and stakeholders.

Moreover, with an increased number of patients who were enrolled for NETs staging and restaging with ^{68}Ga DOTATOC PET/CT, the demand for theranostic with ^{177}Lu DOTATATE was raised and multiple patients were enrolled in early 2018 with very good results and declining chromogranin A level. They are currently in remission and maintenance therapy.

In conclusion, the overall approach for theranostics and therapy implementation in Dubai faced some challenges that were not related to technical or financial issues, but to a lack of effective coordination between health authorities at the Emirates level in the public and private sectors, a potential source of insufficient or slow growth in theranostics practice. Nevertheless, theranostics offer great hope and an improvement in quality of life for cancer patients. On the other hand, the local and federal governments of the UAE strongly support innovations in health care, and reducing the number of deaths due to cancer is one of the UAE's national agendas. Therefore, it is only a matter of time to overcome challenges and put this form of treatment to optimal use for large numbers of patients.

Theranostics Applications in Lebanon

Cancer is a prevalent cause of death in Lebanon. Although there are no official statistics regarding the incidence and prevalence of cancer in Lebanon, its detriment is evident in every demographic group in Lebanon.

Thankfully, cancer care in Lebanon has undergone noteworthy amelioration over the decades. Advancements in diagnostics and therapeutics, founding multiple cancer centers, and applying multidisciplinary approaches in management have contributed to improvements in cancer care in the country. Currently, there are more than 17 centers that provide diagnostic nuclear medicine services in Lebanon, and only seven of these deliver therapeutic services. The major centers are: the American University of Beirut Medical Center, Mount Lebanon Hospital, and Sahel General Hospital. At the forefront of providing cancer care to Lebanese citizens as well as individuals of different nationalities and ethnicities, the American University of Beirut Medical Center is at the forefront of providing cancer care to Lebanese citizens as well as individuals of different nationalities and ethnicities.

In Lebanon, clinical application of radioactive iodine began in the late 60’s and early 70’s. To be more specific, the first case where ^{131}I was implemented in the clinical diagnosis of differentiated thyroid cancer was in 1969. As it was still considered a novelty in the field, it was administered under international and institutional guidelines, serving as an exemplar and pioneer in that regard for more than 50 years.

Another explored aspect in the field of theranostics is the use of MIBG. It was implemented as early as 2004. Firstly, it is used for the clinical diagnosis of malignant pheochromocytoma. Management of such patients is discussed in a tumor board setting. Pathologists, surgeons, and medical and radiation oncologists gather and share their input to provide optimal care to cancer patients. It followed shortly; it was used, specifically in the pediatric age group, in the diagnosis of neuroblastoma. The Children's Cancer Center of Lebanon (CCCL) at AUBMC works hand in hand with specialists in different fields to provide the most appropriate care to ensure an ideal outcome for patients. It is a prime example of multidisciplinary management.

The use of PET/CT with radiolabeled somatostatin analogs (^{68}Ga DOTA-peptide) in the diagnosis of neuroendocrine tumors began in 2007, shortly after the first Germanium-68/Gallium-68 (^{68}Ge/^{68}Ga) generator installation. To date, there are over 700 completed scans, paving the way for other parts of peptide PET imaging and peptide-based radionuclide targeted treatment. While peptide receptor radionuclide therapy (PRRT) has been implemented in Lebanon since 2007, using ^{177}Lu DOTA-TATE following the international guidelines has shown a fascinating outcome in terms of patients’ condition and disease stabilization. Several studies have shown the higher accuracy of 68Ga DOTATOC PET/CT for the detection of NET lesions as compared to conventional imaging.

In December 2015, under the supervision of Dr. Haidar et al., innovative approaches were made to introduce ^{68}Ga PSMA PET/CT in restaging of patients with high-risk prostate cancer (PCa), and it appears that ^{68}Ga PSMA PET/CT appears to be an invaluable imaging modality in the assessment of high-risk prostate cancer patients. In January 2019, PET/CT PSMA became the gold standard in the staging and restaging of high-risk prostate cancer patients at AUBMC. In December 2020, the FDA approved Gallium 68 PSMA-11 (Ga 68 PSMA-11) as the first ever drug for positron emission tomography (PET) imaging of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer, especially patients with suspected prostate cancer metastasis. In the setting of prostate cancer restaging and an increase in PSA values, ^{68}Ga PSMA PET/CT is increasingly replacing traditional imaging modalities at AUBMC [24]. It is also becoming more widely used in the staging of high-risk prostate cancer because of its accuracy and can help achieve the best treatment options for a given patient [24].

It was not until September 2016 when ^{177}Lu PSMA-617 was introduced in the AUBMC Nuclear Medicine Department. ^{177}Lu PSMA-617 was implemented for the first time for the treatment of metastatic castration-resistant prostate cancer.

The Lebanese Liquidity Crisis

The Lebanese liquidity crisis is an ongoing financial crisis affecting Lebanon that became fully apparent in August 2019, and was further exacerbated by both the COVID-19 pandemic in Lebanon (which began in 2020) and the 2020 Beirut port explosion. The shortage of U.S. dollars, which are used in everyday transactions in Lebanon, and the crash in the value of the Lebanese pound have undercut the country's ability to pay for imports. There is also significant inflation, which has caused a massive loss of purchasing power and an increase in poverty. This, inevitably has affected the practice of medicine as well. Obtaining MIBG has become a hardship on its own. Therefore, medical centers had to make do with what was available and affordable in this healthcare crisis. For example, ^{68}Ga DOTATATE PET/CT has been used instead of MIBG for the clinical diagnosis of NETs. Nonetheless, medical centers in Lebanon are holding on to the silver lining and going full throttle in the face of this adversity.

Theranostics Applications in Iraq

In Iraq, malignant neoplasms represented the third leading cause of death in 2018, after ischemic heart disease and cerebrovascular diseases. The total number of new cases of cancer in Iraq during the year 2019 according to the last Iraqi cancer registry was 35,864 with an incidence of 91.66/100,000 P. The trend of the incidence rate of new cases of cancer increased from the year 1994 (38.91/100,000 P) to the year 2019 (91.66/100,000 P). Breast and lung cancer were the most common cancer types to be encountered in the Iraqi population. The total number of cancer deaths during the year 2019 was 10,957, with a mortality rate of 28/100,000 P.

The first of November 1919, is the day of the establishment of the Institute of Radiation in Iraq, the nucleus of the peaceful use of radioactive isotopes for medical purposes. From that time, many of the radiation equipment and devices were started to give diagnostic and therapeutic services to the health sector, until 1958, when the first training course for the peaceful uses of radioactive isotopes was held, and work began with the use of radioactive iodine ^{131}I in the diagnosis and treatment of thyroid disorders in 1959. During the sixties to eighties, Iraq used different kinds of radioisotopes in diagnosis and therapy. After that, Iraq suffered from severe sanctions that were carried out because of wars for more than two decades, which was enough to paralyze nuclear medicine services. This resulted in a significant decline and shortage of both radioactive materials and devices in a country that was known to be one of the pioneers in this field in the region for more than half a century.

Iraq was relieved of international sanctions and restrictions in 2003, allowing it to resume nuclear activities. The Iraqi health sector, particularly the private sector, moved aggressively toward investing in nuclear medicine and cyclotron facilities, resulting in a quantum leap that took only three years to establish medical centers equipped with the most advanced technology and nuclear medicine devices. This provided a great service to the Iraqi patients by enabling them to obtain nuclear medicine services locally, sparing them the travel expenses.

Iraq inaugurated its first cyclotron project at the Amir Al-Momineen Specialty Hospital in Najaf, equipped with the first GENtrace cyclotron from GE in the world; another cyclotron and nuclear medicine facilities at Media Medical Center in Erbil; Al-Andalus Hospital in Baghdad; and Amal Al-Hayat Hospital in Najaf; and there are other projects that have been just completed or are in progress. These centers mainly use FDG PET/CT for tumor imaging in addition to conventional nuclear medicine imaging using a gamma camera.

Radioactive iodine treatment and imaging is currently the only use of theranostic applications in Iraq. Radioiodine treatment has recently been used in the private sector after it was limited to one government hospital.

This development was accompanied by a qualitative improvement in medical services, including the production and use of new radiopharmaceuticals used in PET. Amir al-Momineen Hospital has been the first and leading hospital in Iraq to implement the international standards (GMP) and started producing ^{18}F-PSMA for prostate cancer imaging and ^{18}F-NAF for bone scans inside the hospital. Several dozens of patients were examined with very good results, in addition to the use of 68Ga PSMA and 68Ga DOTATATE in prostate and neuroendocrine tumor imaging, respectively, thus paving the first ground for the use of Theranostics in Iraq after establishing a dedicated isolation ward for inpatient admission to start employing 177Lu PSMA-617 in castration resistant metastatic prostate cancer cases and 177Lu DOTATATE in neuroendocrine tumors as well as MIBG therapy for neuroblastoma, in addition to other therapeutic radioisotopes.

Most emerging medical centers in Iraq aspire to collaborate with pioneer cancer centers in order to benefit from their expertise in the field of Theranostics and best provide these unique medical services to Iraqi cancer patients.

Theranostics Applications in Egypt

Since Egypt has just exceeded about 100 million people, a dramatic increase in PET/CT machine utilization has been witnessed in the past 5 years, making them one of the cornerstone exams used in the initial diagnosis and follow-up of cancer patients. Currently, there are about 600–700 daily FDG PET/CT exams on approximately 60 PET/CT machines performed all over Egypt.

^{68}Ga PSMA PET/CT imaging for cancer prostate patients was first introduced in Egypt in late 2017, which was followed one year later by cyclotron production of ^{18}F PSMA in late 2018. This allowed for easier adoption of this exam on a lot of sites without the need for heavy investments in ^{68}Gallium generators and infrastructure. Currently, there are about 150–200 PSMA-PET/CT cases per month.

Moving to neuroendocrine tumor imaging, ^{68}Ga DOTATATE PET/CT was started in late 2018 in Egypt, with only a few centers (3-4) doing the exam, leading to about 40 cases per month.

Therapy using ^{177}Lu started in January 2019 for a neuro-endocrine patient, then followed in the same year for cancer patients with prostate cancer in mid-2019. Currently, only 1 center in Egypt is doing ^{177} Lu therapy routinely, doing about 4 doses per month.

The biggest challenge in Egypt is the reimbursement of expenses. The diagnostic and therapeutic parts of theranostics are still not reimbursed and are being paid directly by the patients. Such technology is expensive and not affordable for the general public, which acts as a big barrier to its wider adoption.

The future will pave the way for more diagnostic PET/CT tracers to be explored. For diagnostic purposes, tracers like fluorine-18-desoxyphenylalanine (F-DOPA), fibroblast-activation-protein inhibitor (FAPI), and 16a-18F-fluoro-17b-estradiol (FES) will be implemented in the near future for diagnostic purposes, while on the therapeutic side, actinium-225-PSMA (^{225}Ac-PSMA) therapy is soon to be established for advanced mCRP cases.

Finally, a bright future is anticipated for the nuclear medicine field in Egypt, with a huge impact on patient management already made and only waiting for re-imbursement to facilitate its wide adoption with easy patient access.

Theranostics Applications in Kuwait

According to the World Health Organization (WHO), Kuwait is considered a high-income country with one of the most advanced healthcare infrastructures in the region. The government of Kuwait has spent more than $11 billion on the construction of new infrastructure for healthcare as it seeks to prioritize the transformation of its healthcare sector. The healthcare sector in Kuwait will likely face rapid growth over the next five years due to the huge investment in the country's healthcare infrastructure. This growth will also include an increase in the therapeutic and diagnostic radiation services provided to the public sector.

Nuclear medicine is well established in the country, with the availability of advanced imaging systems and established diagnostic and therapeutic procedures. There are a total of 12 centers in Kuwait with the latest nuclear medicine equipment and technology [as shown in Figure 4]. Nuclear medicine services in oncology are provided mainly by the Kuwait Cancer Control Center (KCCC) and the Jaber Al Ahmad Center for Nuclear Medicine and Molecular Imaging (JAC).

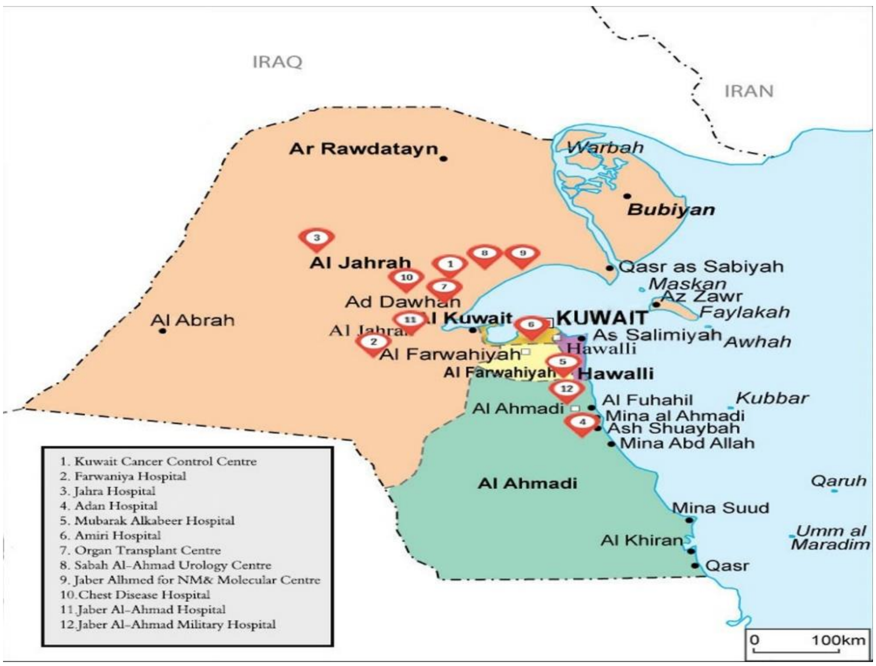

Fig4 – Distribution of Nuclear Medicine Centers in Kuwait.

The KCCC is a comprehensive center dedicated entirely to the purpose of providing cancer care. It was founded in 1968. It has a 200-bed hospital complex with over 600 highly qualified medical staff. KCCC treats over 2000 new cancer patients each year from Kuwait and the region. KCCC was established as a major public hospital with the goal of providing tertiary health care diagnostic imaging services, such as PET-CT, SPECT-CT, and possibly future PET-MRI services, to the population. The KCCC has traditionally served as the primary counterpart for IAEA technical cooperation assistance. In November 2018, IAEA awarded KCCC as regional resource center in Nuclear Medicine for ARASIA countries.

Therapeutic nuclear medicine in Kuwait has developed consistently over the last 50 years. starting with the first radionuclide therapy in 1964 with radioactive iodine for thyroid cancer. A vast range of radionuclide therapy options is available in the KCCC like ^{131}Iodine in patients with DTC and benign thyroid disease, ^{90}Y-Therasphere, ^{90}Y-ibritumomab tiuxetan (Zevalin), Strontium-89 bone pain palliation, ^{177}Lu-DOTATATE for neuroendocrine tumors (NET), ^{131}Iodine MIBG therapy and radio-synovectomy. The historic timeline of radionuclide therapy in Kuwait is shown in Table 2. In KCCC, ^{177}Lu PSMA-617 PSMA was validated for mCRP cases in 2015. Targeted alpha radiolabeled ^{225}Ac-PSMA is emerging as a promising new modality for the treatment of mCRP [25]. ^{225}Ac-PSMA therapy can be used in patients who are unresponsive to ^{177}Lu PSMA therapy or show pronounced bone marrow infiltration [25]. ^{225}Ac-PSMA radiation consists of short-ranged alpha particles which kill tumor cells but spare the bone marrow cells [25]. Recently, we have done a few cases of ^{225}Ac-PSMA alpha therapy in patients who are unresponsive to ^{177}Lu PSMA therapy or show pronounced bone marrow infiltration [25]. We have found possible advantages of alpha 225Ac-PSMA therapy over 177Lu beta therapy and this should be further explored in a larger population or study [25].

Table 2 -History of radionuclide therapy in Kuwait

Year	Radioisotope	Treatment
1964	^{131}I	Thyrotoxicosis
1964	^{131}I	Thyroid Cancer
1971	Radio-phosphorus -32	Polycythemia
1997	Stronium-89	Bone Therapy
2004	Y-90 Zevalin	Lymphomas
2004	^{131}I-MIBG	Neuroendocrine Tumors
2007	Radionuclide Synovectomy	Arthritis
2009	Y-90 Therasphere	Liver tumors
2014	^{177}Lu-PSMA-617	Prostate cancer
2017	^{225}Ac-PSMA-617	Prostate cancer
2018	^{177}Lu DOTATATE	Neuroendocrine Tumors

Future Insights

Over the last decade, there have been a great number of excellent and rapid advancements in nuclear medicine and molecular imaging fields throughout the Arab world. These advancements change the direction of a field previously known for its imaging capabilities to deeply engage in precise drug delivery tailored for the specific characteristics of an individual patient's disease.

Radioactive iodine was the prototype in this field. However, the discovery of the hallmarks of cancer [26], and the recent advances in molecular and genetic analysis of cancer cells, have paved the way for rapid and very promising advances in nuclear theranostics. Despite its huge success over the last seven decades, there is still room for improvement in that aspect, and hopefully it's now achievable with the introduction of the newly emerging ^{124}I PET tracer. ^{124}I is a positron emission tomography (PET) radiotracer that drives more accurate results by utilizing the improved sensitivity and high spatial resolution provided by PET/CT. It can provide higher sensitivity in the detection of recurrent or metastatic processes. However, there are drawbacks and challenges when implementing this agent because it has a complex decay scheme and is relatively expensive [27].

Promising antitumor effects are being observed in patients with metastatic castration-resistant prostate cancer who were treated with ^{177}Lu-labeled PSMA-ligands theranostics. Further advancement in this area is anticipated with the use and availability of targeted radionuclide therapy of Actinium-225-labeled prostate-specific membrane antigen ligands (^{225}Ac-PSMA), an alpha emitter which carries much more efficient linear energy transfer in a short path length, exerting more DNA damage. However, future randomized controlled trials are being conducted to determine its therapeutic impact and outcome when compared to other approved treatment modalities [28].

Radium 223 (which is a calcium-mimicking radioisotope that has been approved for therapeutic purposes for metastatic bone disease in patients with mCRP cancer) delivers alpha particles at cellular levels to metastatic bony deposits [29]. However, the high cost and logistics of operations limit their widespread use outside the United States and Europe. Experts in the field from the Arab World believe that PSMA-based radionuclide therapy is a valid alternative option. Nevertheless, efforts will be made to make this agent available for the patients in our region who are suffering from merely extensive bone metastases.

In the field of molecular brain imaging, it's anticipated that many of the current experiments and trials will provide clinical value in the upcoming years. The first amyloid PET tracer was approved some years ago [30], while many other PET tracers such as a-synuclein, TDP43, and ubiquitin are awaiting approval since they reflect the histopathologic properties of different forms of dementia and movement disorders. As a result, this will allow for a shift toward prodromal or pre-symptomatic disease staging and diagnosis in high-risk patients (e.g., those with rapid-eye-movement sleep disorder in Parkinson's disease or those with subjective cognitive impairment in Alzheimer's disease) and will provide a unique opportunity for these patients to receive preventive measures as early as possible [31].

In cardiovascular settings, small molecules, nanoparticles, or even cell products, are under development to target various pathologies of the myocardium, vessel wall, conduction system, or valves. Increasingly, radiopharmaceuticals that are meant to be useful for other applications turn out to be of value for cardiovascular imaging detection. Examples include the use of sodium fluoride for imaging of atherosclerosis and valvular calcification or the use of several tumor-binding agents such as DOTATATE or methionine for imaging inflammation in the vessel wall and myocardium [31].

Nano-theranostic strategies in cardiovascular imaging include a wide array of clinical uses and require further studies and trials. However, those studies are still a long way from being implemented on a large scale in the general population, but the future of nano-therapy on its own looks promising.

Conclusion

Theranostics envisions a ground-breaking clinical approach in the field of nuclear medicine that is to be guided by a "patient-centered" vision. In this light, well-trained specialists will be required for theranostic applications, who will be able to manage not only the technological aspects of the field but also to deliver more innovative oncological therapies in a multidisciplinary setting. However, more research is needed to better understand how much this innovative approach can improve patients' quality of life and impact their survival, keeping in mind cost effectiveness concerns.

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علاجات الطب النووي الموجهة بالتصوير الجزيئي في الوطن العربي: اخر التطورات والتحديات

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الملخص

يهتم مجال الطب النووي بتوفير المواد المشعة التي يتم توظيفها لأغراض التشخيص والعلاج وذلك عن طريق دمج الكثير من ناقلات الاستهداف الجزيئي، مثل الببتيدات مع النويات المشعة لغاية توجيه هذه المواد المشعة نحو المنطقة المستهدفة لتشخيص العلاج وتقديمه في نفس الوقت. من خلال هذا النهج أصبح بالإمكان تقديم العلاج المناسب للمريض في الوقت المناسب عن طريق معرفة نوع العلاج الذي يمكن ان تحدث الاستجابة علية وبالتالي تجنب استخدام العلاجات الغير فعالة التي يمكن ان يؤدي استخدامها الى الحاق اضرار جانبية. في الآونة الأخيرة شهد مجال الطب النووي توفير الكثير من الحلول العلاجية والتشخيصية بالأدوية المشعة النووية والتي أصبحت حاليا معتمدة في تشخيص وعلاج الكثير من الحالات السرطانية المستعصية. ومن الأمثلة على ذلك هو استخدام اللوتيشيوم−177 والجاليوم−68 لأغراض علاج وتشخيص مرضى سرطان البروستات العالي الخطورة. لا زالت البحوث والتطويرات مستمرة في هذا المجال لتوظيف الكثير من المواد المشعة لاستهداف الخلايا السرطانية دون التأثير على الانسجة المحيطة. الهدف من هذه المقالة هو تسليط الضوء على التطورات التي يشهدها هذا المجال في ارجاء الوطن العربي مع الاخذ بنظر الاعتبار تحديد مستوى الصعوبات والتحديات التي واجهتها الدول العربية الرائدة خلال مشوارها للوصول إلى الطموحات المتوقعة في هذا المجال الواعد.

الكلمات الدالة: الطب النووي، النويات المشعة، الوطن العربي، العلاج بالأدوية المشعة، التشخيص بالأدوية المشعة.