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ABSORBED ENDOTHERAPEUTIC RADIATION DOSE AND THE FUTURE OF THERANOSTICS

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Abstract: **The use of nuclear radiation to diagnose, image and stage complex diseases such as cancer and its subsequent therapy makes nuclear medicine one of the most viable, dependable and effective healthcare practices in the developed world while it gains ground in developing countries. However, the practice is technically speckled with the risks of radiation overexposure particularly in therapy where radiation absorbed by the tumour tissues determine the success or otherwise of treatment while normal tissues are vulnerable. This paper reviews the methods to estimate absorbed radiation dose through the combination of diagnostic and therapeutic radionuclides in one radiopharmaceutical, also called theranostics with emphasis on the quest for nuclear data for the production of these special radionuclides in order to furnish and advance quantitative methods that will sustain the approach and put the risks due to nuclear radiation at modicum.**

Keywords: **nuclear radiation, radionuclide, theranostics, absorbed radiation, radiopharmaceutical, overexposure.**

1. INTRODUCTION

The use of nuclear radiation for diagnosis and treatment of different types of cancer has become a well-established practice in all developed countries and some countries of the developing world. The two major means of application in nuclear medicine are nuclear diagnostics and therapeutic (Choiński & Łyczko, 2021).

For diagnosis, the most popular techniques include Single Photon Emission Computed Tomography (SPECT) which entails introduction of a short lived radionuclide, attached to a suitable pharmaceutical into the patient followed by measurement of accumulation and movement of activity from outside (Rösch et al., 2017). SPECT involves gamma emitting radionuclides whose emission is detectable from a gamma camera(Zubaida & Ahmad, 2019). The other technique is called Positron Emission Tomography (PET) and employs the use of photon energy detection from positron– electron annihilation from which a PET machine detects and produces 2D and subsequently 3D images of the body by which the diseased site is captured and analyzed (Dash et al., 2015).

Treatment in nuclear medicine is referred to as therapy and involves the use of highly ionizing radiation applied to the disease whence the radiation destroys the diseased cells. This forms the first clinical application of nuclear medicine when in the beginning of 1940's I^{131} radioiodine was adopted for the therapy of thyroid disease (Mango, 2017)

For the two main nuclear medical applications – diagnosis and therapy each demand a special kind of radionuclide (Rösch et al., 2017) whose choice is based upon its decay features. In diagnosis the principle basically provides for radiation to the patient to be as low as possible to achieve the required imaging quality. However, in internal radiotherapy (endoradiotherapy) there is the ultimate need to deposit in the disease or malignant tissue a well-defined radiation dose to achieve the desired disease killing therapeutic effect(Yordanova et al., 2017). This approach is called Targeted Radionuclide therapy (TRT) which is conceptualized with the potential to deliver therapeutic radiation more specifically to tumor cells in a way as to minimize damage to surrounding normal tissues (Li et al., 2017)

However, the bodily distribution of this therapeutic radionuclide is variable among patients (Li et al., 2017), but the common nuclear medical practice is what is termed one-dose-fits-all or activity per unit body weight which is likely to cause deleterious effects to normal tissues in some patients. For instance, a fixed high activity of 2.8 – 7.4 GBq of I^{131} is often used to treat thyroid cancer (Mikolajczak et al., 2021). Conversely, more than 10 per cent of patients received blood doses exceeding the dose limit that will lead to myelotoxicity (Li et al., 2017) and 80 per cent of lesions studied received a dose deposition of less than 80 Gy. This study suggests that a fixed activity administration either give low amounts of therapeutic agent to avoid harm to normal tissues at the expense of loss of efficacy to tumour cells or give too much to potentially harm normal tissues by over exposure (Roesch & Martin, 2023). Strigari et al has shown that personalized (individual-tailored) treatment planning will increase the rate of survival and enhance clinical efficacy by showing strong correlation between absorbed dose, toxicity and treatment response (Buatti & Kiess, 2021). Further, uncertainties of activity quantification due to imaging limitations as well as post processing errors hamper achieving accuracy in individualized organ dose assessment. Hence the necessity for developing accurate, precise and streamlined methods for individualized patient dose estimation underlies the future of TRT.

Effects of radiation Exposure

Nuclear radiation has the capacity to harm human body in many ways; an example is causing burns and hair loss (Samuel, Sanny & William, 2016). However, the quantity of radiation which is expressed in many different units determines the extent of damage. One prominent unit of radiation is radiation dose unit also called **rad**. One rad is equal to 0.01 of a joule of nuclear energy per kilogram of body tissue. Radiation damage comes from the ionizing radiation (from alpha, beta, gamma or x rays) that pass through the tissue, the type of tissue is also a factor as some tissues can regenerate in case of low range radiation exposure while higher range may cause tissues death. On a general note, radiation damage apart from instigating onset of cancer in patients treated can cause a number of odious effects from diminution in red and white blood cell counts, temporary sterility, nausea, vomiting to serious consequences including malfunction of small intestine and blood vessels in which case the survival rate is quite low.

Radiopharmaceuticals in Advances Nuclear Medicine

When medical radioisotope is combined with a vector molecule which can be a pharmaceutical formulation, peptide, ligand or some other complex compatible chemical compound, a radiopharmaceutical is formed. It is the central factor in the theranostic approach which can be given by oral or interstitial routes to treat tumours. Most radiopharmaceuticals come in injectable form (Choiński & Łyczko, 2021). Due to the emission of lethal radiation, these radioactive medicines have the capacity to destroy cancer cells at target sites (Müller et al., 2018). Hence cancers associated with brain, thyroid, bones and lymphoma are treated with radiopharmaceuticals.

Another purpose for use of radiopharmaceuticals is diagnosis, and drugs used in this operation are called ‘tracers’. In comparison with therapeutic radionuclides, diagnostic nuclide radiation is smaller as related by ‘as low as reasonably acceptable (ALARA) norm. The contemporary concept of molecular imaging, therapy and clinical diagnosis, basically the notion in intrinsic radiation (endoradiotherapy) is categorised into gamma (γ) emitters, beta (positron β+ or electron β−) emitters and alpha emitters or their combinations (Dellepiane et al., 2023). Tc99m, a gamma ray emitter is the most widely used diagnostic radionuclide in clinical and preclinical studies, others such as I123 and Ga67 are also used. Positron emitting radionuclides F18, C11, O15, Zr89 and β− emitters Re186, 188, Sr89 and Y90 are in prevalent use (Rösch et al., 2017). The following table indicates the nuclides used in diagnosing the major body organs and the relative radiative activity.

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Table I: Diagnostic Radionuclides

Organ	Radionuclide Used	Activity
Bone	Sr87 F18	1mCi 1mCi
Brain	In113m	7 – 10mCi
Lungs	Tc99 I131 In113m	1 mCi 0.15 – 0.3 mCi 1mCi
Kidney	Hg197	1.50mCi
Pancreas	Se75	0.2mCi
Spleen	Cr51	0.3mCi
Placenta	Cr51 Tc99	0.05mCi 0.5 – 1mCi

The merits of nuclear medicine are numerous such as non-invasiveness and it gives a better means of identifying precise tumour region as well as its beneficial diagnosis of rebellious maladies such as endocrine disorders (Pupillo et al., 2018). Further, a better quantitative analysis is realisable with radiomedicine with numerous tools available. PET facilitates evaluation of Standard Uptake values (SUV) (Gallivanone et al., 2017). Some common therapeutic radionuclides are given in Table II below.

Table II: Therapeutic Radionuclides

Radioisotope	Emission	Half-life	Treatment
Co60	B γ	5.3 yrs	External cancer therapy
I131	β–	8.0 days	Thyroid tumour
Lu177	β–	6.6 days	Brachytherapy
Cu67	B γ	62 hours	HER2 positive cancer
Y90	β–	64 hours	Breast and bronchial cancer

The Status of Nuclear Imaging

Diagnostic imaging using gamma and positron emitting radionuclides has become the gold standard in nuclear medical investigations. Gamma radiation is used in single photon emission computed tomography (SPECT) while positron emitting radionuclides are utilized in positron emission tomography (PET).

SPECT

SPECT systems integrated with computed tomography (CT) are now useful for both whole body imaging (Planar) and tomographic imaging (Dash et al., 2015). Further, quantitative analysis with SPECT imaging is determined through conversion of acquired counts in terms of absorbed dose distribution (in Gy) which is invaluable for dosimetry and radionuclide therapy planning. Scatter correction is also realized using the triple energy window method (Li et al., 2017) whilst image resolution recovery techniques that enhance image quality are accessible by precise characterization of the shape of the point-spread function and that depends on the distance from the gamma camera. A rotational variation exists on account of the collimator septa's hexagonal configuration. Incorporation of reconstruction algorithm with point-spread function model is subsequently applicable (Yordanova et al., 2017). Whereas image degradation effects such as scatter, blurring and attenuation can be corrected to certain extent, partial volume and quantification errors perch to degrade SPECT images.

PET

In clinical practice, PET is employed for post radionuclidic therapy and management, however, PET is highly valuable in treatment planning, dosimetry and treatment assessment after radiotherapy. PET, like SPECT is similarly used for correction techniques. PET attenuation correction is achieved through resolving attenuation correction sonogram which basically works on CT data coregistration(). Single scatter simulation method is used for scatter correction in clinical practice (Dellepiane et al., 2022) while delayed-event subtraction method is administered for random count correction. The difference in photon annihilation time bequeaths information about the location of annihilation and line of response. Image

quality is nowadays enhanced using time of back projection step reconstruction(Gallivanone et al., 2017) while the availability of time of flight estimation has given way for low positron abundance imaging nuclides such as 90Y. The shape of the point-spread function is useful to improve image quality due to intrinsic resolution of PET detectors through incorporation during reconstruction method and this is referred to as resolution recovery (Uddin et al., 2020). On the whole, regular improvement of enhanced resolution and sensitivity helps to provide precision in standard uptake value (SUV) determination which offers good index of absorbed dose evaluation.

PET/MRI

PET integration with magnetic resonance imaging (MRI) provide over PET/CT, the advantages of higher soft tissue contrast which is essential for treatment planning, dosimetry and post radionuclide therapy assessment (Dash et al., 2015). Additionally, the technique provides simultaneous coregistration of MR images which facilitates accurate dose evaluation(). MRI is also employable in determining the tolerable dose with least organ damaging activity of radionuclide. Its demerits however include high costs and use of ferromagnetic implants contradictory to MRI(Kumar & Ghosh, 2021).

Theranostics

The term Theranostics refers to the permutation of a diagnostic test with a therapeutic procedure (Wang, 2022), in other words, it denotes a material that possesses both diagnostic and therapeutic capabilities (Li et al., 2017). Theranostic approach delivers therapeutic drugs and diagnostic imaging agents at the same time with the same dose. This makes an occasion for TRT tracers (Funkhouser, 2002). Theranostics as a concept was first put forwards by Herzog et al in the1990's (Wang, 2022) and launched by Funkhouser in 2002 (Li et al, 2017). The main idea behind theranostics is the use of radionuclidic power to determine patient's response to a specific radiopharmaceutical, to track the initial results of treatment and finally personalise and adopt the treatment for the patient (Pierce et al., 2021).

Table III: Theranostic Pairs

Radiotheranostic Pair	Half Lives
64Cu/67Cu	12.7 h / 2.6 d
86Y/90Y	14.7 h / 2.7 d
89Zr/90Y	3.3 d / 2.7 d
123I/131I	13.2 h / 8.0 d
124I/131I	4.2 d / 8.0 d
124I/186Re	4.2 d / 3.7 d
124I/188Re	4.2 d / 17 h
68Ga/67Ga	1.13 h / 3.3 d
68Ga/177Lu	1.13 h / 6.6 d
18F/177Lu	1.83 h / 6.6 d
18F/223Ra	1.83 h / 11.4 d
111In/225Ac	2.8 d /10 d
89Zr/225Ac	3.3 d /10 d
89Zr/227Th	3.3 d /18.7 d

Theranostic Radionuclides Production

I^{131} was the first conceptual radiotheranostic nuclide, used in 1946 by Dr. S. Hertz to treat thyroid disorder (Loveless et al., 2020). I^{131} decays by beta emission to Xe^{131} which further emits gamma radiation to reach its ground state. The first radionuclidic pairs used in theranostics were $^{86Y/90}Y$ with positron emitting ^{86}Y chosen to combine with electron (β^{-} ^{90}Y for breast cancer therapy (Roesch et al, 2022).

Several radionuclide combinations of the same element received considerations as good candidates for theranostics including $^{83}Sr/^{89}Sr$, $^{44}Sc/^{47}Sc$, $^{61}Cu/^{67}Cu$, $^{124}I/^{131}I$ and $^{152}Tb/^{161}Tb$. The characterization is that the first radionuclide is a beta emitter and the second is electron emitter. The benefit of this integration is that the chemical properties of the nuclide pairs are the same thereby facilitating subsequent pharmacological studies (Hall & Haskali, 2022). However, not all these nuclides are available, several of them are not yet commercially available. This is followed by extension in recent years to use

chemically similar isotopes to replace unavailable nuclide pairs. A good example is ^{68}Ga/^{177}Lu pair, ^{68}Ga is produced by ^{68}Ge/^{68}Ga generator or with cyclotronic acceleleration while ^{177}Lu is reactor produced (Pillai et al., 2003).

As stated earlier, absorbed radiation dose of the radiotherapeutic nuclide is critical to achieving effective therapy just as it stands to pose toxicity in the event of over exposure and hence the need to quantify absorbed dose (Rösch et al., 2017). The ultimate goal of theranostics is extraction of absorbed dose in the individual patient which is achieved through the use of diagnostic decay scheme that serve to provide dosimetric information of the individual patient (Gallivanone et al., 2017).

Radionuclide Production Data, A Review

Sharifian et al, (2019) calculated production cross section of ^{86}Y, ^{87}Y, ^{88g}Y via the ^{89}Y(p,x) reaction for incident energies up to 50 MeV. Choinski et al (2001) produced ^{90}Y through thermal neutron irradiation of natural Yttrium. (Dellepiane, Casolaro, Mateu, Scampoli, Voetena & Braccini, 2022) measured ^{61}Cu reaction cross section from Zn(p,α) ^{61}Cu reaction at 18 MeV and found good agreement with the few data available including Szelecsenyl et al (2005), Udolin et al (2007) and Asad et al (2014). Samar et al (2012) also reported evaluation data for ^{67}Cu via ^{68}Zn(p,2p)^{67}Cu reaction and recorded partial agreement with TALYS and EMPIRE productions. ^{67}Cu limited availability has been identified as the major drawback to its application in theranostics (Krasnovskaya et al., 2023).

Mikolajzak et al (2021) reported ^{44}Sc and ^{47}Sc production data using accelerator and reactor processes respectively. ^{40}Ca(α,p)^{43}Sc and ^{40}Ca(α,n)^{43}Ti to give ^{43}Sc reaction used accelerator up to 20 MeV. Proton irradiation production was also reported by Domnanovich et al (2017) resulting in high yield of ^{43}Sc. Carzaniga et al (2019) reported ^{43}Sc production with deuteron bombardment of enriched ^{40}Ca target while MIkolajzak et al reported ^{44}Sc production from direct irradiation of enriched ^{44}Ca target or via Titanium generator. Krajewski et al (2013) reported accelerating protons on ^{44}Ca target to produce ^{44}Sc, likewise Alliort et al (2015) reported a 3 hour bombardment of ^{44}Ca to produce ^{44}Sc.

Uccelli et al. (2022) reported ^{186}Re production from the ^{185}Re (n,g)^{186}Re reaction. Mastern et al (2017) reported cross sections for proton induced reactions on ^{186}W target, in addition, Ali et al (2018) reported deuteronic particle induced reaction with ^{186}W target. However, only the work of Scott et al (1968) is devoted to ^{186}W irradiation with alpha particles and ^{3}He because data on production is scarce and likewise ^{188}Re production. ^{149}Tb, ^{152}Tb and ^{155}Tb were reputedly produced through high energy proton irradiation of Tantalum target (Müller et al., 2018). Production of ^{161}Tb used ^{160}Gd (n,g)^{161}Gd - ^{161}Tb as reported by Lehenberger et al (2016) in a concept similar to no carrier added production. Kumar & Ghosh (2021) reported 13 cross sections for ^{124}I production through different reaction channels while Koning (2013) reported cross sections for ^{131}I production.

2. OUTLOOK AND CONCLUSION

Essentially, there is a strong requirement to pursue, explore and inculcate innovation into production of new theranostic radionuclides because production of new nuclides will enhance their application into manufacture to make way for precision, specificity and sensitivity across a broad spectrum of diseases so as to be able to put radiation dose and its effects to the barest possible minimum. Further, development of new biomarkers and imaging agents would contribute to more accurate disease verification and facilitate precise dosimetric profile of patients. However good and precise a theranostic procedure could be, its first a function of the integrated radionuclides with good and suitable decay properties plus a seamless chemical behavior to be able to sift through patient's metabolic regime without and comorbidities.

Further, improvement of dosimetric precision surely involves research and development to improve activity calibration and analysis. Several advanced imaging techniques using theranostics and in the pipeline (Li et al, 2017) and they include functional radionuclide imaging techniques such as planar SPECT, PET imaging for different organs including heart, liver, lungs, kidney, bone marrow and tumors as well as bremsstrahlung imaging. Other important quantitative methods include planar scintigraphy which is based on calculating the geometric mean of two conjugate counting views integrated with effective attenuation attenuation correction, Quantitative SPECT to provide 3D spatial information to solve the problem of organ overlap which limits the success of planar scintigraphy.

All these chiefly owe their functionality to radiation energy from radionuclide emission of theranostic nuclides and it consequently follows that adequate education and training of nuclear medical personnel will improve their appreciation of nuclear emissions and how to use them in enhancing predictions and in conducting risk benefit analysis in order to arrive at the best medical decisions to select the best radiotheranostic approach for each patient.

While the risk of radiation dose cannot be completely eliminated, it could be effectively put to minimum through measurements, experiments and simulations of nuclear reactions in order to establish the radionuclides that will deliver lethal dose to diseases and be most friendly with normal tissues.

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