

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,400

Open access books available

133,000

International authors and editors

160M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Recent Advances in Biodistribution, Preclinical and Clinical Applications of Radiolabelled Iodine

Khaled Soliman, Ahmed Alenezi, Abdullah Alrushoud, Salman Altimyat, Mousa Bakkari and Hanaa Alshikh

Abstract

Adequate understanding of radiopharmaceutical distribution in the body of the patient has both spatial and temporal characteristics and they are the key factor to consider when planning successful radio pharmaceutical therapy, because they are an integral part of the radiation dosimetry calculations of any proposed personalized treatment. In this chapter we will focus on radioiodine therapy for thyroid cancer patients since it is a widely known practice in clinical oncology. Factors affecting the radioiodine organs' distribution will be examined in sufficient details using the available published research in the scientific literature. The literature will be reviewed extensively and summarized in this chapter. Another aim is to provide the medical practitioners with a quick reference guide to this clinically important area of expertise; often mastered by medical physicists with background in radiation physics, mathematics and medical imaging analysis. This chapter will cover recent advances in the area of radioiodine biodistribution modeling with applications in preclinical and clinical studies.

Keywords: radioactive iodine, biodistribution, clinical applications, recent advances

1. Introduction

This chapter will focus on presenting a review of the current situation regarding the use of radioiodine labeled agents in clinical and preclinical nuclear medicine imaging and radionuclide therapy. We will show the actual clinical applications and summarize the preclinical and clinical research efforts undergoing today in this dynamic field of medicine. These agents were found to be interesting since they can be applied to both imaging the disease and for therapy, by delivering a well localized radiation dose to a target tissues or tumor volume within the human anatomy. This delivery is carried out by the so called carrier systems such as, monoclonal antibodies or fragments of those and also by nanoparticles both inorganic and organic and microspheres. These carriers will carry the radioactivity of the radionuclide to the targeted biological site. There are two types of targeting the first is direct targeting, when the pharmaceutical accumulation in a tissue or site is done through inherent pathophysiological characteristics; or indirect which occurs if the used carries possess higher affinity to bind to a particular cell type or tissue. The good example of such radiopharmaceutical is tositumomab

(¹³¹I-labeled anti-CD20 antibody), which received Food and Drug Administration (FDA) approval for the treatment of Non-Hodgkin's lymphoma in 2003.

2. Biodistribution modeling

Physical and temporal variability of the iodine –¹³¹ activity distributions in tissue constitute what is commonly called bio distribution models. The models are based on what is known in mathematics as compartmental modeling. For the sake of radiation dose calculations scientist may use different models to estimate the activity present in the patient body and the fraction of the radioactivity released from his or her body using simple two compartment model. More rigorous models also exist, having more than five compartments.

Biodistribution experiments are also published and new ones are still being published it is a dynamic field of research. The same apply for different radiopharmaceuticals. Organs Residence time is one important factors being measured while developing a bio distribution experiments leading to the proposal of a new bio distribution model.

Factors altering such models are very important to be aware of, because the alteration in the bio distribution will directly impact the radiation dose calculations and therefore the safety of the patients undergoing radioiodine therapy. To the best of our knowledge there are no general agreement on the methods or standards applied when reporting bio distribution studies. Therefore we will attempt to summarize the ones in the literature.

2.1 Biokinetic data

Biokinetic data are variables that describe the bio distribution space time functions.

Among the most common of these variables are: the uptake fraction by the organ example the thyroid, the excreted fraction as (urine or feces), the biological half-life or time in a specific organ or body tissues like blood, thyroid, and intestine for example. The fractions are mostly given as % and the time are often given in days most of the times in the case of radioactive iodine. Biokinetic data for radioactive iodine are reported in ICRP-30 [1].

2.2 Radionuclide delivery system

Radionuclide delivery systems are now as antibodies, nanoparticles both inorganic and organic and finally as Microspheres.

In this reference good information is given on targeted radionuclide therapy for the thyroid cancer treatment. Parallelism is shown between preclinical animal models in rats and mice versus humans [2].

Translation of the experimental findings and research results is an issue that warrants the attention of the researcher; in this case the range of radiation in tissues and the organ sizes needs to be considered. Also the difference among the metabolism and metabolism rate models used directly affects the biodistribution in the animal or the human under study.

2.3 Compartmental biological modeling

Compartmental models are used for internal radioisotope ingestions or injections dosimetry since the seventies. We are referring to the ICRP publication 30 published in 1979. In that documents several compartmental models are proposed, we focus on the model proposed for iodine metabolism in humans.

In order to apply the model a set of differential equations has to be solved simultaneously to obtain the biodistribution of iodine in human body. The equations can be solved numerically using algorithm included in software like Mathematica or Matlab.

Biokinetic models parameters are taken for healthy individuals. In order to apply the models to cancer patients for example, the metabolic data has to be customized to represent their actual metabolism status. Currently, scientists are recommending the use of personalized radiopharmaceutical therapy where each therapeutic procedures is planned based on the individual patient data and not using the generic data from reports like ICRP and others.

The following 4 differential equations are for the model in **Figure 1**:

$$dq_1 / dt = -(\lambda_p + \lambda_{12})q_1 \quad (1)$$

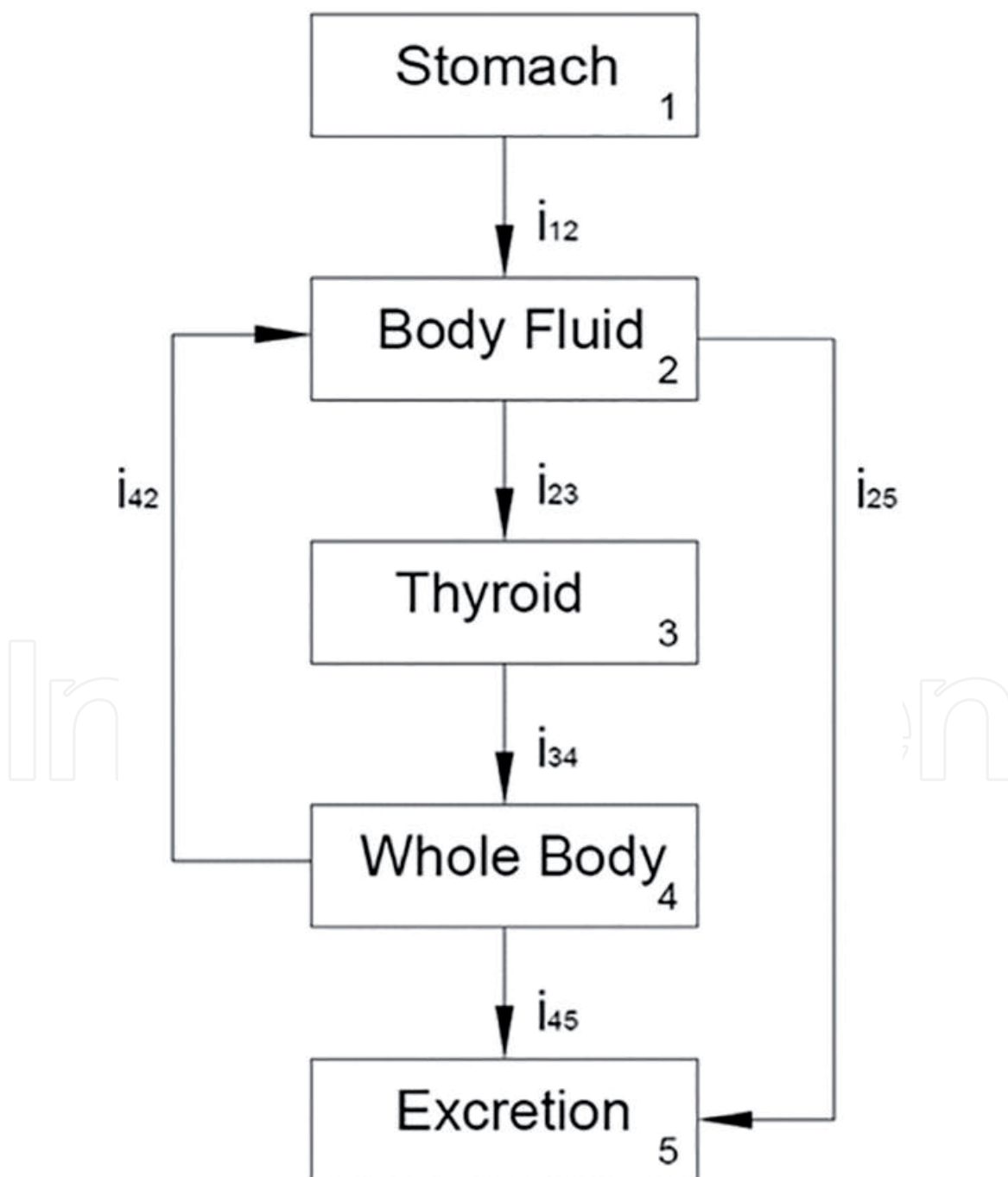


Figure 1.
Five compartments human body biokinetic model of iodine as per ICRP-30 report.

$$dq_2 / dt = \lambda_{12}q_1 - (\lambda_p + \lambda_{25} + \lambda_{23})q_2 + \lambda_{42}q_4 \quad (2)$$

$$dq_3 / dt = \lambda_{23}q_2 - (\lambda_p + \lambda_{34})q_3 \quad (3)$$

$$dq_4 / dt = \lambda_{34}q_3 - (\lambda_p + \lambda_{42} + \lambda_{45})q_4 \quad (4)$$

This five compartment model is the one proposed by the –30 to represent the biokinetic model of iodine in healthy individuals.

After solving the system of simultaneous four differential equations above the solution yield the following.

$$T_{1/2}(\text{thy}) = 80 \text{ d}, T_{1/2}(\text{Body Fluid}) = 0.25 \text{ d}, i_{23}(\text{thy}) = 30\%, i_{25}(\text{excretion}) = 70\%.$$

These results are for the healthy individuals, solving the same system for thyroid cancer patients yields the following [3, 4]:

$$T_{1/2}(\text{thy}) = 0.66 \text{ d}, T_{1/2}(\text{Body Fluid}) = 0.52 \text{ d}, i_{23}(\text{thy}) = 12\%, i_{25}(\text{excretion}) = 88\%.$$

We can see that there is a significant difference in the values obtained. Where the importance of personalized dose estimates, the analysis of the results dictates the importance to take into account the pathology of the patients and his thyroid disease status and diagnosis before interpreting the results of any biokinetic experiment or data analysis.

2.4 Biodistribution studies and biokinetic models

The radiopharmaceutical kinetic data often known as Biodistribution is a function of space and time. Imaging the whole body or specific region using planar scintillation Gamma camera can be used to obtain the necessary data for the study. The accuracy of this method is better when the radiopharmaceutical is localized in a specific area of the body or organ and this region do not overlap with other uptake area in the planar projection.

A region of interest (ROI) is determined in order to estimate the absolute amount of radioactivity in the organ. Modern Gamma cameras provide capability to delineate ROI of nay shape and to perform statistical analysis on the pixels inside the ROI to obtain the number of counts per pixel inside the ROI and the count rate.

Sequential imaging as a function of time postadministration of the radiopharmaceutical provides the time dependence of activity (time-activity curve) [5]. In this reference a full description of the imaging based method using planar gamma camera, SPECT and PET are described in great details.

Clinical and preclinical imaging protocols are published by different groups of scientists worldwide. Imaging is the key part of the bio distribution data acquisition experiment and constitutes the primary data for the model that will be proposed based on the results obtained during the experiment.

Imaging acquisition at different times after oral administration of a known activity of I-131 1100 MBq is the most common used with human subjects. Using a clinical gamma camera scanned data form the organs of interest, example the

stomach using an region of interest (ROI) is converted to counts per pixel per sec. Will be acquired and data will be extracted for further analysis.

2.5 Image- based, patient- specific dosimetry

Such technique will allow the distribution of the agent in tumors and normal organs to be quantified [6]. Dosimetry as implemented in RPT may be thought of as the ability to perform the equivalent of a pharmacodynamic study in treated patients in real time [7]. When patient dosimetry is performed it allow prediction of treatment success based on reported results in the literature, it is then possible to calculate both normal tissue and tumor doses.

Organ uptake, Remainder of body uptake, Assumed waste. Derivation of the biological half –life values in different organs: they are theoretical estimations of the time-dependent quantity of I-131 in various compartments.

In Ref. [7] the authors have found that estimated biological half-life's obtained via the biokinetic model of radioiodine for thyroid cancer patients was found to strongly deviate from those recommended by Eckerman's suggestion for healthy male.

2.6 Organs residence times

By definition lambda is given by:

$$\lambda = \text{Ln}(2) / T_{1/2} \quad (5)$$

Where $T_{1/2}$ is the half-life. it could be the biological (T_b), physical (T_p) or effective (T_{eff}) half-life depending on the application.

Knowing that:

$$1 / T_{\text{eff}} = 1 / T_b + 1 / T_p \quad (6)$$

The biological half-life of radiopharmaceuticals is organ dependents. We will observe dissimilar values for different organs.

Time integrated activity coefficients (TIAC) are known also as organs residence times. They are proportional to the radiation absorbed dose by the organ or body tissue.

The radiopharmaceutical effective half-life is different for each organ in the body. And they are dependent of the biodistribution or the individual organ uptake fraction of the total injected activity. The same applies to the tumor tissues targeted by the radiopharmaceutical therapy; in our case here it is the remaining of the post ablation thyroid tissues treated using I-131.

3. Radioactive iodine treatment for thyroid cancer patients

In many medical applications involving the administration of iodine-131 (^{131}I) in the form of iodide (I^-), most of the dose is delivered to the thyroid gland [3].

To reliably estimate the thyroid absorbed dose, the following data are required: the thyroid gland size (i.e. mass), the fractional uptake of ^{131}I by the thyroid, the spatial distribution of ^{131}I within the thyroid, and the length of time ^{131}I is retained

in the thyroid before it is released back to blood, distributed in other organs and tissues, and excreted from the body [4, 8–10].

Estimation of absorbed dose to non-thyroid tissues likewise requires knowledge of the time course of activity in each organ. Such data are rarely available, however, and therefore dose calculations are generally based on reference models. The MIRD and ICRP have published metabolic models and have calculated absorbed doses per unit intake for many nuclides and radioactive pharmaceuticals. Given the activity taken into the body, one can use such models and make reasonable calculations for average organ doses. When normal retention and excretion pathways are altered, the baseline models need to be modified, and the resulting organ dose estimates are subject to larger errors.

Even if the uptake of iodine is very specific to thyroid tissue, side effects from off-target accumulation are common. Frequent short-term side effects after ^{131}I therapy of patients with differentiated thyroid cancer are gastrointestinal symptoms, pain or swelling in the neck or salivary glands, while frequent late effects are functional problems with salivary glands [11–15].

The hypothalamus-pituitary-thyroid (HPT) axis is an example of an endocrine feedback loop that is known to have a circadian rhythm [16].

Patients with chronic renal failure exhibited significant salivary gland, oral, nasal, and gastric activity 1 week after radioiodine administration [17].

3.1 Sodium/iodide symporter (NIS)

Active iodide (I^-) transport in both the thyroid and some extra-thyroidal tissues is mediated by the Na^+/I^- symporter (NIS).

The cDNA encoding NIS was isolated in 1996, marking a major breakthrough in thyroid research that led to the subsequent characterization of NIS at the molecular level. Functional NIS is found in several extra-thyroidal tissues, such as the salivary glands, stomach, and lactating breast, as well as in primary and metastatic breast cancers. The latter findings have raised the possibility that NIS-mediated $^{131}\text{I}^-$ treatment may be effective in breast cancer. One of the most remarkable properties of NIS is that it transports different substrates with different stoichiometries. TSH is the primary regulator of NIS in the thyroid at both the transcriptional and post-transcriptional levels. At the molecular level, excess I^- may have a deleterious effect on the thyroid by modifying NIS mRNA stability and increasing the production of reactive oxygen species. Thyroidal NIS function is also regulated by direct cross talk between NIS and a K^+ channel [18].

3.2 Future perspective and applications

In the last two decades, NIS has become an important player in the use and optimization of gene therapy owing to its capacity as a reporter and as a therapeutic gene. NIS could be introduced into virtually any cell or tissue for imaging and/or therapeutic purposes. NIS is becoming the counterpart for human studies of green fluorescent protein and luciferase, which have been used extensively in cells and other organisms.

NIS expression and activity correlate with cell viability because only living cells can accumulate I^- . NIS also offers higher detection sensitivity, because it actively transports its substrates rather than simply binding a substrate stoichiometrically. Moreover, NIS can translocate a variety of substrates, which can be detected using different systems, such as gamma cameras, PET, and SPECT (single-photon emission computed tomography) combined with computed tomography (CT) [18].

4. Newly introduced I-131 labeled radiopharmaceutical therapy agents

Radiopharmaceutical therapy (RPT) is emerging as a safe and effective targeted approach to treating many types of cancer. In RPT, radiation is systemically or locally delivered using pharmaceuticals that either bind preferentially to cancer cells or accumulate by physiological mechanisms. Almost all radionuclides used in RPT emit photons that can be imaged, enabling non-invasive visualization of the biodistribution of the therapeutic agent. Compared with almost all other systemic cancer treatment options, RPT has shown efficacy with minimal toxicity. With the recent FDA approval of several RPT agents, the remarkable potential of this treatment is now being recognized [6]. We will mention a few emerging clinical development of radioiodine labeled RPT agents newly available or still under development at the present time. RPT development is a multidisciplinary endeavor, requiring expertise in radiochemistry, radiobiology, oncology, pharmacology, medical physics and radionuclide imaging and dosimetry.

Theranostic is the general concept of using a radionuclide- labeled agent that may be imaged to guide radiopharmaceutical therapy; a radionuclide that may be used for both imaging and therapy, and it is the new trend in RPT.

I-131 meta- iodobenzylguanidine (mIBG): for Adrenergic receptor tumors; the active uptake mechanism via the adrenaline transporter and storage in presynaptic neurosecretory granules. FDA approved but clinical trials are ongoing. This radiopharmaceutical can be used to treat patients with neuroblastomas [19].

mIBG radiolabelled with high- specific- activity iodine-131 was recently approved by the FDA for the treatment of adult and pediatric patients aged 12 years or older with unresectable metastatic pheochromocytoma or paraganglioma.

I-131- labeled CLR131 for Pediatric cancer, head and neck cancer, multiple myeloma, leukemia, lymphoma. The radio-labeled phospholipid ether analogue targeting cancer cell- specific lipid raft microdomains. It is still undergoing the phase of clinical trials and testing.

I-131- labeled CLR1404 for unresponsive solid tumor, multiple myeloma. The radio-labeled phospholipid ether analogue targeting cancer cell-specific lipid raft microdomains. It is still undergoing the phase of clinical trials and testing.

4.1 Antibody based radionuclide therapy

Radiolabeled sdAbs prove to be promising vehicles for molecular imaging and targeted radionuclide therapy of metastatic lesions in the brain. Administration of [I-131]-2Rs15d and [Ac-225]-2Rs15d alone and in combination with trastuzumab showed a significant increase in median survival in 2 tumor models that remained largely unresponsive to trastuzumab treatment alone [20]. Puttemans et al. [21] have described the use of the anti-HER2 sdAb 2Rs15d, coupled to ¹¹¹In or ¹³¹I for detection via PECT/CT, and coupled to ¹³¹I or ²²⁵Ac for targeted radionuclide therapy (TRNT) of HER2^{pos} brain lesions and compare its therapeutic efficacy and systemic toxicity to that of trastuzumab, a clinically-approved anti-HER2 treatment. They have demonstrated that radiolabeled sdAbs are ideal vehicles for targeted radionuclide therapy and molecular imaging, not only for systemic disease, but also for metastatic lesions in the brain. Moreover, histopathological analysis after therapy revealed no significant early toxicity. Dosimetry based on ex vivo biodistribution data confirmed most activity is retained within the kidneys until 48 h after administration, however after extrapolation to therapeutic activities the cumulative absorbed dose (25 Gy) remains close to the considered toxicity threshold of 23 Gy to kidneys [21].

The amount of ¹³¹I- tositumomab prescribed to patients was determined by assessing the whole- body clearance rate, so that the amount administered was adjusted to deliver the same whole- body absorbed dose in all treated patients [21], making it the first RPT agent whose package insert specified an absorbed dose- based treatment planning procedure. Such an approach was, in part, necessitated because the radioiodine in iodine-¹³¹- labeled antibodies is cleaved (due to dehalogenation) from the antibody if the radiolabelled antibody construct is internalized.

4.2 Iodine-131 labeled Metuximab

Radioimmunotherapy using antibodies injection is another application of I-¹³¹ in oncology. Administered to patients suffering from hepatocellular carcinoma (HCC), the product will target the hepatic cancer cells while sparing other adjacent tissues. The whole body biodistribution is required in order to perform radiation dosimetry, evaluate the risk from the treatment and to ensure patient safety.

4.3 I-¹³¹ - labeled a CD45

I-¹³¹ - labeled a CD45 for Bone marrow transplant preparation.

The I-¹³¹ based antibody targeting CD45+ cells for bone marrow ablation before transplantation. It is still undergoing the phase of testing and planned clinical trials. Early studies showed the potential to image the radioiodinated antibodies using SPECT [22, 23].

The radiolabelled antibodies were used for total body irradiation in preparation for bone marrow transplantation (BMT). report results of a study on patients with acute myelogenous leukemia in a phase I clinical trial where results showed that it is possible while appending I-¹³¹ to M195 antibody to deliver beta emitter particles to the targeted cells in the bone marrow, it was also possible to image the disease in the bone marrow.

The tumor-homing property of mesenchyme stem cells (MSCs) allows targeted delivery of therapeutic genes into the tumor microenvironment. The application of sodium iodide symporter.

(NIS) as a theranostic gene allows noninvasive imaging of MSC biodistribution and transgene expression before therapeutic radioiodine application. Linking therapeutic transgene expression to induction of the chemokine CCL5/RANTES allows a more focused expression within primary tumors, as the adoptively transferred MSC develop carcinoma-associated fibroblast-like characteristics. Although RANTES/CCL5-NIS targeting has shown efficacy in the treatment of primary tumors, it was not clear if it would also be effective in controlling the growth of metastatic disease. To expand the potential range of tumor targets, we investigated the biodistribution and tumor recruitment of MSCs transfected with NIS under control of the RANTES/CCL5 promoter (RANTES-NIS-MSC) in a colon cancer liver metastasis mouse model established by intrasplenic injection of the human colon cancer cell line LS174t. Results show robust MSC recruitment with RANTES/CCL5-promoter activation within the stroma of liver metastases as evidenced by tumor-selective iodide accumulation, immunohistochemistry, and real-time polymerase chain reaction. Therapeutic application of ¹³¹I in RANTES-NIS-MSC-treated mice resulted in a significant delay in tumor growth and improved overall survival. Conclusion: This novel gene therapy approach opens the prospect of NIS-mediated radionuclide therapy of metastatic cancer after MSC-mediated gene delivery [24].

4.4 Newly introduced radioiodine labeled nanoparticles and microspheres

in the area of preclinical development regarding tumor targeted therapy using radioiodine labeled molecules an active research work is undergoing using Nano and microsphere technologies. The good example of such radiopharmaceutical is tositumomab (131I-labeled anti-CD20 antibody), which received Food and Drug Administration (FDA) approval for the treatment of Non-Hodgkin's lymphoma in 2003.

Initial clinical trials of 131I- labeled iodized oil (131I- labeled Lipiodol) were completed in the late 1980s/early 1990s (285–288), and clinical investigations of this treatment modality continued until 2013 (NCT00116454, NCT00870558 and NCT00027768).

Administration of 131I- labeled Lipiodol in the adjuvant setting, after resection or radiofrequency ablation for hepatocellular carcinoma, yielded a 6- month increase in recurrence free survival and a 24- month increase in median overall survival [25].

RPT has proven to be an effective cancer treatment when other standard therapeutic approaches have failed. However, despite more than 40 years of clinical investigation, RPT has not become a part of the cancer treatment armamentarium in the same way as other therapies. 'Targeted' cancer therapies are associated with clinical trial failure rates of 97% (ref. 1), partly because the agents targeted a pathway that was not involved in promoting the cancer phenotype². By contrast, RPT has been unsuccessful owing to a failure to adopt and rigorously evaluate this treatment modality, which may be explained in part by the multidisciplinary nature of the treatment.

Additional challenges facing the development and application of RPT include public perception and fear of radioactivity as well as the perceived complexity of the treatment.

The need for a new specialty or subspecialty to provide the multidisciplinary training needed to safely and effectively administer RPT agents to patients and subsequently manage them. Such a specialty or subspecialty would require training in nuclear medicine, radiation oncology and also general oncology as delivery of radiation is involved, the participation of medical physicists familiar with both imaging and radionuclide dosimetry is important.

The article by Jongho Jeon [25], reviews recent progress in cancer therapy using radiolabeled nanomaterials including inorganic, polymeric, and carbon-based materials and liposomes. The article first provides an overview of radiolabeling methods for preparing anticancer agents that have been investigated recently in preclinical studies. Next, they discuss the therapeutic applications and effectiveness of beta or alpha emitter-incorporated nanomaterials in animal models and the emerging possibilities of these nanomaterials in cancer therapy [26].

In contrast to biologics or chemotherapeutics, both radiation delivery and the biological response to radiation may be mathematically modeled and used to understand the parameters of a treatment that are most important in influencing efficacy and toxicity. The capability to use multiple agents in one carrier is very unique about nanomaterials [27].

5. Conclusion

Unlike chemotherapy and external beam radiation therapy RPT has not yet been established as a treatment modality in oncology. Mainly because lots of suggested

RPT agents are still undergoing clinical trials and some are still in the preclinical stage. The known fact is that, the tumor response to RPT can be mathematically modeled and also the radiation dosimetry is well established [24, 25]. There are research projects underway that focus on the use of combination therapy using targeted RPT along with chemotherapy for example in the treatment of resistant tumors that cannot be treated uniquely by traditional therapy like chemotherapy, this area of research is also quit active at the present time [28].

One challenge is the validation studies and the regulatory approval of clinical software packages that need to be established prior to routine clinical use is still underway. Certainly this area of research and development is very dynamic and requires multidisciplinary team work including oncology, nuclear medicine, imaging sciences and medical physics; and clinically also it will probably require some kind of new medical subspecialty. The medical physicist should be trained in both imaging based and radionuclide dosimetry methods. As medical physicists we see this as an opportunity for future medical physicist starting his or her career to specialize in this new evolving area of clinical medical physics.

Conflict of interest

The authors declare no conflict of interest.” or delete this entire section.

Author details


Khaled Soliman^{1*}, Ahmed Alenezi², Abdullah Alrushoud¹, Salman Altimyat¹, Mousa Bakkari¹ and Hanaa Alshikh¹

1 Medical Physics Department, Prince Sultan Military Medical City, Riyadh, Saudi Arabia

2 College of Applied Medical Sciences, King Saud University Riyadh, Saudi Arabia

*Address all correspondence to: ksoliman@psmmc.med.sa

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] ICRP 1979. Limits of intakes of Radionuclides by workers, ICRP Publication 30 (part 1). Ann. ICRP 2 (3-4).
- [2] Spetz J, Rudqvist N, Forssell-Aronsson E. Biodistribution and dosimetry of free ^{211}At , ^{125}I - and ^{131}I - in rats. *Cancer Biother Radiopharm.* 2013 Nov;28(9):657-664. doi: 10.1089/cbr.2013.1483. Epub 2013 Jun 22. PMID: 23789969.
- [3] Brill, A. B., Stabin, M., Bouville, A. and Ron, E. Normal Organ Radiation Dosimetry and Associated Uncertainties in Nuclear Medicine, with Emphasis on Iodine-131. *Radiat. Res.* 166, 128-140 (2006).
- [4] Chen CY, Chank PJ, Changlai SP, Pan LK. Effective half-life of iodine for five thyroidectomy patients using an in vivo Gamma Camera approach. *L. Radiat. Res;*48:4856-4493 (2007).
- [5] Siegel JA, Thomas SR, Stubbs JB, Stabin MG, Hays MT et al. MIRD pamphlet No.16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. *J Nucl Med* 1999;40:37S-61S.
- [6] Longcor, J. & Oliver, K. Phase 1, open-label, dose escalation study of I-131-CLR1404 (CLR 131) in patients with relapsed or refractory multiple myeloma. *Blood* 134, 1864 (2019).
- [7] Sgouros G, Bodei L, McDevitt MR, Nedrow JR. Radiopharmaceutical therapy in cancer: clinical advances and challenges. *Nature Reviews* 2020; 19: 589-608. <https://doi.org/10.1038/s41573-020-0073-9>.
- [8] Charlotte K. Andersson^{1*}, Mikael Elvborn¹, Johan K. E. Spetz¹, Britta Langen¹ & Eva B. Forssell-Aronsson^{1, 2} Biodistribution of ^{131}I in mice is influenced by circadian variations. *Scientific reports, nature research open.* 2020 10:15541.
- [9] Bolch, W. E., Eckerman, K. F., Sgouros, G. & Thomas, S. R. MIRD pamphlet N. 21: a generalized schema for radiopharmaceutical dosimetry—standardization of nomenclature. *J. Nucl. Med.* 50, 477-484. <https://doi.org/10.2967/jnumed.108.056036> (2009).
- [10] Huang C-C, Lin Y-H, Kittipayak S, Hwua Y-S, Wang S-Y, Pan L-K (2020) Biokinetic model of radioiodine I-131 in nine thyroid cancer patients subjected to in-vivo gamma camera scanning: A simplified five-compartmental model. *PLoS ONE* 15(5): e0232480. <https://doi.org/10.1371/journal.pone.0232480>
- [11] Kolbert KS, Pentlow KS, Pearson JR, mSheikh A, Finn RD, Humm L, Larson SM. Prediction of absorbed dose to normal organs in thyroid cancer patients treated with ^{131}I by use of ^{124}I PET and 3-Dimensional internal dosimetry software. *J NUcl Med* 2007; 48:143-149.
- [12] Lu, L., Shan, F., Li, W. & Lu, H. Short-term side effects after radioiodine treatment in patients with differentiated thyroid cancer. *Biomed. Res. Int.* 2016,4376720. <https://doi.org/10.1155/2016/4376720> (2016).
- [13] Almeida, J. P., Sanabria, A. E., Lima, E. N. & Kowalski, L. P. Late side effects of radioactive iodine on salivary gland function in patients with thyroid cancer. *Head Neck* 33, 686-690. <https://doi.org/10.1002/hed.21520> (2011).
- [14] Klein Hesselink, E. N. *et al.* Effects of radioiodine treatment on salivary gland function in patients with differentiated thyroid carcinoma: a prospective study. *J. Nucl. Med. Off. Publ. Soc. Nucl. Med.* 57, 1685-1691.

<https://doi.org/10.2967/jnumed.115.169888> (2016).

[15] Pashnehsaz, M. *et al.* Gastrointestinal side effects of the radioiodine therapy for the patients with differentiated thyroid carcinoma two days after prescription. *World J. Nucl. Med.* **15**, 173-178. <https://doi.org/10.4103/1450-1147.174703> (2016).

[16] Philippe, J. & Dibner, C. Thyroid circadian timing: roles in physiology and thyroid malignancies. *J. Biol. Rhythms* **30**, 76-83. <https://doi.org/10.1177/0748730414557634> (2015).

[17] Clement, S. C. *et al.* Intermediate and long-term adverse effects of radioiodine therapy for differentiated thyroid carcinoma—a systematic review. *Cancer Treat. Rev.* **41**, 925-934. <https://doi.org/10.1016/j.ctrv.2015.09.001> (2015).

[18] Silvia Ravera, Andrea Reyna-Neyra, Giuseppe Ferrandino, L Mario Amzel, Nancy Carrasco Annual review of physiology **79**, 261-289, 2017.

[19] Schoot, R. A. *et al.* The role of ¹³¹I metaiodobenzylguanidine (MIBG) therapy in unresectable and compromising localized neuroblastoma. *Eur. J. Nucl. Med. Mol. Imaging* **40**, 1516-1522 (2013).

[20] Aktas A, Kazak K, Kocabas B, Aras M, Tutuncu NB, Gencoglu A. The biodistribution of radioiodine on posttherapy iodine-131 scan in thyroid cancer patients with chronic renal failure. *Nucl Med Commun.* (2008) **29**(11): 943-948 [DOI: 10.1097/MNM.0b013e32831089e0]. PMID: 18836371.

[21] Puttemans J, Dekempeneer Y, Eersels JL, Hanssens H, Debie P, Keyaerts M, Windhorst AD, van der Aa F, Lecocq Q, Breckpot K, Morgenstern A, Bruchertseifer F, Lahoutte T, Devoogdt N,

D'Huyvetter M. Preclinical Targeted α - and β^- -Radionuclide Therapy in HER2-Positive Brain Metastasis Using Camelid Single-Domain Antibodies. *Cancers (Basel)*. 2020 Apr 21; **12**(4):1017. doi: 10.3390/cancers12041017. PMID: 32326199; PMCID: PMC7226418.

[22] Wahl, R. L. The clinical importance of dosimetry in radioimmunotherapy with tositumomab and iodine I 131 tositumomab. *Semin. Oncol.* **30**, 31-38 (2003).

[23] Larson, S. M. *et al.* Imaging of melanoma with I-131-labeled monoclonal antibodies. *J. Nucl. Med.* **24**, 123-129 (1983).

[24] Mach, J. P. *et al.* Tumor localization in patients by radiolabeled monoclonal antibodies against colon carcinoma. *Cancer Res.* **43**, 5593-5600 (1983).

[25] Jongho Jeon. Review of Therapeutic Applications of Radiolabeled Functional Nanomaterials. *Int. J. Mol. Sci.* **2019**, **20**(9): 2323 [doi:10.3390/ijms20092323]. PMID: 31083402.

[26] Knoop K, chwenk N, Schmohl K, Müller A, Zach C, Cyran C, Carlsen J, Böning G, *et al.* Mesenchymal Stem Cell-Mediated, Tumor Stroma-Targeted Radioiodine Therapy of Metastatic Colon Cancer Using the Sodium Iodide Symporter as Theranostic Gene. *J Nucl Med* 2015; **56**:600-606 [DOI: 10.2967/jnumed.114.146662].

[27] Kim, D., Shin, K., Kwon, S.G., Hyeon, T. Synthesis and Biomedical Applications of Multifunctional Nanoparticles. *Adv. Mater.* **2018**, **30** (49), e1802309. PMID: 30133009.

[28] ICRP publication 140. Radiological protection in therapy with radiopharmaceuticals. (2019) ICRP. Published by SAGE.