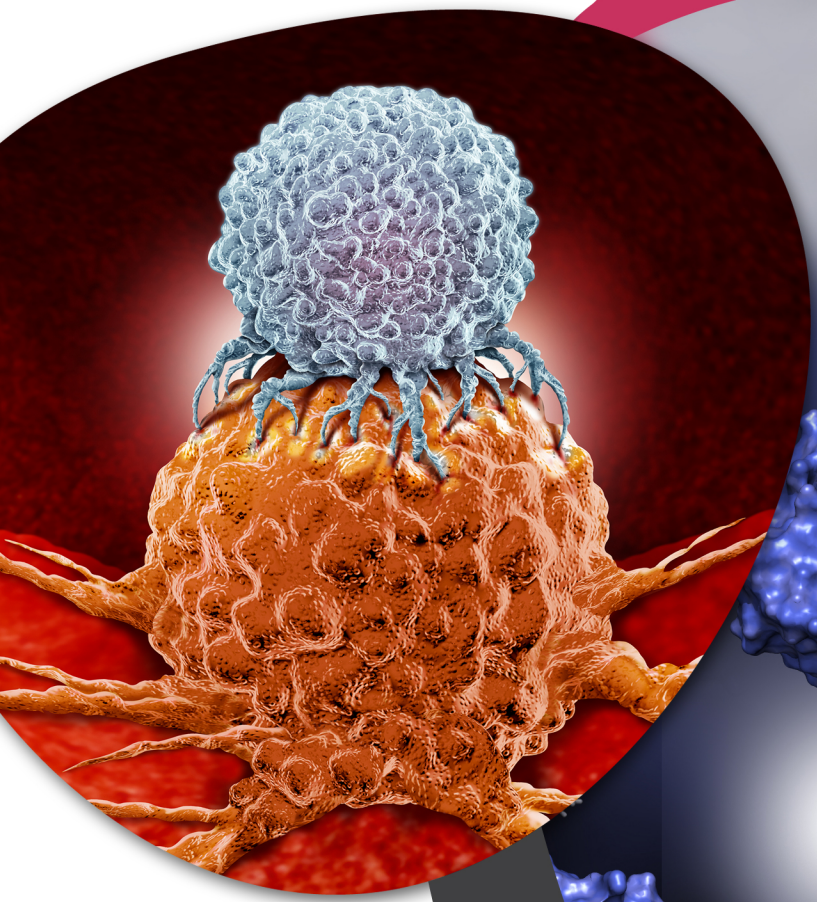
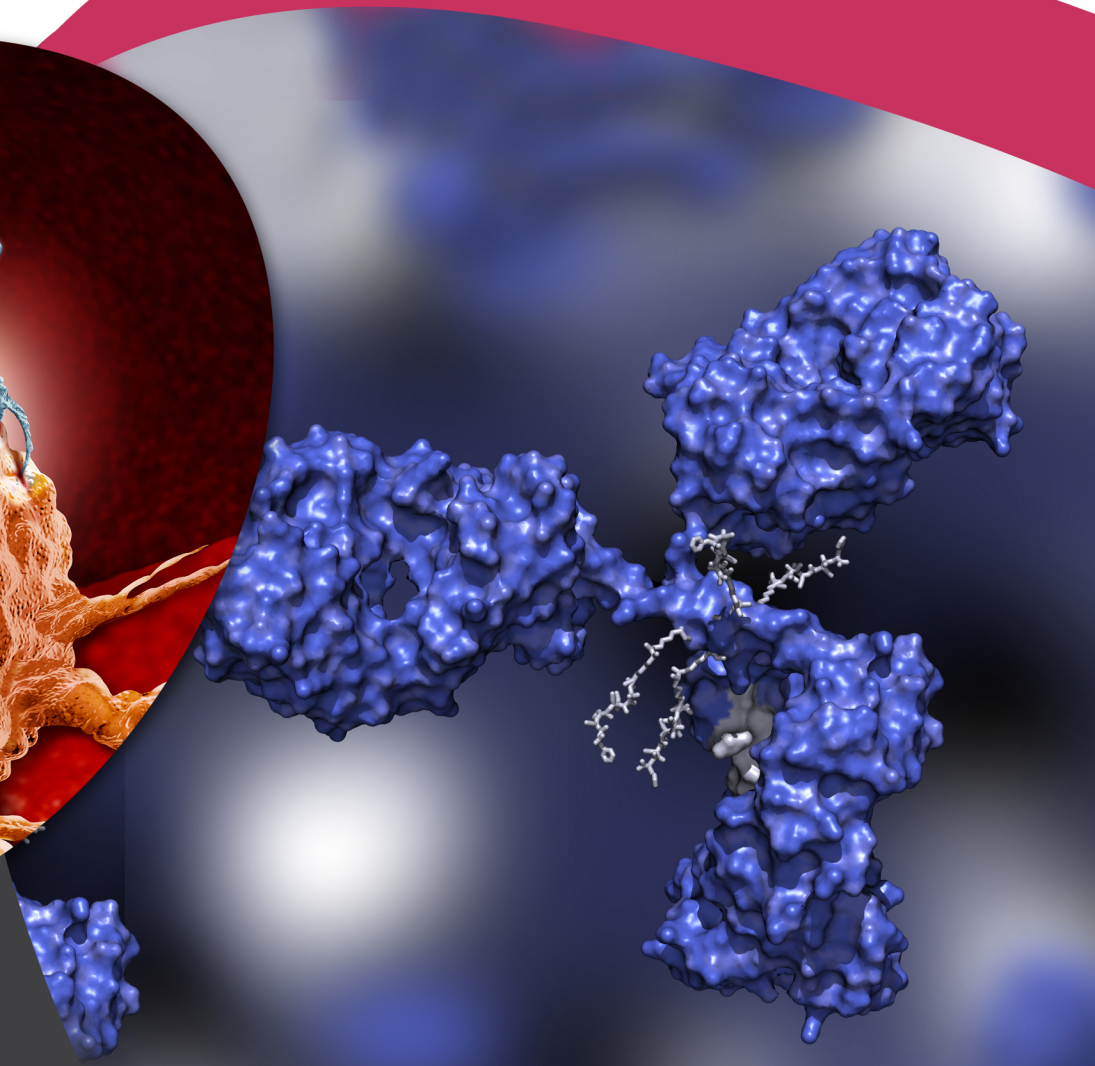
THE EVOLUTION OF RADIONANOTARGETING TOWARDS CLINICAL PRECISION ONCOLOGY:

A FESTSCHRIFT IN HONOR OF KALEVI KAIREMO





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The Evolution of Radionanotargeting towards Clinical Precision Oncology: A Festschrift in Honor of Kalevi Kairemo

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FOREWORD

The last decade has seen the emergence of radionanotargeting as a practice changing therapeutic approach in the clinic, particularly in the field of oncology. This has extended from regulatory approvals for radiolabeled peptide therapy in somatostatin-expressing tumors [1], to impressive results with radiolabeled peptides and antibodies against prostate-specific membrane antigen (PSMA) in prostate cancer patients [2], and exciting results for a broad array of radiolabeled engineered protein and peptide-based therapeutics and nanoparticles extending from preclinical studies into human trials [3 - 5]. The breadth of clinical activity across countries and in different clinical areas clearly demonstrates the momentum for the field.

The ability of molecular imaging with radiotracers to identify targets suitable for therapy in individual patients was established decades ago with 131I as an exemplar of precision oncology, and which now extends to an impressive array of cellular, microenvironment and immune targets which can be used for therapeutic approaches [3, 4]. The principles of therapeutic drug development utilizing an initial imaging based approach, which eliminates the potential for error of biopsy results for assessment of genomic or protein expression profiles in tumors, has been built on painstaking validation and pioneering work over many years [5 - 7]. The development of novel targeting and radiochemistry approaches, protein design, preclinical validation, and extension into carefully conducted human trials, has provided the basis for the current approach to treating patients utilizing targeting molecules and an image-guided, or "theranostics" approach.

In addition to the developments in targeting techniques, imaging and therapeutic radionuclide approaches, the technology developed in this field has also led to new ways to improve drug development. Through sophisticated radioimaging studies, new drugs can be assessed for biodistribution, pharmacokinetics and pharmacodynamics, which can dramatically impact patient and dose selection, and clinical development programs [6, 7]. This approach is being increasingly used by pharmaceutical companies and biotech as they develop new therapeutics.

"The Evolution of Radionanotargeting towards Clinical Precision Oncology" provides an overview of key advances in the field of radionanotargeting, and the directions in which this area of medicine will have an impact on patient care. Our colleague, Prof Kalevi Kairemo, has been a pioneer in this field through his research and clinical translation of novel radiolabeled therapeutics. This has required his pursuing a ground-breaking multidisciplinary approach to science, development of significant expertise across the fields of chemistry, biology, engineering, physics and clinical medicine, and the ability to assemble teams for a common scientific purpose. We have enjoyed the collaboration, scientific endeavour, and friendship of Kalevi for almost 30 years, beginning with our time spent working together at Memorial Sloan-Kettering Cancer Centre, and we can attest to his insight, determination, and commitment to the field and patient care throughout this time (Fig. **1**). This Festschrift book provides a wonderful outline of the field and his achievements over many years.

Fig. (1))
International Symposium on Radiopharmaceutical Therapy (WARMTH), Helsinki City Hall, November 2018: Homer Macapinlac, Steven Larson, Kalevi Kairemo, Andrew Scott.

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PREFACE

This is a remarkable book honoring Professor Kalevi Kairemo's work, and it is fitting that the table of contents for the book were finalized by the World Theragnostics Day on 31.3.2021, which is precisely 80 years after the first radioiodine treatment was performed by Saul Hertz on 31.3.1941. The idea for the topic/title of this book came from discussions about the partially unrecognized role of radioisotopes in the development of targeted drug development. In fact, the radionuclide approach is nearly always included in the first tools used in research when *in vitro* findings are transferred to the *in vivo* level. Usually, new cellular elements are needed for applications to determine their location *in vivo* in preclinical animal models and, ultimately, in humans. In these applications, radioactive isotopes have had a major role. Protein targeting was the first step towards more specific targeting, starting from the concept of receptors in the cell membrane with specific binding and functional capacity. The use of antibody-augmented targeting increased further, and evolution continued towards increasingly small cell structures. Nanotargeting has been derived even against DNA and RNA and thus shows extreme specificity. Gene therapy and antisense radionucleotide therapies are examples of the highest specificity possible against cell structures. Radionuclides and their molecular constructs have the potential to be developed into therapies involving *in vivo* imaging of targets followed by the application of active agents with higher radioactive doses. Radioactivity makes visualization possible and may augment therapeutic effects. Thus, radionanotargeting has a large application base and is developing towards theragnostics. All this research is based on multiomics, which involves multiple elements: genomics, transcriptomics, proteomics, metabolomics, microbiomics, epigenomics, exposome, imaging, and precision medicine. Multiomics is an approach that is also featured on the cover of this book.

This book contains a unique collection of articles that will deepen the understanding of targeting with radioactive isotopes. Radioactivity with low trace doses can enable one to visualize targets, providing the possibility of simulating events before using higher doses with stronger effects. This is a perfect situation for cancer therapy. Radiotargeting has evolved from targeting proteins through other cellular macromolecules, *e.g.*, DNA, towards specific gene targeting with antisense techniques. Hopefully, we will see gene silencing therapeutics in clinical oncology in the near future. This development has already been fascinating, and radiotargeting has had a major role in it.

This book starts with a foreword to this research field by Andrew M. Scott, Homer A. Macapinlac and Steven M. Larson. Radionanotargeting and theragnostics are subjects for the next segment in the form of four chapters. Imaging is dealt with in three chapters before the therapy segment, which includes sections for thyroid cancer, head and neck cancer, genitourinary cancers and neuroendocrine neoplasms. The segment on theragnostics is covered in four chapters. In addition, nanoparticles and precision oncology have their own segments. The supporting sciences segment consists of four sections: metabolic imaging, cardiovascular radionuclide imaging, combined and bone therapies. Radiobiology is covered

in one chapter before three chapters dedicated to a patient experience segment. The final segment consists of Professor Kairemo's own memoir "Seven decades in health care" and memoirs from colleagues." Finally, there is a personal introduction to Kalevi Kairemo with a photographic cavalcade of his participation in WARMTH. I am sure that this complex issue will be covered comprehensively and will open up new avenues for future innovations.

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CHAPTER 1

Molecular Imaging in the Development of Antibody-Drug Conjugates

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Abstract: Antibody-drug conjugates (ADCs) are novel drugs that deliver a potent cytotoxic payload to the tumor site, by exploiting the specificity of a monoclonal antibody (mAb) to tumor antigens expressed on cancer cells. ADCs allow the delivery of drugs to tumor cells or microenvironment while minimizing toxicity to normal tissue. More than 80 ADCs worldwide are currently under clinical development, of which nine have already received FDA approval. Molecular imaging can play a vital role in evaluating the biodistribution and pharmacokinetics of ADCs for optimal patient selection and early clinical trial development. This chapter provides an overview of ADC structure and design, outlines approved ADCs, discusses the role of molecular imaging in drug development, and highlights clinical and pre-clinical experience with radiolabelled ADCs [1].

Keywords: Antibody, Antibody-drug conjugate, Diabody, Drug development, Molecular imaging, Target antigens.

INTRODUCTION

Antibody-drug conjugates (ADCs) are targeted agents that deliver toxic payloads at the tumor site by linking a monoclonal antibody with specificity for a tumor antigen to a cytotoxic drug or toxin *via* a linker. This mechanism improves the efficacy of drug treatment whilst reducing systemic exposure and toxicity [1].

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There are currently more than 80 ADCs worldwide under clinical development, with nine having received regulatory approval by FDA for use in the USA and eight approved by the European Medicines Agency (EMA) [1 - 4].

Successful development of an ADC requires an intricate understanding of ADC *in-vivo* properties, drug delivery parameters, target expression, and the mechanism of therapeutic action that can be validated in pre-clinical models and extended into clinical trials. Molecular imaging has successfully been utilized in ADC development to study the biodistribution and pharmacodynamics of ADCs, detect heterogeneity between lesions, determine tumor target expression, predict response to the ADC, inform patient selection and assist in decisions in drug development in early phase clinical trials [1, 5].

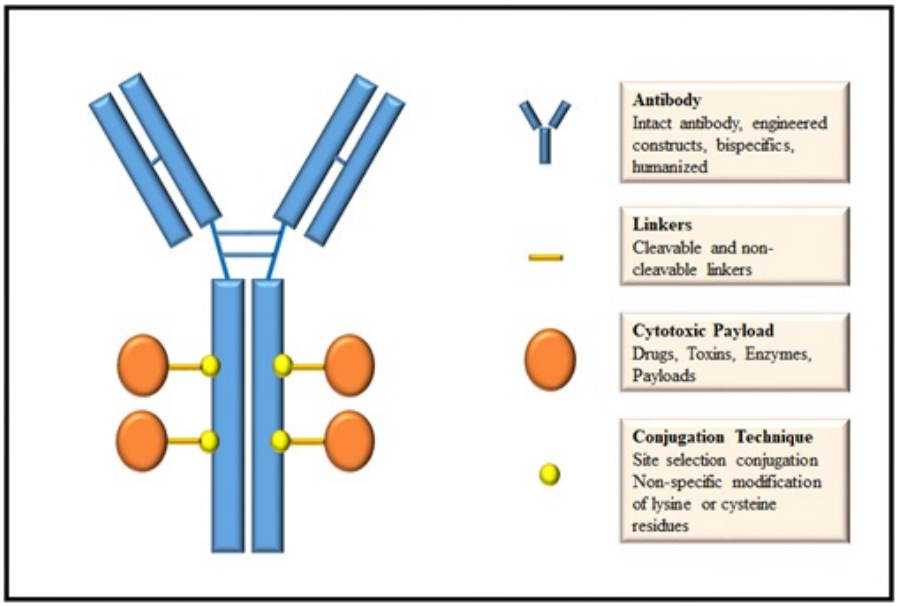

Fig. (1). Structure of antibody-drug conjugate [adapted from 1].

ANTIBODY-DRUG CONJUGATES AS A CANCER THERAPEUTIC

Design and Structure

ADCs comprise a tumor antigen-specific monoclonal antibody (mAb) or related engineered construct conjugated *via* a stable chemical linker to a potent cytotoxin. Guided by the specificity and high affinity of antibodies for antigens on tumor cells, these three components can deliver normally intolerable drugs or payloads directly and specifically to cancer cells [1] (Fig. **1**).

Mechanism of Action

Once the ADC is bound to its target antigen, the ADC-antigen complex is internalized into the cell *via* pinocytosis clathrin- or caveolae-mediated endocytosis [1, 6]. Internalisation of the ADC results in trafficking through an early endosome, formed by inward budding of the cell membrane, which matures into a late endosome prior to fusing with lysosomes. The cleavage mechanisms usually occur in early or late endosomes for ADCs with cleavable linkers. In contrast, a more complex proteolytic cleavage is required by cathepsin B and plasmin in the lysosomes for ADCs with non-cleavable linkers. Once inside the lysosome, the ADC is degraded, and free drug payload is released into the cell cytoplasm, leading to cell death [1, 7]. The mechanism of cell death is dependent on the type of cytotoxic payload, for example, by microtubule disruption or DNA targeting. ADCs are typically administered intravenously due to poor oral availability [1, 6].

Clinical Development and Design

Target Antigen Selection

Appropriate selection of a target antigen is a critical step for the success of an antibody-drug conjugate. An appropriate target antigen should have the following features: 1) antigen abundance on the tumor cell or microenvironment target surface to be available for binding by circulating ADC, 2) preferential expression on tumor cells with a minimal expression on healthy tissue to minimize off-target toxicity, 3) minimal secretion in the circulation to avoid sequestration in the blood compartment of the ADC, thus limiting available ADC for tumor targeting, 4) ability to internalize efficiently upon ADC binding, and 5) appropriate intracellular trafficking and degradation to allow the cytotoxic payload to be released [1, 8 - 12]. More than 50 known antigens have been used as targets in ADCs in both pre-clinical and clinical development [1] (Table **1**).

Table 1. ADC target agents in development and current practice (adapted from 1).

Targets	Indication
CD25, CD33, CD123 (IL-3Rα), FLT3	Acute myeloid leukemia
CD38, CD46 (MCP), CD56, CD74, CD138, CD269 (BCMA), endothelin B receptor	Multiple myeloma
Axl, alpha v beta6, CD25, CD56, CD71 (transferrin R), CD228 (P79, SEMF), CD326, CRIPTO, EGFR, ErbB3 (HER3), FAP, Globo H, GD2, IGF-1R, integrin β-6, mesothelin, PTK7 (CCK4), ROR2, SLC34A2 (Napi2b), SLC39A6 (LIV1A ZIP6)	Lung cancer
CD25, CD30, CD197 (CCR7)	Hodgkin's lymphoma

CHAPTER 2

Preclinical Applications with Phage Display-derived Peptides

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Abstract: A lot of effort has been devoted to convert phage display-derived peptides to more stable peptidomimetics and only a few such peptides have been examined in preclinical trials. The applications of short peptides include radio-isotope labelling for imaging purposes and targeting a virus or nanoparticle to specific tissue or cell.

Keywords: Cancer, Integrins, Peptides, Proteinases, Tumor Invasion.

I met Kalevi Kairemo for the first time in 1999 when he had invited me to give a talk of the phage display-derived peptides that can possibly be used as radiolabels to image tumors [1]. Due to traffic congestion, I was late for the seminar, but Kalevi, Sirkka-Liisa Karonen and others who worked at that time in Helsinki University Hospital, patiently waited. I learned that besides standard iodination, peptides can be radiolabeled *e.g*. with Iodine-123 (^{123}I), Technetium-99m (^{99m}Tc), Fluorine-18 (^{18}F), Gallium-68 (^{68}Ga), Copper-64 (^{64}Cu), Indium-111 (^{111}In), Lutetium-177 (^{177}Lu), Yttrium-90 (^{90}Y), or Bismuth-213 (^{213}Bi) [2]. In the following years, we ended up studying several small molecular weight peptides in mouse tumor models *in vivo* or patient samples *in vitro*, and even a company was established to pursue these goals.

One of the first peptides to be radiolabeled was CTTHWGFTLC, which was obtained by biopanning with matrix metalloproteinase-9 [3]. The peptide is quite specific, although low-affinity inhibitor of the proteolytic activity of matrix metalloproteinase-9 and -2, also known as gelatinases, which play a role in tumor cell migration and degradation of extracellular matrix [4]. Iodinated CTTHWGFTLC homed in tumors in the mouse much in the same way as the phage encoding it does [5]. Phage display also yielded peptides, which prevented the formation of the dimer of matrix metalloproteinase-9, suggesting a specific

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function for the dimer in cell-surface localization and mediating pericellular proteolysis [6 - 8]. However, further preclinical applications with these peptides turned out to be difficult, probably because gelatinases are expressed by both host and tumor cells, and there are protein substrates, some of which suppress tumor growth while others promote it. The accumulated knowledge of matrix metalloproteinase function and inhibitor pharmacology may now allow the development of chemicals better suited for use either as radiolabels or therapeutics [9].

Matrix metalloproteinases may also be utilized to activate a prodrug or imaging agent, which *in vivo* will likely occur mostly on a restricted cell surface area rather than in the extracellular space filled with natural inhibitors. Integrins make a class of cell-surface proteins capable of binding a variety of extracellular proteins, even proteinases, but whether this focuses on a proteolytic zone for the purpose of cell movement has been little studied [8]. Using the phage display derived peptides, we found evidence that a set of integrins can bind matrix metalloproteinase-9, making it possible to form a triple molecular complex, called "invadosome", between the integrin, proteinase, and a substrate [8, 10]. Usually, phage display-derived peptides are linear chains consisting of L-amino acids, the peptide bonds of which are easily degraded by proteinases, but whenever two disulfide bonds occur, the peptide is expected to be structurally constrained and more stable, as was found with one of the leukocyte beta2 integrin-binding peptides CLLGCFCGC [11]. Earlier, we had found a similarly double-cyclic peptide ACDCRGDCFCG by biopanning with the alpha(V)beta(5) integrin (the peptide initially called "ACDC" but renamed to "RGD-C4" to avoid confusion…) [12]. Several types of RGD-motif-containing peptides have been used for radio imaging of tumors [13]. Still, hardly any studies have been carried out to image the immune cells expressing beta2 integrins or leukemia cells overexpressing the hypoxia-associated beta2 integrins, apparently due to lack of suitable reagents.

While phage display libraries have been increasingly used in cell culture and *in vivo* pannings in the mouse and even in human subjects [14], peptides have been discovered that can mediate internalization of bacteriophage particles to cells, *e.g via* binding to neuropilin-1 [15 - 17]. Interestingly, the peptides may shed light on how pathogenic human viruses gain entry to cells, as there may not be many different routes for internalizing large-sized virus particles. Possible cell entry routes include clathrin-mediated, caveola-dependent, and clathrin- and caveola-independent endocytosis, and in particular micropinocytosis, which may all be possibly examined by phage display libraries [18]. For many viruses, including HIV, herpes simplex virus-2, Epstein-Barr virus (EBV), and the foot and mouth disease virus (FMDV), the cell recognition is first mediated by an RGD-dependent integrin before the endocytosis, and even the SARS-COV-2 spike

protein contains an RGD sequence although it is unclear whether it is functional [19]. The primary cell surface receptor of SARS-COV-2 in most cells is ACE2 protein, but neuropilin-1 can be involved in the next steps of the endocytic pathway [20, 21]. Overall, phage-displayed peptides continue to be valuable research tools when searching for biologically relevant sequences, but the peptide diversity displayed in libraries greatly exceeds that presented in natural proteins, and there is no simple way to convert phage display peptides to more stable peptidomimetics.

CONSENT FOR PUBLICATION

Not Applicable.

CONFLICT OF INTEREST

The author confirms that this chapter contents have no conflict of interest.

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CHAPTER 3

Perspectives in ^{11}C and ^{18}F Radiochemistry

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Abstract: The state-of-the-art of carbon-11 and fluorine-18 radiochemistry for positron emission tomography (PET) is presented. From the latest developments in labelling methodology, a picture of future challenges is drawn. The exploration of novel reactivity to allow ^{11}C-labelling, alongside a particular focus in making such reaction compatible for clinical production, is presented to be key in ^{11}C-tracer discovery. ^{18}F is envisioned to be at the heart of further development in PET. Broadening imaging strategies towards pre-targeting approaches, together with the use of modified antibodies or peptides, constantly challenges the field of radiofluorination for new and efficient labelling methods applicable to complex molecules. Translation of biorthogonal reactions into radiolabelling methods appears as a valuable option to address these issues and is expected to be a significant advance in upcoming ^{18}F-tracer developments.

Keywords: Carbon-11, Fluorine-18, Positron emission tomography, Radiochemistry.

INTRODUCTION

Positron emission tomography (PET) is an imaging technique that provides physio-pathological information non-invasively. Because of its high sensitivity, PET became an essential tool for patient diagnosis for various pathologies, with widespread applications in oncology, brain disease and the evaluation of cardiac function, amongst others [1]. PET is also employed to follow-up and evaluate treatment efficacy and plays an important role in drug development. To fulfill its functional imaging purpose, PET relies on the use of radiotracers containing β^+

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emitting radionuclides, allowing for detection of the gamma photons produced upon positron/electron annihilation. Clinically used radionuclides include the β^+ emitters ^{11}C, ^{13}N, ^{18}F and ^{68}Ga. Radiometals, such as ^{64}Cu and ^{89}Zr, are also employed, despite their mixed radioactive decay, which only partially occurs by the productive β^+ emission. The physical properties of each radionuclide [2] and its available production and labelling methods (Table **1**) determine the opportunities and limitations of their clinical applications. The extremely short half-life ($t_{1/2}$ = 10 min) of ^{13}N restricts labelling procedures to enzymatic methods that yield ^{13}N-labelled amino acids [3]. ^{13}N is mostly used in its simplest form, as $[^{13}N]NH_3$, for the imaging of myocardial perfusion to diagnose coronal artery disease. The radiometal ^{68}Ga has an advantageous half-life of 67.8 min but suffers from high energy β^+ decay, which results in long-range penetrating positrons (R_{mean} = 3.5 mm and up to R_{max} = 9.0 mm), ultimately resulting in lower spatial resolution of the acquired images. In addition, labelling with ^{68}Ga or other radiometals requires the presence of a chelator in the structure of the tracer, thus presenting a strong limitation for tracer design. ^{11}C and ^{18}F present advantageous physical properties due to their half-life, allowing for synthetic modifications and low positron energy ranges that ensure a good spatial resolution for PET. Considering these factors, it is not surprising to notice the prevalent use of ^{11}C and ^{18}F in clinical practice [4]. However, labelling procedures for ^{11}C- and ^{18}F-radiotracers need improvements regarding reaction time and robustness. These methods are often complex and require highly specialized operators and infrastructure (specific lab equipment, cyclotron, *etc*.).

Table 1. Physical properties of the main PET-radionuclides.

Radionuclide	Half-life $t_{1/2}$	E_{mean} (MeV)	R_{mean} (mm)	Prevalent Labelling Method
^{11}C	20.4 min	0.386	1.2	S_N2, carbonylation
^{13}N	10.0 min	0.492	1.8	Enzymatic
^{18}F	109.8 min	0.250	0.6	S_N2, S_NAr, “click” chemistry
^{68}Ga (89% β^+)	67.8 min	0.836	3.5	Chelation
^{64}Cu (18% β^+)	12.7 h	0.278	0.7	Chelation
^{89}Zr (23% β^+)	78.4 h	0.396	1.3	Chelation

The choice of the molecular structure of the radiotracer is crucial in PET, and it should fulfill several criteria, which include the easy and reproducible production of the PET-tracer, high specificity and affinity, high molar activity of the tracer (particularly in case of low target expression), lipophilicity that ensures the efficient reaching of the target, and low rate of metabolism,. The structures likely to become PET-tracers are too often restricted by the limited number of labelling methods available for a given radionuclide and the characteristics of the

radionuclide, in particular half-life, regarding the scope of applicable transformations. To overcome these limitations, the development of novel methodologies is necessary to enable more (late-stage) transformations, ultimately broadening the scope of accessible PET-tracers. Such methodology would ideally be fast, enable the introduction of radionuclides in metabolically stable positions, and be robust, with a special focus on including automated syntheses, thereby providing new opportunities in PET-tracer synthesis (extended scope, diverse targets, multimodal imaging, *etc*.) to expect an impact on future developments in PET-imaging [5].

^{11}C - EXPANDING THE TOOLBOX

Carbon is an element present in almost every biologically active molecule, rendering ^{11}C is a valuable radionuclide. On the one hand, the half-life of ^{11}C ($t_{1/2}$ = 20.4 min) offers great opportunities when it comes to drug development and the possibility of performing repeated studies during one single day. Moreover, as a result of the short half-life, the use of ^{11}C results in a lower radiation dose for the patient compared with other radionuclides used in nuclear medicine [6]. On the other hand, the development of synthetic procedures leading from ^{11}C-production to tracers for PET-imaging, that would be compatible with such a short half-life represents an important challenge. ^{11}C is produced in a cyclotron, by the ^{14}N(p,α)^{11}C nuclear reaction. Addition to the N_2-target gas of small amounts (typically 5 to 10%) of H_2 or O_2, results in the production of [^{11}C]CH_4 or [^{11}C]CO_2, respectively; these simple molecules constitute the two key precursors of ^{11}C-chemistry. In practice, in-target production of [^{11}C]CO_2 is higher yielding and therefore preferred, with the opportunity of reduction into [^{11}C]CH_4 post-production. Over the past decades, many other building blocks, derived from [^{11}C]CH_4 or [^{11}C]CO_2, have been synthesized and used in labelling procedures (Scheme **1**).

Considering the variety of electrophiles and nucleophiles that can serve as ^{11}C building blocks, it is striking to notice the major dominance of labelling procedures by S_N2 reactions, with either [^{11}C]CH_3I or [^{11}C]CH_3OTf as electrophile [7], for the synthesis of PET-tracers used in the clinic (Fig. **1**). S_N2 reactions, with [^{11}C]CH_3I or [^{11}C]CH_3OTf, allow for the formation of heteroatom-$^{11}CH_3$ functionalities, known to be prone to metabolic degradation, thereby enabling access to only a few privileged structures *via* such strategy. Carbonylation reactions using [^{11}C]CO or [^{11}C]CO_2 are less commonly used but have also found applications in clinical tracer production [8 - 10]. Carbonylation reactions have a prominent role to play in ^{11}C-labelling as they provide access to carbonyl functionalities, an abundant motif in biologically active molecules. A large part of methylation opportunities remains poorly addressed by current labelling methods,

CHAPTER 4

Introduction to Radionanotargeting in the 1990's: Dosimetry and Optimization of Antisense Oligonucleotide Radiotherapy *in Vivo*

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Abstract: Radiolabeled oligodeoxynucleotides (ODNs) have the potential of having both direct antisense inhibition and radiation effects being derived against the most specific target, a DNA/RNA sequence. Nuclear DNA is the primary target for ionizing radiation, and low-energy electrons with short ranges are responsible for the radiotoxicity of Auger electron emitters. Antisense technology has begun to provide an alternative approach for manipulating the expression of specific genes. Here, we optimize the label of ODNs with Auger-emitting radionuclides by calculating subcellular dose distribution. We show that for subcellular targeting, internal labels ^{35}S and ^{32}P give the lowest variation in estimated absorbed nuclear dose in our cell model with defined dimensions (nuclear diameter, 6-16 μm ; cellular diameter, 12-20 μm).

Keywords: Antisense, Dosimetry, Oligonucleotide, Radionanotargeting.

INTRODUCTION

Antisense oligomers may serve as a vehicle for carrying radioactive compounds into a particular location. Radiolabeled oligodeoxynucleotides (ODNs) have the potential of having both direct antisense inhibition and radiation effects. Antisense ODNs are derived against the most specific target, a DNA/RNA sequence constituting an attractive tool for specific therapeutic applications [1]. An antisense ODN binds to its complementary counterpart in mRNA, as reverse complementary strands of DNA or RNA hybridize with a specific target mRNA

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sequence. Hybridization forms a duplex that prevents mRNA utilization and also promotes its destruction by RNase H. This results in the inhibition of mRNA translation into protein and can block cellular processes. Binding to DNA requires the formation of a triple helix with the target DNA duplex., The specificity of triplex-forming processes, is comparable with that of complementary strand pairing in DNA duplex. The primary target for ionizing radiation is nuclear DNA, and the radiotoxicity of Auger electron emitters is mainly due to low-energy electrons with short ranges (1-10 nm) [2]. If the decays occur in close proximity to DNA, the combined action of the Auger electrons results in molecular damage to DNA [3].

Dose Calculation: From Macro to Micro

The accumulated dose from internally administrated radionuclides is usually estimated using the principles and formalism of the Medical Internal Radiation Dose (MIRD) scheme [2, 4]. In the MIRD scheme, the dose D [in grays (Gy)] at the target organ (T) is calculated as a sum of the dose component from the target organ itself (T ← T) and dose components from different source organs (N_k) to the target (T ← N_k):

$$D = \widetilde{A_T} \cdot S(T \leftarrow T) + \sum_k \widetilde{A_{N,k}} S(T \leftarrow N_k) \quad \textbf{(1)}$$

where $\widetilde{A}_T$ represents the cumulated activity [unit, becquerel·seconds (Bq ·s)], *i.e.*, the number of nuclear disintegrations in an organ or target during the time interval of interest. S represents the fraction of dose per nuclear disintegration (unit, Gy/Bq·s) that emits from the source organ or target and is absorbed in the target [2]. The absorbed dose in the target organ can be macroscopically divided into two components: the dose from the penetrative radiation (such as X-rays and 31 quanta) and the dose from the nonpenetrative radiation (such as β particles) [2]. For β-emitting radionuclides, the dose rate D (unit, Gy/sec) can be calculated in a spherically symmetric situation as shown in Eq. (2):

$$\dot{D} = A\Delta\Phi_\beta(r) \quad \textbf{(2)}$$

where the dose rate in a selected point is calculated at a distance r from the source activity A. $\Delta = n_\beta E_{av}$ gives the emitted energy per nuclear disintegration with an average number of emitted particles n_β and average energy E_{av}. $\Phi_\beta(r)$ gives the specific absorbed energy at the selected point [2]. If the activity concentration C (activity per unit mass: Bq/kg or Bq/g) is constant inside a spherical volume [2], Eq. (2) can be written as

$$\dot{D} = C\Delta\Phi_{\beta}(r) \quad \textbf{(3)}$$

where absorbed fraction $\Phi_{\beta}(r)$ for spherical geometry can be calculated by the method of Leichner [5], 15 using a volume integral:

$$\Phi_{\beta}(r) = G_0 \int_V \frac{e^{-\mu' r}}{4\pi r^2}\left\{1 + [d_1(\mu' r) + d_2(\mu' r)^2 + d_3(\mu' r)^3]e^{-(d_4-1)\mu' r}\right\}dV \quad \textbf{(4)}$$

with energy-specific constants μ', d_1,d_2,d_3,d_4, and G_0. This method was used to calculate the dose at the center of a water-equivalent sphere with a uniform ^{32}P, ^{33}P, or ^{35}S activity concentration inside and zero activity outside as a function of sphere mass [5]. The nuclear S factor can be written as a sum:

$$S(N \leftarrow N, Cy, Cs) = p_N S(N \leftarrow N) + p_{Cy} S(N \leftarrow Cy) + p_{Cs} S(N \leftarrow Cs) \quad \textbf{(5)}$$

where the p values represent the relative activity content of the nucleus (N), cytoplasm (Cy), and cell surface (Cs).

Owing to the continuous energy spectrum of β particles the central dose is expected to increase until a radius larger than the maximum range of the β particles is reached. With this method, it is possible to compare the dosimetry of β dosimetry of β theoretically theoretically β-emitting nuclides in the treatment of tumors of different sizes [2]. We selected the following radionuclides for calculation: ^{32}P, ^{35}S, chromium -51 (^{51}Cr), gallium-67 (^{67}Ga), indium-111 and -114m (^{111}In and ^{114m}In), iodine-123, -125, and -131(^{123}I, ^{125}I, and ^{131}I), and thallium-201 (^{201}Tl) [2]. The calculation was performed for spherical cell forms of different cellular and nuclear radii [r_c, r_y: 6 and 3µm (I), 6 and 5 µm (II), 8 and 5 µm (III), as well as 10 and 8 µm (IV)], using the cellular level S factors of Goddu *et al*. [2, 6]. In these situations the(spherical) nuclear volume fractions of the whole (spherical) cell are 13% (I), 58% (II), 24% (III), and 51% (IV), respectively [2]. Three different activity distributions were considered: published cellular level distribution of oligonucleotide phosphorothioates ISIS 2105 and ISIS 292221 and the uniform activity distribution. The activity outside the cell was not taken into account [2].

We optimize the label of ODNs with Auger-emitting radionuclides by calculating subcellular dose distribution [2, 7-9]. We show that for subcellular targeting, internal labels ^{35}S and ^{32}p give the lowest variation in estimated absorbed nuclear dose in our cell model with defined dimensions (nuclear diameter, 6-16 µm; cellular diameter, 12-20 µm). The doses vary considerably depending on cellular dimensions when using Auger emitting isotopes; however, in small cells they may

CHAPTER 5

Role of SPECT/CT Imaging with Gamma-emitted Radionuclides in Personalized Treatment of Cancer Patients

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Abstract: Radiopharmaceuticals are a well-known form of ionizing radiation, emitting gamma photons. They are used in clinical routine for cancer patients; nuclear medicine utilizes oncotropic cationic complexes such as ^{99m}Tc-Sestamibi/Tetrofosmin (MIBI/TF); radioiodine ^{123}I /^{131}I; radiolabeled somatostatin (SST) derivatives ^{111}In-Octreoscan/^{99m}Tc- Tektrotyd; diphosphonates ^{99m}Tc-MDP /HEDP; nanoparticles ^{99m}Tc-Nanocoll and *etc*. The tracer accumulation to tumor cells is dependent on blood perfusion, biodistribution, cellular proliferation, oxygen consumption, receptor status, and other factors in different tumors. Besides multiple imaging methods for evaluating malignant diseases, new hybrid SPECT/CT imaging can provide accurate diagnostic information about the presence and staging of neoplastic diseases as well as unique biological characteristic information, such as quantification of cellular proliferation or SST-receptor status. The SPECT component of the hybrid SPECT/CT images provides information about the functional activity of the primary neoplastic tumor and the secondary metastatic lesions, whereas the CT component is needed for the anatomy of the "hot" lesions seen in the nuclear medicine modality. This may result in a reduced number of false-positive and false-negative results and increased sensitivity and specificity of the nuclear medicine studies. The SPECT/CT examinations may find a different clinical value in oncology. Combined SPECT/CT images enable discovering primary occult tumors, visualizing local or distant metastases for accurate NM-staging, and evaluating therapy response. SPECT/CT images can be used for radiotherapy planning to delineate target and functional gross tumor volumes.

Keywords: ^{123}I/^{131}I, ^{123}I/^{131}I -MIBG, ^{111}In-Octreoscan, ^{99m}Tc-MDP/HEDP, ^{99m}Tc-Nanocoll, ^{99m}Tc-Sestamibi, ^{99m}Tc-PSMA, ^{99m}Tc-Tektrotyd, ^{99m}Tc-Tetrofosmin, Neuroendocrine tumors, Prostate cancer, Sentinel lymph nodes, SPECT/CT, Thera(g)nostics, Thyroid cancer.

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INTRODUCTION

Nuclear medicine and metabolic radiotherapy are among the leading trends in the individualized approach to cancer diagnosis and treatment. The main purpose of these radionuclide methods is accurate assessment of the individual features of the disease for each patient, in order to personalize the treatment, optimize the therapeutic response and minimize toxicity. Nuclear medicine is characterized by the use of various radiopharmaceuticals to determine the physiological nature of diseases affecting different organs non-invasively, applying quantitative analysis of the tracer uptake and biodistribution. This approach examines the functions of the organs; it is possible to detect and monitor the disease early (before the appearance of anatomical abnormalities) and to measure the changes in the physiology of the body. The appearance of three-dimensional (3D) images is known as single-photon emission (SPECT), and positron emission tomography (PET) computed tomography, and the integration of this 3D image with an anatomical image provided by computed tomography (CT) and magnetic resonance imaging (MRI), revolutionized the acquisition and interpretation of functional images of nuclear medicine [1].

Radiopharmaceuticals for SPECT emit gamma photons. They are used routinely in clinical oncology: nuclear medicine methods include oncotropic cationic complexes such as ^{99m}Tc-Sestamibi/Tetrofosmin (MIBI/TF); radioiodine ^{123}I /^{131}I; radiolabeled somatostatin (SST) derivatives ^{111}In-Octreoscan®/^{99m}Tc- Tektrotyd®; diphosphonates ^{99m}Tc-MDP /HEDP; nanoparticles ^{99m}Tc-Nanocoll® and *etc.* The uptake to tumor cells is dependent on blood perfusion, biodistribution, cellular proliferation, oxygen consumption, receptor status, and other factors in different tumors. Besides multiple imaging methods for evaluating malignant diseases, new hybrid SPECT/CT imaging can provide accurate diagnostic information for detection and staging of neoplasms as well as about biological tumor characteristics, such as quantitative cellular proliferation or SST-receptor status. The SPECT component of the hybrid SPECT/CT images provides information about the functional activity of the primary tumor and the secondary metastases, whereas the CT component is needed for the precise anatomical localization of the "hot" lesions seen in the SPECT images. This may reduce the number of false-positive and false- negative results and increase the sensitivity and specificity of the nuclear medicine studies. The SPECT/CT examinations may find a different clinical value in oncology [2, 3]. Hybrid SPECT/CT images enable the discovery of occult primary tumors, to visualize local or distant metastases for accurate NM-staging, to evaluate therapy response. Hybrid SPECT/CT images can be used for radiotherapy planning to delineate target (CTV) and functional gross tumor volumes (GTV) [4].

The first SPECT/CT device produced for commercial distribution was introduced by General Electric in 1999 [5, 6]. The CT component comprised of a low-dose fixed pot put with a maximum tube current of 2.5 mA [7]. Since 2004, the introduction of multislice CT has shown the great clinical benefits of similar CT image quality. After 2013, SPECT/CT as a hybrid modality offers a full range of technical options (allowing correction for attenuation, scattering, partial volume, and movement). This brought the potential for a stable absolute quantitative assessment of the studied parameters in clinical practice [8, 9]. The introduction of SPECT/CT in nuclear oncology increases the specificity and accuracy of the diagnostic approaches, which is of an important clinical value in choosing and planning individual therapy in cancer patients.

The renewed interest in metabolic radionuclide treatments using ^{90}Y and ^{177}Lu in oncology in the context of precision medicine (known in nuclear medicine as theragnostics) focuses on the molecular characteristics of the tumor and individual treatment planning. Theragnostics is a rapidly expanding field of nuclear medicine that combines diagnostic and therapeutic tools. Theranostics is the " Diagnostic Tool that helps to define the right Therapeutic Tool for a specific disease or "we see what we treat" [10]. Term coined first by John Funkhouser, 1998 in connection with the design and application of the Herceptin test (PharmaNetics CEO) in clinical practice at the same time the concept of Personalized Medicine appeared [11]. Concerning radionuclides, the term "Theragnostics" was created by Prof. Suresh Srivastava (Brookhaven National Laboratory, USA) in 2010 [12].

In recent years, ^{90}Y has been increasingly replaced by ^{177}Lu in clinical practice. The characteristic γ- and β-decaying emissions of ^{177}Lu allow imaging the distribution of activity in the body after its application and calculation of the dosimetric radiation of individual organs and systems [13]. Individualized dosimetry is preferred to fix or based on patient weight or body surface applied activities. Individualized dosimetry requires absolute activity measurements to deliver target doses that are as high as they are safely achievable, which can only be calculated after correction for deteriorating physical phenomena such as photon scattering, photon attenuation, partial effect detector volume and dead time [14, 15].

Increasingly accurate scattered radiation correction techniques and iterative reconstruction methods have greatly improved the capabilities of modern SPECT/CT systems to achieve qualitative images and quantitative calculations comparable to PET/CT. It is expected that the applications for quantification and individual dosimetry will lead to the development of additional applications of SPECT/CT.

CHAPTER 6

Radionanotargeting and Precision Radiotherapy Planning in Patients with Breast Cancer

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Abstract: Purpose: Through this work dedicated to the study of molecular imaging capabilities for radiotherapy planning in patients with breast cancer, we would like to acknowledge our gratitude and pay respect to one of the most prominent world-class researchers in nuclear medicine, Kalevi Kairemo. **Materials and Methods:** In this retrospective study, we present our experience of molecular imaging in more than 1,800 women with breast cancer. Participants underwent Mammoscintigraphy/Breast molecular imaging with 99mTc-MIBI for detection of multicentric (MC) breast cancer and SPECT-CT imaging for the diagnosis of multiple (>2) metastatic axillary lymph nodes involvement. In order to evaluate the variability of SLNs localisation and determine how this data may influence the efficacy of the above-mentioned therapeutic strategy, we retrospectively analysed the results of SPECT-CT examinations with 99mTc labelled nanocolloids. All of these findings were evaluated according to impact for subsequent individual radiotherapy planning. **Results:** We found out that sensitivity, specificity and accuracy of Scintimammo-graphy/Molecular breast imaging (SMG/MBI) with 99mTc -MIBI in the diagnosis of multicentric breast cancer (MC) was 84.3%, 98% and 96.3%, respectively. More of that, the sensitivity of SMG was significantly superior to ultrasound (52.3%) and mammography (54.0%). This advantage was more evident in women with dense breasts. Nowadays, we routinely use SMG/MBI for selecting the best candidates for conservative surgery and postoperative partial breast irradiation. An accurate diagnosis of metastases in regional lymph nodes (LN) can significantly affect the radiotherapy strategy. The prospective evaluation of SPECT-CT with 99mTc -MIBI in 184 primary patients with early breast cancer indicates high sensitivity (94%-96%) of SPECT-CT in the diagnosis of extensive (more than 2 metastases) axillary LN invasion. In these patients, additional SPECT-CT visualisation of individual lymph flow pattern with 99mTc-nannocolloids can be effectively used for 3D planning of simultaneous whole breast and sentinel lymph nodes irradiation.

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Conclusion: Our accumulated experience in using SMG/MBI and SPECT-CT imaging with tumor-seeking and nanocolloids radiopharmaceuticals 99mTc labelled provides a high informative value and broad usability perspectives in developing cutting-edge radiotherapeutic methods in patients with early and regional breast cancer.

Keywords: Breast Cancer, Lymphatic Mapping, Metastatic Lymph Nodes, Molecular Breast Imaging, Radionanocolloids, Radiotherapy Planning, Scintimammography, Sentinel Lymph Nodes, SPECT-CT.

Radiation therapy is an important component of the radical combined treatment of breast cancer patients. It provides 65% - 75% of loco-regional recurrence decrease and a true increase of the overall survival [1]. It has to be noted that radiation technologies are constantly improved. For example, accelerated partial breast irradiation (APBI) is widely used after the conserving treatment in patients with early breast cancer. These methods provide a considerable decrease in radiating surrounding normal tissues, a decrease in radiation volume, and a decrease in radiation therapy duration. In patients with locally advanced stages of breast cancer, special attention should be paid to defining the optimal radiotherapy volume applied to the regional lymph nodes. As both literature data and our own experience show, methods of molecular visualisation, especially methods of hybrid anatomical and functional visualisation make it possible to contribute a lot to the development of the directions mentioned above [2, 3].

The clinical value of APBI was determined by a number of prospective multicentre randomized studies [4, 5]. Clinical recommendations to specify the main stages of APBI were devised based on these studies. In particular, the first main stage in selecting patients for possible APBI is the accurate diagnosis of multifocal (MF) and multicentric (MC) breast cancer [6]. For a long time, mammography and ultrasound examination were considered standard methods of diagnosing MC/MF breast cancer, but its diagnostic accuracy in women with small lesions and/or dense breast tissues could be significantly compromised [7, 8]. Cwikle JB, *et al.* showed high information of mammo-scintigraphy/breast molecular imaging in the diagnosis of MC/MF breast cancer. They found out that in the diagnosis of MC/MF disease, the sensitivity of this imaging was more than twice as high as for the combination of US and MMG [9].

Since 2003 in N.N. Petrov National Medical Research Cancer Centre of Oncology scintimammography/molecular breast imaging (SMG) with 99m-Tc-MIBI has been performed in more than 1,800 women. In 410 patients, we compared the accuracy of SMG, mammography and US in the diagnosis of MC breast cancer. Finally, MC disease was histologically confirmed in 51 (12.4%) of 410 evaluated women. The sensitivity of breast imaging with 99mTc-MIBI (84.3%) was

significantly superior to US (52.3%) and MMG (54.9%) (Table **1**). Taking into account the comparable specificity of all 3 modalities, the diagnostic accuracy of SMG was the best in the group. As mentioned above, mammography represents the methods of reference in the diagnosing and staging of breast cancer, but as was reported by many authors, its sensitivity could be significantly compromised in women with dense breast tissues (Fig. **1**). That is why we compared the diagnostic criteria of MMG and SMG in women with normal and dense breast tissues [10]. Our data show that SMG in women with a high breast tissue density is characterized by a higher sensitivity and accuracy in detecting MC breast cancer (Table **2**).

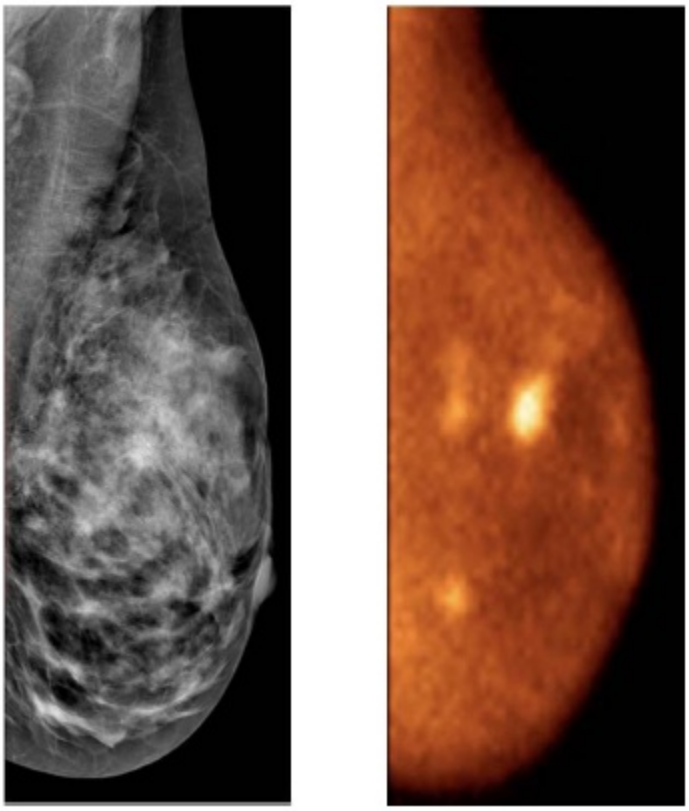

Fig. (1). Medio-lateral-oblique mammogram (A) and oblique scintimammogram (B) of 47-year-old woman with breast carcinoma. Only one tumor with indistinct margins has been clearly identified in heterogeneously dense (type C) breast tissue. Multiple lesions of intensive ^{99m}Tc-MIBI uptake were clearly detected on scintimammogram. Invasive non-specified multicentric breast cancer was confirmed by the pathological examination.

CHAPTER 7

The Diagnostic Potential of Radiolabelled Neurotensin in PET Imaging of Patients with Pancreatic Cancer: Results from *In Vivo*, Animal And Human Studies

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Abstract: In nuclear medicine, multiple peptide receptors are recognized as potential diagnostic and therapeutic targets. ^{68}Ga-NT-20.3 radiopharmaceutical has been developed for diagnosis of neurotensin receptors. Three neurotensin receptors subtypes have been cloned: NTR-1, NTR-2 and NTR-3. NTR-1 is the most commonly expressed neurotensin receptor. High NTR-1 expression has been observed in various tumours including pancreatic ductal adenocarcinoma. ^{68}Ga-labelled NT ligand was successfully applied in *in vitro*, animal model as well as in human. The results on humans demonstrated that PET radiopharmaceutical ^{68}Ga-NT-20.3 is safe and well tolerated. Based on the published data, NTR-1 is promising target for the development of radioactive analogues for both imaging and therapy in patients with primary and metastatic pancreatic ductal adenocarcinoma.

Keywords: ^{68}Ga-NT-20.3, Neurotensin, Neurotensin receptor, Pancreatic cancer, PET.

The incidence of pancreatic cancer is increasing [1]. Moreover, the average life expectancy of 5% at 5 years shows that the prognosis for patients with pancreatic cancer has not improved over the past 20 years [2]. Most patients with pancreatic cancer present with unresectable tumours and progress to metastatic or locally advanced disease even in the asymptomatic stage. Surgery can be the best option with an approximately 20% survival rate at 5 years [2].

Tumour marker CA 19-9 is not useful for primary diagnosis or screening of patients with pancreatic cancer because of its low positive predictive value and potential false positives in inflammation, infection, or biliary obstruction [3, 4].

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The major role of imaging in the management of patients with pancreatic cancer is to determine tumour size and vessel involvement, stage the disease, assist radiotherapy or surgical planning, assess treatment response, and monitor recurrence. Guidelines of the National Comprehensive Cancer Network recommend X-ray, Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) as first-line imaging modalities in patients in whom pancreatic cancer or ductal dilation is suspected [5]. Endoscopic ultrasound (EUS) with fine-needle aspiration is used to characterise pancreatic or secondary liver lesions, with a diagnostic accuracy of 95% [2, 6].

Positron Emission Tomography/Computed Tomography (PET/CT) is widely used in oncology because of its high sensitivity for the detection of 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG) avid lesions. However, its poor specificity in distinguishing inflammatory from malignant processes makes its use debatable. Current European Society of Medical Oncology guidelines states that ^{18}F-FDG PET/CT 'does not currently add much staging information in most patients with the resectable disease and cannot be recommended [2]. Newer radiopharmaceuticals for the characterisation of pancreatic lesions include fibroblast activation protein inhibitors labelled with ^{68}Ga (^{68}Ga-FAPI).

In recent decades, peptide receptors served as a diagnostic and therapeutic target. The overexpression of neurotensin (NT) receptors on pancreatic ductal adenocarcinoma (PDAC) offers opportunities for imaging and peptide-targeted therapy [6].

NEUROTENSIN AND NEUROTENSIN RECEPTORS IN PANCREATIC DUCTAL ADENOCARCINOMA

The peptide NT was isolated from the bovine hypothalamus by Carraway *et al.* in 1973. In the central nervous system, NT is involved in dopamine transmission, inhibition of food intake, hypothermia and analgesia. In the peripheral nervous system, NT affects hypotension, lipid digestion, pancreatic and biliary secretion, colonic motility and growth of normal intestinal mucosa and pancreas [7, 8]. Additionally, in the peripheral nervous system, NT affects the growth of multiple malignancies: pancreatic cancer, colon cancer, prostate cancer, breast cancer, hepatocellular cancer, non-small cell lung cancer, and gliomas [6, 9 - 15].

As an endocrine agent in the periphery, NT participates in each step of cancer progression, ranging from cell transformation, malignant cell proliferation, and survival, to metastatic spread. NT acts through a seven-transmembrane, G-protein-coupled receptor called NT receptor (NTR). Using *in-vitro* autoradiography, NTR was first described in 1998. As shown by cell staining, NTR is mainly present on the plasma membrane. Cytoplasmatic staining is

probably caused by the internalization of NTR. *In-vitro* studies on Panc-1, a PDAC cell line, showed that NT induced DNA-synthesis and cell proliferation acts through protein kinase C [15], which mediates mitogenic signaling. The NTR ligand complex is rapidly internalized and degraded into lysosomes through clathrin-coated vesicles [16]. There are three NTR subtypes: NTR-1 (high-affinity NTR), NTR-2 (low-affinity NTR), and NTR-3 (Sortilin 1, a single transmembrane domain sorting receptor). The most commonly expressed NTR is NTR-1. NTR-2 shares 64% homology with NTR-1. NTR-3 is not specific for NT and binds a variety of ligands [6].

Various tumours present high NTR-1 expression [9 - 15]. Immunohistochemistry confirmed high NTR-1 expression in PDAC, much higher than in neuroendocrine pancreatic tumours, normal pancreas, or chronic pancreatitis. NTR-1 is present in 75% to 90% of PDAC [17 - 19]. The varying presence of NTR-1 receptors is most probably due to different amounts of non-tumourous, NTR-1 negative cells in PDAC, including mesenchymal cells and stroma. Abnormal expression of NTR-1 appears in the early stages of malignant cell transformation [20, 21], but there is no correlation between NTR-1 expression and tumour aggressiveness. As, for example, in prostate cancer, NTR-1 expression does not correlate with Gleason score [22], and it is no different in well or moderately differentiated (grades 1 and 2) and poorly or undifferentiated (grades 3 and 4) PDAC [18]. However, NTR-1 mRNA levels are higher in advanced (stages III and IV) than in early PDAC tumours [23]. Other pancreatic malignancies such as insulinoma express only 33.3% of NTR-1 [20]. The normal pancreas does not express NTR, but 22.7% of tissue samples in pancreatitis expresses NTR by autoradiography [20, 23]. This can change the most common imaging problem – differentiating benign from malignant pancreatic lesions. Based on the selectivity of NTR-1 expression in PDAC, NTR may be used for diagnosis and therapeutic targeting [6].

Diagnostics of Pancreatic Ductal Adenocarcinoma with Radiolabelled Neurotensin Analogues: Preclinical Data

NT, a 13-amino acid peptide, has the following structure: pGlu-Leu-Tyr-Glu-Asn-Lys-Pro-Arg-Arg-Pro-Tyr-Ile-Leu-OH. The carboxy-terminus of NT (9-14) represents the truncated sequence of the natural agonist NT. A variety of NTR-1 imaging agents has been produced by modifying this sequence [23]. The in-vivo stability of the NT analogue has a major impact on tumour uptake.

Chemically modified derivates of the naturally occurring NT can be labelled with gamma (^{111}In, ^{67}Ga) or positron (^{64}Cu, ^{89}Zr, ^{44}Sc and ^{68}Ga) emitting radionuclides and used effectively in diagnostic nuclear medicine [6].

NT peptide fragment 6-13, Ac-Lys(DOTA)-Pro-Arg(NCH_3)-Arg-Pro-Tyr-Tle-Leu

CHAPTER 8

Dr. Saul Hertz (1905–1950) Discovers the Medical Uses of Radioactive Iodine: The First Targeted Cancer Therapy

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Abstract: Dr. Saul Hertz (1905-1950) conceived and brought from bench to bedside the medical uses of Radioiodine (RAI). Dr. Hertz established the use of radiopharmaceuticals to diagnose and treat disease. He spontaneously posed the question "Could iodine be made radioactive artificially?" to MIT President Karl Compton on November 12, 1936. MGH's Dr. Hertz and his MIT collaborator, Arthur Roberts, Ph. D., were the first and the foremost to develop the experimental data for the medical uses of radioiodine (RAI) and apply RAI in the clinical setting. Dr. Hertz successfully used RAI in diagnosing and treating hyperthyroidism and thyroid cancer, believing that the targeted precision approach held the key to the larger problem of cancer in general. RAI is the first and gold standard of targeted cancer therapies.

Hertz established the Radioactive Isotope Research Institute and The Massachusetts Women's Hospital's their first Nuclear Medicine Department reported as," Opening a new division where radioactive isotopes will be used to study and treat disease."

Keywords: Nuclear Medicine, Precision oncology, Radioiodine (RAI), Theranostics.

A PIVOTAL QUESTION

Dr. Saul Hertz attended a luncheon meeting at Harvard Medical School's Vanderbilt Hall on November 12, 1936. The President of the Massachusetts Institute of Technology (MIT), Karl T. Compton, spoke on the topic, "What Physics Can Do for Biology and Medicine." [1].

Dr. Hertz, the director of the Thyroid Clinic (1931–1943) at Massachusetts General Hospital (MGH), conceived and asked President Compton the pivotal question, "Could iodine be made radioactive artificially?" Hertz had been conducting studies on the use of iodine to replace surgery for treating hyperthyroi-

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dism.. Hertz's question came spontaneously as documented in MGH's Dr. James Mean's letter to The Markle Foundation that sponsored the building of the MIT Cyclotron, stating, "…it at once occurred to Hertz…" [2].

Arthur Roberts, Dr. Hertz's MIT collaborator, wrote to Dr. John Stanbury, the author of *A Constant Ferment: A History of MGH Thyroid Clinic and Laboratory at The Massachusetts General Hospital: 1913–1990* Stanbury was developing his book. Roberts's letter dated April 3, 1991, states, "Your conjecture that it was the outcome of a group discussion has no basis in fact." Stanbury's book has been in publication for many decades and is cited with false information [2, 3].

Dr. Hertz's question brought together the work established in 1896 of E. Bauman's reporting the effect of iodine on the functioning of the thyroid. Bauman found high concentrations of iodine tightly bound to proteins in extracts of the thyroid gland; thyroid extracts were standardized to contain 0.2% iodine in order to maintain equal potency of different preparations [2]. Additionally, in the field of radioactivity, in 1896, Henri Becquerel investigated the newly discovered X-rays that led to studies of how uranium salts are affected by light. Saul Hertz's question brought together the effect of iodine on the thyroid and radioactivity [2]. In 1935, a Nobel Prize was awarded for artificial radioactivity. Hertz's question launched the radioactive iodine (RAI) research that established the cornerstone of Nuclear Medicine.

Laboratory Studies

In early 1937, a collaboration was established between the Massachusetts Institute of Technology (MIT) and Boston's Massachusetts General Hospital (MGH). A young physicist, Arthur Roberts, Ph.D., was hired by MIT's lab director Robley Evans. MGH's Saul Hertz and Arthur Roberts began the first studies to evaluate the effects radioiodine (RAI), on the thyroid. Physicist Roberts produced noncyclotron I-128 based on Enrico Fermi's work. The experiment involved four dozen rabbits. The RAI was administered to rabbits with altered thyroid functioning. Quantitative analysis showed that hyperplastic thyroid glands retained more RAI than normal thyroid glands. The studies demonstrated the principle that radioiodine could be used as a tracer to investigate thyroid gland physiology [2, 4, 5].

At the time of these initial studies, Hertz conceived of RAI in treating thyroid carcinoma.

The original article describing their rabbit study findings was submitted for publication with Hertz and Roberts as the coauthors as they had done the work and written the paper. MIT's Robley Evans, who was the administrator of the lab

at MIT and who had hired the physicist Arthur Roberts, insisted that his name be added to the paper while it was at the publishers. Robley Evans had done no work in constructing the experiment, analyzing the data, or writing the paper. When Arthur Roberts was hired by MIT's Robley Evans, Evans had included a condition of Roberts employment, that Evans as the director of the lab's name be included on any forthcoming papers.

Hertz and Roberts were hopeful that they could go from diagnosis to treatment; however, they knew they would need a larger quantity of RAI with a longer half-life. Cyclotron-produced RAI was needed. University of California Berkeley chemists', Glenn Seaborg and John Livingood, synthesized I-130 and I-131 [2].

MGH's Chief of Medicine, Dr. James H. Means, secured $30,000.00 from the Markle Foundation for the building of MIT's Markle Cyclotron.

The First Therapeutic Use of RAI

On the last day of March 1941, Dr. Hertz rushed over the Charles River Bridge, with RAI produced from the newly built MIT Markle Cyclotron for a hyperthyroid patent. Perhaps a little nervously, she was waiting at the Massachusetts General Hospital, where she was asked to swallow radiation. Hertz's Data Charts (Fig. **1**) detailed that she received 2.1 mCi (77.7 MBq) [6, 7].

Although there had been a few attempts previously to treat bone metastases with P-32, that Monday, effectively marked the beginnings of treatments with radioactive drugs. It also ushered in the dawn of dosimetry as physicist, Arthur Roberts took measurements of uptake with a Geiger counter clicking merrily away by the patient's neck. They collected Elizabeth's urine and found that 20% of the radioactivity was excreted after the first administration and closer to 30% after the second administration. This was a positive sign that a good amount of the radiation was going where it was needed. Elizabeth's thyroid shrank from 35g to 20g after the first treatment but seemed to have rallied a little to 28g after the second treatment. The basal metabolic rate was measured before and after treatment and seen to drop dramatically.

Hertz and Roberts continued to treat about one new patient per month for the rest of 1941. The total estimated RAI given to each of the eight patients ranged from 55 to 230 MBq with an average of 144 MBq. RAI was taken up by the patient's thyroid glands, and the patients did in fact get better. Hertz gave each patient stable iodine beginning 1–3 days after the radioiodine at the insistence of his chief Dr. James Means. Means wanted to protect the patients against thyroid storms. At the American Society for Clinical Investigation Meeting in May 1942, Hertz

CHAPTER 9

Dosimetric Approach to Radioactive Iodine Therapy of Differentiated Thyroid Cancer

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Abstract: My personal memory with Prof. Kalevi Kairemo is related to our coworking for biokinetics of radioactive iodine (RAI), and a couple of international conferences organized by him. I presented my data on the dosimetric approach of RAI treatment for differentiated thyroid cancer (DTC) at the conference in Helsinki. We analyzed the data of our work and published a paper. Here I summarize my experience of working with him. In summary, maximum permissible dose (MPD) therapy with dosimetry is effective for a selected group ofhigh-risk DTC patients. Calculation of MPD is feasible either by tracer and therapeutic doses and either by blood clearance method and metaphase analysis of peripheral blood lymphocytes. The use of recombinant thyroid-stimulating hormone (rhTSH) changes the biokinetics of RAI. It needs further investigation whether rhTSH can be used for MPD therapy of DTC.

Keywords: Differentiated Thyroid Cancer, Dosimetry, Radioactive Iodine Treatment.

INTRODUCTION

My Friendship with Prof. Kalevi Kairemo

Prof. Kalevi Kairemo visited South Korea several times, the first time in 2006 when the World Congress of Nuclear Medicine and Biology was held in Seoul, Korea. I also attended the Congress but had no chance to meet him personally. He also joined a marathon competition in Korea. He is a nearly professional runner. I visited Finland several times, firstly in 2004, to attend the Congress of the European Association of Nuclear Medicine (EANM). Personally, I met Prof. Kairemo in Levi, Finland, November, 2012 during the 7th International as the

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Conference on Radiopharmaceutical Therapy (ICRT). I was newly elected president of the Asia Oceania Federation of Nuclear Medicine and Biology (AOFNMB) in May 2012 and opened a booth to introduce the next Congress of AOFNMB, which will be held in Jeju, Korea. Prof. Kairemo organized another meeting of WARMTH, which was the International Symposium on Radiopharmaceutical Therapy (ISRT) in Helsinki, Finland, November 2018. I attended the meeting and presented my experience of dosimetric approach to radioactive iodine (RAI) therapy for differentiated thyroid cancer (DTC). I accompanied my wife this time. We enjoyed every corner of Helsinki during our stay. I was deeply impressed to see that Prof. Kairemo did almost everything alone for the organization of ISRT 2018. I visited Prof. Kairemo's office in the Docrates Cancer Center after the ISRT and discussed finalizing our work in the biokinetics of radioactive iodine-131 (RAI) in patients with differentiated thyroid cancer (DTC). A photo taken at the Docrates Cancer Center is shown in Fig. (**1**). The work was done by one of my students, Mr. Wonjun Jung, under the supervision of Prof. Kairemo. Mr. Jung stayed at the Docrates Cancer Center for a month as a visiting student in January 2018. He collected data from Prof. Kairemo's patients. Prof. Kairemo and I analyzed the data with Dr. Aki Kangasmäki, a medical physicist, and published a paper in 2019 [1]. I could learn the ideas and philosophy of Prof. Kairemo through private conversations, which have broadened and deepen my insight on both academic and social life. It is my privilege and happiness to share my experience of dosimetry of RAI therapy for DTC, which is deeply associated with my memory of Prof. Kairemo.

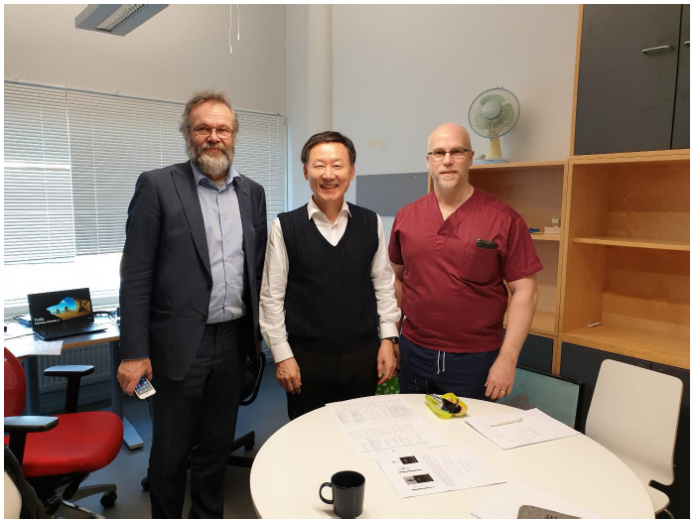

Fig. (1). I visited Prof. Kalevi Kairemo and Dr. Aki Kangasmäki at the Docrates Cancer Center on November 21st, 2018. We discussed how to write our paper which was published the next year [1].

Background of Dosimetric Approach to RAI treatment of DTC

Although RAI treatment is highly effective in patients with DTC, even with distant metastases, repeated RAI treatment is not rare. Metastatic DTC patients usually undergo repeated RAI treatment until the disappearance of RAI uptake or until a cumulative activity becomes 22 GBq. It is common to see that therapeutic efficacy markedly decreases after repeated RAI treatment [2]. Among DTC patients 7-23% develop disant metastasis [3], and 67% of DTC patients with distant metastases become RAI-refractory [1]. In other words, 5-15% of DTC patients become RAI-refractory. The prognosis of these patients is poor. Recently newer kinase inhibitors are being tried for those patients [4].

The dose for treatment of DTC patients with distant metastases is empirically decided between 5.55 and 7.4 GBq. These doses give bone marrow doses far less than 2 Gy, which has reportedly given serious side effects [5]. The exposure dose to the blood reaches 2 Gy is the maximum permissible dose (MPD). It can be calculated by measuring the radioactivity of patient's blood at regular intervals after administering a small amount of RAI. My colleagues and I in S. Korea performed MPD therapy in DTC patients with distant metastasis [6].

SUBJECTS AND METHODS

Patients

A total of 58 patients (9 males and 49 females, average age 50±11 years) among 619 patients with DTC (all papillary thyroid cancer) who underwent total thyroidectomy, and RAI therapy was enrolled. Inclusion criteria were clinical stage 3 (n=11) or stage 4 (n=47); successful follow-up by RAI scan, blood thyroglobulin (Tg), anti-thyroglobulin antibody (TgAb), ultrasonography (US), and F-18 fluorodeoxyglucose (FDG) PET/CT 6 months after RAI therapy.

Determination of Therapy Response

Therapeutic doses are determined by multiple of 1.85 GBq (50 mCi) commercial capsules. Cases with a dose of 7.4 GBq or less were classified as empirical dose (ED) group, and cases with a dose of 9.25 GBq or more were classified as maximum dose (MD) group. The MD was set as the maximum dose not exceeding MPD in consideration of the sales unit. Patients treated in my institute between 1992 and 1999 (4 males and 39 females, mean age 50±11 years) were given ED, while those treated between 2000 to 2001 (5 males and 10 females, mean age 50±12 years) were given MD. There were more males in MD group, but there was no difference in age.

CHAPTER 10

Extent of Surgery and Following Treatment Depending on The Risk Evaluation of Thyroid Cancer

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Abstract: The experience gained in North-West Center for Endocrinology and Endocrine Surgery (St.Petersburg, Russia), performing about 6000 endocrine surgeries annually, shows that in a significant part of patients presenting with differentiated thyroid cancer, it is possible to perform organ-preserving surgeries and to avoid using radioactive iodine therapy. Such tactic are possible only in the settings of the presence of high-quality preoperational cytological diagnostics, thorough following the pre-operative examination protocol (ultrasound examination of the neck area performed by the operating surgeon and by the Head of the clinics, further computed tomography of the chest in all the patients with cytological diagnosis of Bethesda 6, screening of medullary carcinoma using calcitonin blood tests), performing radical resection of the primary tumor with a wide use of preventive central cervical lymph node dissection controlled by intra-operative neuro-monitoring, as well as in the settings of long-term follow-up by the operating surgeons employed in the clinic. Radioactive iodine therapy is an integral phase of therapy for locally advanced tumors and tumors with the presence of distant metastases or high risk of the distant metastatic activity. Making the decision on the necessity of radioactive iodine therapy is possible both based on the evaluation of primary tumor characteristics and the evaluation of blood levels of thyroglobulin and antibodies to thyroglobulin.

Keywords: Central neck dissection, Hemithyroidectomy, Radioactive iodine therapy, Thyroid cancer, Thyroid cytology.

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MEETING IN LAPPEENRANTA

At the end of the year 2009, a very complex situation has arisen in our clinic in Saint-Petersburg regarding treating patients with thyroid cancer using radioactive iodine. The number of operated patients grew up, but sessions of radioactive iodine were almost nowhere to perform. In Russia there was only one nuclear medicine clinic located in Obninsk. That clinic had not kept pace with the increase in the patient flow. At my clinic – North-West Center for Endocrinology and Endocrine Surgery in Saint-Petersburg – the number of thyroid gland surgeries in 2009 has almost reached 1000 (Fig. **1**). That is why, It was of critical importance to search for clinics that arrange radioactive iodine therapy sessions for our patients.

In December 2009, I wrote a letter to Professor Kalevi Kairemo with a request for cooperation in the field of radionuclide therapy for thyroid cancer. Professor has quickly responded, and on 21 of December 2009, I drove my car from Saint-Petersburg to Lappeenranta to meet him. I can still remember this day – at night and in the morning, a vast snowstorm took place, and all the roads were snowbound. I wanted to postpone the trip, but Christmas holidays were ahead, and we had to discuss arranging therapy for patients within short timeframes. I decided to go, despite the severe weather. The trip was difficult - everywhere in the ditches, there were cars skid off the road. Because of the falling snow, I had to drive very slowly and carefully.

Nevertheless, to the end of the day, I was at the Lappeenranta hospital, where professor Kairemo and I discussed all the issues and came to an agreement about our cooperation. The risk during the journey was worth it – from that moment, our patients from Russia started visiting Finland to undergo radioactive iodine therapy. We had arranged therapy predominantly for patients suffering from Graves disease and differentiated thyroid cancer. Our Finnish colleagues have provided a possibility for conducting the qualitative phase of radionuclide therapy, including a very insightful scan of the whole patient body. This allowed our clinic to be one of the first in Russia to provide a complete cycle of therapy for patients suffering from thyroid gland diseases, which has become one of the prerequisites for the rapid increase in the popularity of our clinic. Now we perform the surgical treatment to approximately 6000 patients with diseases of the thyroid gland (predominantly, cancer), parathyroid gland and adrenal glands a year, including children (Fig. **1**). Patients come to us from all the regions of Russia and the countries of the former USSR. Despite the fact that Russia has opened several well-equipped centers for radionuclide therapy in recent years, our clinic holds the leading position in terms of the number of performed surgeries in the country. To

a very significant extent, we owe this to cooperation with colleagues from Finland and personally – to Professor Kalevi Kairemo.

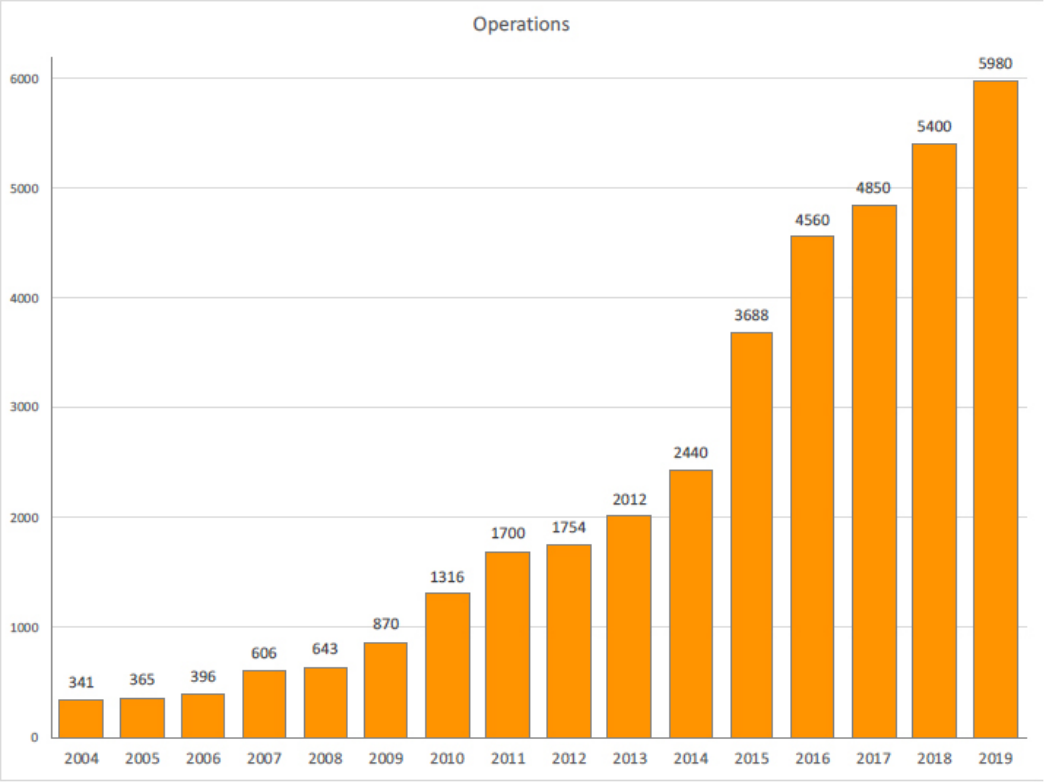

Fig. (1). Number of endocrine surgeries performed at the North-West Center for Endocrinology and Endocrine Surgery.

Strange Attitude

My role in writing this chapter is unusual. It so happened that, in the treatment of patients with thyroid cancer, I perform several tasks in ordinary life not directly related to each other – consulting and managing the patients as an endocrinologist (including non-surgical patients), performing ultrasound examinations and fine-needle biopsy as a radiology physician, performing surgical interventions in adults and children (more than 700 surgeries a year), prescribing radioactive iodine therapy (often with adjusting the optimal activity of the isotope) and performing control procedures to define the results of radionuclide therapy as nuclear medicine physician, prescribing and controlling thyroxine therapy after surgery with general control of therapy results (again as an endocrinologist and as an oncologist), with the follow-up being arranged within a long period of time. On the one hand, such a unification of responsibilities in the hands of one specialist is

CHAPTER 11

The Rise of Biopharmaceuticals and Immuno-PET: Where Pharmacy and Radiopharmacy Meet

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Abstract: The identification of molecular drivers of disease and the compelling rise of biotherapeutics such as peptides, monoclonal antibodies, antibody fragments and non-traditional binding scaffolds, activatable antibodies, bispecific antibodies, immunocytokines, antibody-drug conjugates, enzymes, polynucleotides, therapeutic cells as well as alternative drug carriers like nanoparticles have impacted clinical care but also came with challenges. Drug development is expensive, attrition rates are high, and efficacy rates are lower than desired. Nowadays, almost all these drugs, which generally have a long residence time in the body, can be stably labeled with ^{89}Zr for whole body PET imaging and quantification. Although not restricted to monoclonal antibodies, this approach is called ^{89}Zr-immuno-PET. This contribution summarizes at a high level the historical background, the technical aspects, and the future perspectives of ^{89}Zr-immuno-PET.

Keywords: ^{89}Zr-immuno-PET, Antibody-drug Conjugates, Biopharmaceuticals, Companion Diagnostics, Complementary Diagnostics, Immune Checkpoint Inhibitors, Kalevi Kairemo, Monoclonal Antibodies, Radioimmunotherapy.

THE EMERGING ROLE OF BIOPHARMACEUTICALS

The number of drug approvals has increased from 30 per year on average for the period 2000-2013 to about 50 in the period after [1]. One of the reasons was the rise of biologicals, monoclonal antibodies (mAbs) in particular. In the period 2010-2013, the share of biologicals was about 25% of the new US Food and Drug Administration (FDA) approved drugs; during the period 2014–2018, this was 47% [2]. These comprised hormones, clotting factors, enzymes, vaccines, nucleic acid products, engineered cell-based products and especially mAbs (50% share). With about 600 antibodies at various clinical stages in 2020, these trends can be expected to continue for the coming years [3, 4]. In 2018, the share of biologicals

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was $ 251 billion of the worldwide drug market, valued at about $ 1000 billion/year, and it is expected to reach $ 625 billion in 2026. Also 12 of the top 15 drug blockbusters in 2018 were biotherapeutics, representing $ 88.5 billion of $ 120 billion top-15 sales. These figures are impressive when realizing that the sales of 1 top-15 pharmaceutical equal the total global sales of all radiopharmaceuticals together, diagnostics and therapeutics. Despite these dizzying numbers, the success rate to reach drug approval remained almost constant at around 10% [5], indicating the need for more effective drug development. When looking at these trends, the pertinent question arises of whether there is room for a more prominent role of radiopharmacy and nuclear imaging in the development of biopharmaceuticals.

The Early Days of Imaging Biopharmaceuticals

The introduction of the "magic bullet" concept by Nobel laureate Paul Ehrlich in 1900 followed by the introduction of the hybridoma technology for mAb development by Nobel prize winners Köhler and Milstein in 1975 have marked the starting point for exploiting mAbs for diagnostic and therapeutic purposes [6]. With the latter technology, an unlimited range of mAbs can be obtained against any particular cellular target antigen. Already at an early stage, mAbs were recognized as potential diagnostic agents in nuclear medicine. For this purpose, mAbs were labeled with γ-emitting radionuclides (*e.g.* ^{99m}Tc, ^{111}In, ^{131}I, ^{186}Re) and imaged with a single-photon emission computerized tomography (SPECT) camera. Five ^{99m}Tc- or ^{111}In-labeled murine mAbs were approved by the FDA for diagnostic imaging, among which four for the staging of cancer [7]. It is fair to say that the overall clinical impact of radioimmunodiagnosis was not impressive. Among others, murine mAbs appeared to be suboptimal for human use, targets were not specific enough, while also SPECT imaging left room for technical improvements. As illustrated by Fig. (**1**) for a ^{186}Re-labeled mAb directed against head and neck cancer, the images did not provide much detail on tumor and nontarget organs. The fact that the tumor looked much larger on the image than in reality has to do with the limited spatial resolution of the camera. No anatomical details are visible since SPECT-CTs were not available at that time. And last but not least, quantification was not accurate enough, and this formed a reason to explore the potential of PET for mAb imaging.

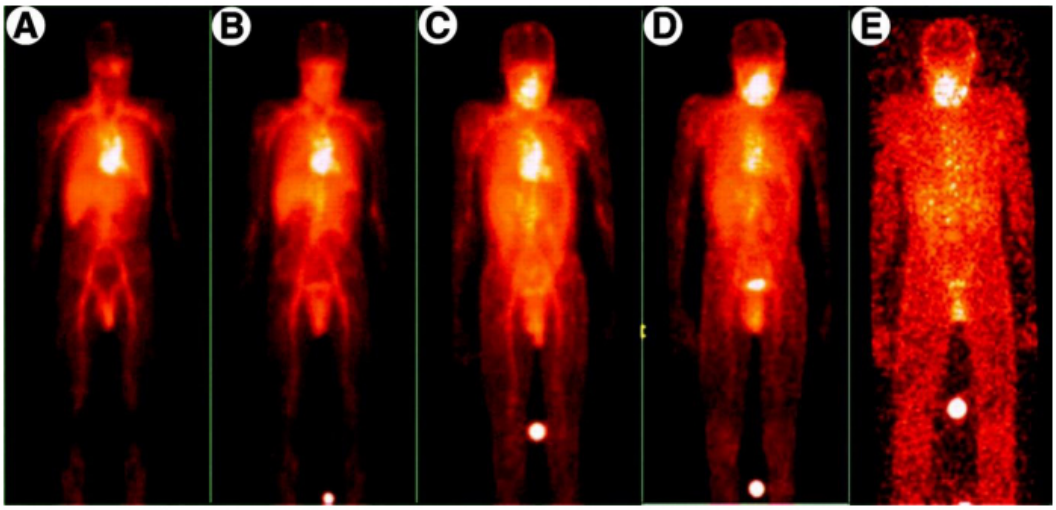

Fig. (1). Planar whole body scans of a patient with a tumor in the right oropharynx. Scans were acquired 1 hour (**A**), 1 day (**B**), 3 days (**C**), 6 days (**D**), and 14 days (**E**) after administration of the ^{186}Re-labeled chimeric monoclonal antibody (c-mAb) U36. Immediately after injection, the mAb resides in the blood pool. Relative uptake of the radioimmunoconjugate in the tumor increases over time, while the tumor becomes better delineated as background activity decreases.

Intermezzo Dedicated to My Friend Prof. Dr. Kalevi Kairemo

It was near the millennium transition that Kalevi and I met for the first time, Kalevi at that time working in Helsinki and Uppsala. It were exciting times for biomedical researchers, especially those who tried to connect molecular biology, molecular diagnosis, molecular imaging, and targeted molecular therapy. The Human Genome Project enabled the discovery of novel disease targets as drivers of disease. Antibody development and applications gained momentum with the introduction of chimeric, humanized, and human versions as well as of antibody fragments. The first naked/unconjugated mAbs (*e.g.*, rituximab, trastuzumab, bevacizumab, cetuximab) as well as radioimmunoconjugates (^{90}Y-ibritumomab tiuxetan; Zevalin® and ^{131}I-Tositumomab (Bexxar®) became approved by the FDA for therapeutic purposes. Although the images shown in Fig. (**1**) were not perfect, they convincingly illustrated that mAbs are capable of specific and selective disease targeting, making mAbs a potential game-changer in drug development and applications. In the field of nuclear imaging, 18-Fluoro-2-deoxy-D-glucose (^{18}FDG) had shown its value for PET imaging in a routine clinical setting for disease diagnosis, staging, and therapy response monitoring. Also, the superiority of PET in comparison to SPECT became clear. PET provides better spatial and temporal resolution and sensitivity and is better qualified for tracer quantification. These developments made Kalevi and me decide to put a concerted effort onto the improved use of mAbs in the radioimmunodetection and radioimmunotherapy of

CHAPTER 12

In the Wake of European Winds and Head and Neck Radioisotope Imaging

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Abstract: The first reported imaging studies with radio-labelled antibodies of head and neck cancer patients were published at the halfway of 1980s. Started with polyclonal anti-CEA antibody, the anti-CEA monoclonal antibody was followed shortly thereafter in the radioimmunoscintigraphy imaging of head and neck tumor patients. Despite a promising platform, the pilot-antibody studies in the latter part of the last millennium have in the end, not yielded a clear advantage or benefit to support clinical decision-making by RIS imaging method in head and neck tumors, neither in terms of diagnostic imaging nor in terms of treatments. The investigated antibodies have not been shown to be sufficiently selective in identifying head and neck tumors.

Keywords: Anti-CEA-antibody, Friendship, Head and neck Tumor, Immunoscintigraphy, Radioisotope.

INTRODUCTION I - FRIENDSHIP

Kalevi is familiar to me from our early ages, so I know something about his nature, character, and purposefulness. Our fathers, in their youth, had been classmates at Jämsä secondary High School in Central Finland in the 40s. They had then continued on their own studying at the University of Helsinki and, with the transition into working life, got married and based their families. The families had been involved with each other that much that we had been playing together randomly at the age of a couple of years already.

Our mutual acquaintance and friendship date back to the higher elementary/secondary school period since 1966. At that time, we started our future-oriented higher education at the Helsinki Normal Lyceum boys' school. Prior to 1966, Kalevi had completed his basic 4 years of elementary school, which he performed at Tehtaankatu Primary School in the southern center of Helsinki. After elementary school, we sought and reached our secondary education at the

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Helsinki Normal Lyceum, where we ended up in the same school class by chance.The Helsinki Normal Lyceum has been one of Finland's leading and most respected secondary schools since 1867, when founded, all the way up to this day.

Our joint trips and events included, among other things, a month-long train ride across Europe all the way to the Peloponnese peninsula in the summer of 1972. An international European Interrail program had launched, which was an affordable tourism opportunity for young people. We were 17 years old, so we had to see the Continent from corner to corner when the opportunity advantageously opened up. Kalevi also traveled again next summer. In 1974, we travelled the European railways crosswise again for a month together (Fig. **1**).

Fig. (1). Somewhere in the Alps in a small village in summer 1974. Kalevi on the left. Erkki on the right.

In his school success, Kalevi was on the top of the class, so the university was the next obvious step. After completing his Master of Science degree in chemistry at the Helsinki University of Technology (Aalto University), Kalevi immediately studied medicine at the University of Helsinki.

After graduating from medical school, his future career development was clear from the start, with an emphasis on research. The suitable clinical research area focused very quickly on medical isotope imaging.

Based on our friendship, the first clinical scientific imaging research subject was discovered in the head and neck area I specialized in. These pilot studies focused on CEA antigen imaging of head and neck tumors with radiolabeled anti-CEA monoclonal antibodies.

INTRODUCTION II - RESEARCH

Imaging studies with the anti-CEA monoclonal antibody or other antibodies at the very end of the last millennium have remained by far the only studies in radioimmunoscintigraphy imaging (RIS) of head and neck cancers. Despite a promising platform, no clinical benefit of anti-CEA or other antibody imaging has been found in head and neck tumors, neither in terms of diagnostic imaging nor in terms of treatments. The investigated antibodies have not been shown to be sufficiently selective in identifying head and neck tumors.

Around the half-way of the 1980s were published the first reported imaging studies with radio-labelled antibodies of head and neck cancer patients. In 1984, Tranter *et al*. [1] released a study of five patients, where they had used 131---radioisotope labelled polyclonal anti-CEA antibody in RIS of head and neck tumor patients.

Shortly thereafter, 111-In-labeled anti-CEA monoclonal antibody has also been used for RIS imaging in small groups of patients. These studies have sought to demonstrate that RIS is a potential imaging modality for both primary tumor and metastasis detection [2 - 5].

Table 1. Monoclonal antibodies used for radioimmunoscintigraphy of HNSCC patients in last millennium (*Polyclonal antibodies).

Year	MAb	No. of Patients	No. of Patients with Neck Involvement	Reference
1984	Anti-CEA (polyclonal)	5	3	Tranter *et al*. [1]
1987	Anti-EGFR	11	3	Soo *et al*. [6]
1990	Anti-CEA (mMAb)	13	6	Kairemo and Hopsu [2]
1990	Anti-CEA (mMAb)	29	1	Kairemo and Hopsu [3]
1991	Anti-CEA (mMAb)	7	3	Timon *et al*. [4]
1993	mMAb 174H.64	21	18	Baum *et al*. [7]
1994	mMAb SF-25	1	1	De Bree *et al*. [10]
1994	mMAb 174H.64	10	1	Heissler *et al*. [8]
1994	mMAb K928	6	6	De Bree *et al*. [10]
1994	mMAb E48/anti-hLy-6D	32	25	De Bree *et al*. [11]
1994	mMAb 323/A3/anti-Ep-CAM	3	0	De Bree *et al*. [10]
1995	mMAb U36/anti-CD44v6	10	9	De Bree *et al*. [12]
1996	mMAb 174H.64	40	6	Adamietz *et al*. [9]
1997	Anti-CEA (mMAb)	20	18	De Rossi *et al*. [5]

CHAPTER 13

Radionuclide Management of Prostate Cancer: Molecular Targeting of Tumour; Strategic Targeting of Patients

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Abstract: The 2020 American Society of Clinical Oncology (ASCO) Guideline for optimum imaging strategies for advanced prostate cancer [1] encompasses patients with newly diagnosed clinical high risk disease, suspected or confirmed metastatic disease, recurrent disease or progressive disease while under treatment. It is recommended that "imaging studies that will not impact or inform treatment decisions should be minimized." It is admitted that "studies have generally shown the superior diagnostic performance of ^{68}Ga-PSMA, ^{18}F-DCFPyL and ^{18}F-PSMA-1007 over other relevant radiotracers in the clinical settings of intermediate to high-risk primary cancer, biochemical recurrence after definitive therapy, and delineation of the extent of metastatic disease and patient eligibility for PSMA-targeted radioligand therapy." "The major impact of PSMA-PET imaging on the management of patients with prostate cancer" is acknowledged. Nevertheless, there will be no ASCO guideline recommendation for PSMA radionuclide theragnostic diagnosis or therapy until the perceived "need to define the potential influence on outcome has been satisfied by additional investigations."

The immediate challenge for nuclear physicians is to design and execute the prospective controlled clinical studies in large representative populations of defined advanced prostate cancer patients. These real-world patients, treated on harmonized standard protocols, in accordance with European Association of Nuclear Medicine (EANM) Guidelines, with primary outcomes of overall survival (OS) and quality of life (QOL), may provide acceptable evidence of efficiency leading to regulatory approval and eventual reimbursement and oncologist acceptance into routine clinical practice. How this desirable outcome may be achieved is the subject of this review of ^{68}Ga/^{18}F-PSMA PET imaging and ^{177}Lu/^{225}Ac-PSMA therapy in which the current status of theragnostics of advanced prostate cancer is explored by reference to scientific communications published in 2020.

Keywords: ^{68}Ga/^{18}F/^{177}Lu/^{225}Ac-PSMA Efficiency, Advanced Prostate Cancer, Nuclear Oncology, Real World Evidence, Theragnostics.

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INTRODUCTION

It is a privilege and an honour to submit this festschrift contribution to celebrate the seminal achievements of Professor Kalevi Kairemo in the field of nuclear oncology. Our World Association of Radiopharmaceutical Molecular Therapy (WARMTH) collaboration was born during an all-day round-trip by taxi from Delhi to Agra in 2008. Whilst my wife learned the art of negotiating Indian traffic from the front seat, Kalevi and I explored the potential of radionuclide diagnosis and treatment of cancer, oblivious to the apparent chaos of the road. Our conversation resulted in an invitation to write a review on individualized patient dosimetry for radiopeptide and radio-immunotherapy of cancer for a special issue of Current Pharmaceutical Design, entitled 'The role of radiopharmaceuticals in drug discovery and development', for which Professor Kairemo was Executive Editor [2]. The next decade of our collaboration on theragnostics, in association with WARMTH, culminated in another invitation to write a review of the WARMTH initiative to obtain real-world evidence (RWE) of efficiency of ^{177}Lu-PSMA radionuclide therapy of metastatic prostate cancer in a special issue of Current Pharmaceutical Design, once again edited by Professor Kairemo [3].

The current status of targeted molecular radionuclide theragnostic outcomes in prostate cancer, as described in the recently published oncology and nuclear medicine literature, is reviewed in order to highlight the fundamental conceptual differences between oncologists and nuclear physicians regarding the clinical application of diagnostic and therapeutic radiopharmaceuticals in the management of cancer. There is an urgent imperative to bridge the manifest disconnect in perceptions of nuclear oncology if radionuclide diagnosis and therapy of cancer is to find its rightful place in mainstream clinical oncology practice.

Nuclear medicine was founded over 75 years ago as a cancer therapeutic speciality, based upon radioiodine treatment of differentiated thyroid cancer (DTC). Evidence of efficiency has been demonstrated in large real-world patient populations with long-term follow-up, such as the 35-year single-centre results in 900 patients achieving overall survival (OS) in 99% of low risk, 95% of the intermediate risk, and 77% of high high-risk DTC [4]. However, no randomised controlled trial (RCT) of Iodine-131 therapy of DTC has ever been performed, and oncologists remain skeptical of its efficacy [5]. The failure of nuclear physicians to perform RCTs also delayed oncologist acceptance of Lutetium-177-octreotate in the efficacious management of gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) for more than a decade [6]. Oncologists ignored the favourable results of numerous non-randomised studies, and the European Neuroendocrine Tumor Society (ENETS) found no place for this

targeted radionuclide treatment in their GEP-NET management guidelines until the publication of the NETTER Study RCT and subsequent FDA approval [6].

Lest history is to repeat itself regarding theragnostic management of prostate cancer, Nuclear physicians must be proactive in performing prospective controlled clinical trials that command acceptance as valid evidence by oncologists and regulatory authorities. The nature of this formidable task will be explored by examination of results and perspectives published during 2020, comparing clinical use of diagnostic ^{68}Ga/^{18}F-PSMA and therapeutic ^{177}Lu/^{225}Ac-PSMA with current clinical oncologist standard approaches to diagnosis, staging and monitoring therapy of prostate cancer.

Current Oncology Practice in Prostate Cancer

Current guidelines recommend a non-targeted trans-rectal ultrasound (TRUS)-guided biopsy in the two million men referred each year in USA and Europe with elevated serum PSA levels (typically >3-4ng/ml). Compliance with recommended TRUS biopsy is around 85%, and after 30 years, it remains the standard procedure for prostate cancer diagnosis, even though tumour detection on the first biopsy is only 30-40%, and not all the gland can be sampled [7]. Furthermore, TRUS biopsies do not discriminate significant prostate cancers from clinically insignificant cancer cells, which are normally dormant in 30% of men over 50 years of age. Many men with indolent disease are advised, or choose, to undergo unnecessary radical surgery or radiotherapy, which does not significantly reduce the risk of metastatic disease or improve survival. In addition, surgery and radiotherapy can cause urinary, sexual and/or rectal dysfunction in over half the men treated [7]. No statistically significant differences are observed between outcomes of clinically localised prostate cancer treated with active surveillance, radical prostatectomy, or external beam radiotherapy; the respective 10 year cancer-specific survival being respectively 98.8%, 99%, and 96.9% [7].

The gold standard pathological Gleason scoring system is also subject to considerable intra-observer variability, and it is evident that “a substantial improvement of the diagnostic paradigm is needed” [7]. Thus, multi-parametric magnetic resonance imaging (mpMRI) has been proposed as a first-line test that is deemed to have the potential to transform the management of prostate cancer. mpMRI comprises multiplane T2-weighted imaging, axial diffusion-weighted imaging and axial T1-weighted imaging, performed before, during, and after intravenous administration of contrast agents. On the basis of well-performed diagnostic accuracy studies and RCTs, in which mpMRI-targeted biopsies consistently outperform systematic TRUS biopsies, this diagnostic approach is rapidly becoming the standard-of-care and is now recommended in international

CHAPTER 14

Ga-PSMA PET/CT for Patients with Prostate Cancer with PSA Relapse

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Abstract: In Danish guidelines for imaging of patients with prostate cancer and PSA relapse, PSMA PET/CT is the recommended restaging modality. A multicenter study has been initiated to analyze findings of ^{68}Ga-PSMA PET/CT scans for patients with prostate cancer with PSA relapse. This report details preliminary findings of 779 patients in six cohorts from three continents. At the time of the restaging, the PSA values were grossly similar between the six cohorts, with an important subgroup of the patients having PSA values < 1 ng/ml. Patients who initially underwent radical prostatectomy had lower PSA values at the restaging than patients who were initially treated with external beam radiation therapy or brachytherapy. Even for patients with restaging PSA values < 0.5 ng/ml, some patients had positive sites in extra pelvic lymph nodes and bones. Patients were followed up to 7 years after the restaging PSMA PET/CT. In multiple Cox regression analysis of 196 patients, only the number of positive sites on ^{68}Ga-PSMA PET/CT significantly predicted overall survival ($p = 0.0001$). The findings illustrate why restaging PSMA PET/CT change salvage treatment for up to half of the patients with PSA relapse compared with planned salvage treatment based on only conventional imaging modalities like CT and bone scans.

Keywords: PET/CT, Prostate cancer: prostate specific membrane antigen, Restaging.

INTRODUCTION

The topic of patients with prostate cancer and PSA relapse is truly relevant for me personally. A close relative with prostate cancer in 2011 underwent PET/CT scanning for PSA relapse in Oslo, Norway and had a positive site in a pararectal lymph node in the pelvic region on the restaging PET/CT. The patient was advised to go to the Docrates Cancer Center in Helsinki, Finland, and undergo radiation therapy with Rapid arc technology [1]. I visited the relative in Helsinki

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during the radiation treatment and was introduced to the high-standard technical facilities at the Docrates Cancer Center by assistant professor Timo Kiljunen [2].

The radiation therapy for the patient was successful, as documented in a publication in an Italian journal of oncology [3]. A later PSA relapse was treated with a new series of radiation therapy at the Docrates Cancer Center. To open the association from restaging PET/CT to salvage treatment in a broader perspective, professor Kalevi Kairemo at the Docrates Cancer Center and I summarized in a systematic review the experience at that time with staging choline PET/CT for patients with prostate cancer [4].

Professor Kalevi Kairemo thought the summary was important and presented our findings at many conferences on nuclear medicine all over the world. First, we submitted a paper version of our analyses, but reviewers were negative. Nevertheless, professor Kalevi Kairemo remained encouraging, and the systematic review was published [4]. Professor Kalevi Kairemo also invited me to submit a review on existing radionuclides for imaging for an issue of a journal of radiopharmaceuticals he edited [5].

In addition, as I had participated in several courses on systematic reviews, professor Kalevi Kairemo and I made a second systematic review on radiolabeled choline PET/CT elucidating technical aspects [6]. Professor Kalevi Kairemo mentioned Marina Hodolic, who in 2015 hinted me on PSMA PET/CT as a promising modality for staging and restaging PET/CT diagnostics [7].

I am a Danish oncologist who previously published research on testicular germ cell tumors. So the alliance with professor Kalevi Kairemo in science was a wonderful lift in my academic afterlife. for my relative and the third episode of PSA relapse made professor Timo Joensuu at the Docrates Cancer Center conclude 1) that the patient should use restaging ^{68}Ga-PSMA PET/CT to govern the further treatment and 2) that it should be ^{177}Luthetium based PSMA radioligand therapy (PRLT). The patient could get the treatment at the University Hospital in Innsbruck, Austria.

In the meantime, I had contacted PET centers in Australia as to PRLT for patients with only lymph node metastases (LNM). But Australian PET centers reacted negatively to the idea. The PET centers argued that PRLT was an experimental treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). According to international guidelines from the European Association of Nuclear Medicine [8, 9], the PET centers should institute PRLT as a compassionate treatment for candidate patients after they had failed all available established treatments for mCRPC.

Professor Irene Virgolini, head of the Department of Nuclear Medicine at the University Hospital in Innsbruck, had a documented interest in PRLT for patients with prostate cancer and thought the guidelines did not prohibit treatment of lymph node metastases before chemotherapy [10 - 12]. So the relative was treated with PRLT in Innsbruck before treatment with established chemotherapy. In 2016, I presented the case as a poster at the 4th World Conference on Theranostics in Melbourne, Australia, arranged together with the Peter McCallum Cancer Center in Melbourne. The conference included a whole day on nuclear medicine and prostate cancer.

During the following years, my relative patient was followed at the University in Innsbruck and had repeat episodes with PSA relapse. But the important finding was his prostate cancer remained PSMA-positive, and the patient remained to respond to further series of PRLT. Through three years of follow-up, the patient underwent five series of cycles with PRLT [13]. The treatment was effective and without severe adverse effects.

Professor Richard Baum was chief for the Department of Nuclear Medicine at the Zentralklinik Bad Berka in Germany, and the Department had been a pioneer for PRLT of prostate cancer [14]. Consultant Harshad Kulkarni published a review of the experience with PRLT for prostate cancer at the Zentralklinik Bad Berka [15]. An exciting finding was that patients with only lymph node metastases (LNM) responded better to PRLT than other patients with more widespread mCRPC.

Professor Richard Baum invited me to visit the Zentralklinik Bad Berka and accepted that we did a detailed re-evaluation of the patients with LNM treated with PRLT. During the period where we worked on the evaluation of the LNM cohort, correspondence with consultant Nat Lenzo, Australia, together with Danielle Meyrick, added a similar group treated in Australia. The German results were reproduced and slightly surpassed in the cohort from Australia.

Privately, it had been argued that the good results at Zentralklinik Bad Berka were "incredible" due to postulated "deficiencies of the health system in the Eastern part of Germany". So the inclusion of the Australian cohort was important to falsify the counterargument [16]. Ironically, many of the patients treated at the Zentralklinik Bad Berka were not from the Eastern part of Germany. For instance, a patient was referred for PRLT at the Zentralklinik Bad Berka from the Memorial Sloan Kettering Cancer Center in New York, USA.

A review of patients treated with PRLT at the Zentralklinik Bad Berka confirmed the overall survival was better when PRLT was given for patients with only LNM than for patients with bone, lung, and liver metastases [17].

CHAPTER 15

Imaging Bladder Cancer

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Abstract: Imaging plays an important role in the management of bladder cancer (BCa). Cystoscopy, ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are the commonly used imaging modalities. Introduction of positron emission tomography (PET), a molecular imaging modality, with CT or MRI offers precise anatomical reference. Certain molecules labeled with radiotracers such as Fluorine-18 and Carbon-11 have been evaluated for their potential applicability in PET imaging. However, urinary excretion of Fluorine-18 and the very short half-life of Carbon-11 restrict their use. Copper-64 labeled peptide TP3805 (^{64}Cu-TP3805) targeted to BCa cell-specific receptors demonstrated promising results in detecting BCa and its metastasis by PET imaging. A description of all these imaging modalities and their recent advances, together with their potential advantages and limitations, are presented.

Keywords: ^{64}Cu-TP3805, Bladder Cancer, Computed Tomography, Cystoscopy, Imaging, Magnetic Resonance Imaging, Positron Emission Tomography, Ultrasound.

INTRODUCTION

Bladder cancer (BCa) is a common health disorder with an estimated 83,730 new projected cases and 17,200 deaths in the United States alone in 2021 [1]. It is the fourth most common cancer in men but comparatively less common in women. BCa represents spectra of diseases ranging from recurrent noninvasive tumors to aggressive invasive tumors associated with high mortality [2]. Bladder cancer is broadly divided into non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), which account for 80-85% and 20-25% of bladder cancers, respectively [3]. Nearly 90% of all bladder tumors termed as transitional cell carcinoma, originate from the urothelium, the epithelial lining of the bladder. Transitional cell carcinoma is staged according to the tumor type, its

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invasion to lymphatic nodes, and its distant metastasis, using a Tumor Node Metastasis (TNM) system [4].

A brief overview of the TNM staging of BCa is presented in Table **1** [5]. Nonurothelial cancer in the bladder is rare, and includes squamous cell carcinoma (less than 5%), adenocarcinoma (2%), small cell tumors (0.5%), and lymphoma [4].

Table 1. TNM staging of bladder cancer.

Stage	Stage Grouping	Description
0a	Ta	Non-invasive papillary carcinoma (Ta). Cancer develops toward the hollow center of the bladder not in the connective tissue or muscles of the bladder wall.
	N0	Cancer has not outspread to adjacent lymph nodes (N0)
	M0	Cancer has not outspread to distant sites (M0)
0is	Tis	Non-invasive carcinoma (Tis), also known as flat *carcinoma in situ (CIS)*. Cancer develops in the inner lining of the bladder only not towards the hollow part of the bladder. Not invaded to connective tissue or the bladder walls muscles.
	N0	Cancer has not outspread to adjacent lymph nodes (N0)
	M0	Cancer has not outspread to distant sites (M0)
I	T1	Cancer has developed into the layers of the connective tissue but has not reached the muscle layer of the bladder wall (T1).
	N0	Cancer has not outspread to adjacent lymph nodes (N0)
	M0	Cancer has not outspread to distant sites (M0)
II	T2a or T2b	Cancer has grown into the inner (T2a) or outer (T2b) muscle layer but has not completely passed through the muscles to reach the surrounding fatty tissue.
	N0	Cancer has not outspread to adjacent lymph nodes (N0)
	M0	Cancer has not outspread to distant sites (M0)

(Table 1) cont.....

Stage	Stage Grouping	Description
IIIA	T3a, T3b or T4a	Cancer has developed into the layer of fatty tissue surrounding the bladder through the muscle layer (T3a or T3b). Cancer might have outspread into the prostate, seminal vesicles, uterus, or vagina, but it's not growing into the pelvic or abdominal wall (T4a).
	N0	Cancer has not outspread to adjacent lymph nodes (N0)
	M0	Cancer has not outspread to distant sites (M0)
	OR	
	T1-4a	The cancer has: developed into the connective tissue layer under the bladder wall lining (T1), OR into the bladder wall muscle layer (T2), OR into the layer of fatty tissue surrounding the bladder (T3a or T3b) OR it might have outspread into the prostate, seminal vesicles, uterus, or vagina, but it's not grown into the pelvic or abdominal wall (T4a).
	N1	Cancer has outspread to 1 adjacent lymph node in the true pelvis (N1)
	M0	Cancer has not outspread to distant sites (M0)
IIIB	T1-T4a	The cancer has: developed into the connective tissue layer under the bladder wall lining (T1), OR into the bladder wall muscle layer (T2), OR into the layer of fatty tissue surrounding the bladder (T3a or T3b), OR it might have outspread into the prostate, seminal vesicles, uterus, or vagina, but it's not grown into the pelvic or abdominal wall (T4a).
	N2 or N3	Cancer has outspread to 2 or more lymph nodes of the true pelvis (N2) or to lymph nodes alongside the common iliac arteries (N3).
	M0	Cancer has not outspread to distant sites (M0).
IVA	T4b	Cancer has developed into the pelvic or abdominal wall through the bladder wall (T4b).
	Any N	Cancer might or might not have outspread to adjacent lymph nodes (Any N).
	M0	Cancer has not outspread to distant sites (M0).
	OR	
	Any T	Cancer might or might not have developed into nearby organs through the wall of the bladder (Any T).
	Any N	Cancer might or might not have outspread to adjacent lymph nodes (Any N).
	M1a	Cancer outspread to distant lymph nodes (M1a).
IVB	Any T	Cancer might or might not have developed into nearby organs through the wall of the bladder (Any T).
	Any N	Cancer might or might not have outspread to adjacent lymph nodes (Any N).
	M1b	Cancer spreads to 1 or more distant organs, such as the liver, lungs or bones (M1b).

Adapted from [5].

CHAPTER 16

Radiomolecular Therapy of Neuroendocrine Character, Positive for sst_2 Receptor Hepatocellular Malignancies

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Abstract: In 1996, Krenning *et al*. injected the radiopeptide for the first time intravenously.[111]In-Octreotide as a new treatment approach, today, worldwide known as Peptide Receptor Radionuclide Therapy (PRRT) to confront unresectable neuroendocrine tumors. We started treating this rare category of neoplasms in our Institution in 1997, exclusively injecting intra-arterially, initially [111]In Octreotide, in high doses, focused our interest on multiple liver metastases (particularly, less than 20 mm, in diameter) after catheterization of the hepatic artery ["Aretaieion Protocol"]. The radiopeptide was infused in repeated high activity, ranging per session from 4.070 GBq (110 mCi) to 5.920 GBq (160 mCi) with a time interval between sessions of 6-8 weeks, seeking to achieve a tumor absorbed dose according to the dosimetry followed, over 70 Gy (tumor mass 10 gr). When [90]Y DOTA-TOC was used (3 folds in total, in bi-monthly intervals between sessions), the infused activity was 4.1± 0.2 GBq per patient, per session, whereas when n.c.a. [177]Lu-TOTA-TOC was injected (6 folds in total, in bi-monthly intervals between sessions), the activity was 7.0 ± 0.4 GBq per patient, per session. Follow-up at tri-monthly intervals was performed by means of ultrasonography (US) and every six months, by contrast, material-enhanced computed tomography (CT) and / or magnetic resonance tomography (MRI). This therapeutic procedure is described in detail, based on the experience in more than 800 hundred catheterizations, analyzing its advantages and limitations as a first-line treatment scheme for the management of this rare category of tumors.

Keywords: Auger electrons, Hepatic artery catheterization, Liver Neuroendocrine Tumors, N.C.A. [177]Lu-DOTA-TATE, PRRT, Internal Conversion electrons, Intra-arterial infusions, [111]In-Octreotide, [90]Y-DOTA-TOC.

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INTRODUCTION

The most frequently expressed somatostatin receptor subtype apart of the 5 discovered and cloned is the subtype sst2, in the majority of the neuroendocrine tumors, and not only [1, 2]. The radiolabelled with indium-111 (^{111}In), yttrium-90 (^{90}Y) or lutetium-177 (^{177}Lu) somatostatin analog peptides [-octreotide,-DOTA^{0}--Phe^{1}-Tyr3-octreotide (DOTA^{0}-TOC) or -DOTA^{0}-D-Phe^{1}-Tyr3-octreotate (DOTA^{0}-TATE)] bind with high affinity to this sst2 subtype receptor (22 ± 3.6 nM for ^{111}In, 11 ± 1.7 nM for ^{90}Y, 1.5 ± 0.4 nM for ^{177}Lu) and moderate to the sst3 (182 ± 13 nM for ^{111}In, 389 ± 135 for ^{90}Y, 453 ± 176 nM for ^{177}Lu) and sst5 (237±52 nM for ^{111}In, 114 ± 29 nM for ^{90}Y, 547 ± 160 nM for ^{177}Lu), respectively [3, 4]. ^{111}In emits γ-photons of two energies (172 and 245 keV) used for imaging [5] and Auger and Internal Conversion electrons for therapy. ^{90}Y is a pure β^- emitter of an $E\beta$ max = 2.27 MeV energy, used for therapy, whereas ^{177}Lu emits γ-photons of two energies (113 KeV and 208 KeV) and β^- particles of Eβ max = 0.497 MeV for imaging and therapeutic purposes, respectively. After i.v. application, the radiopharmaceuticals are internalized into the tumor cell by fluid-phase endocytosis within 1hr p.i. and degraded into the lysosomes, close to the nucleus, where they are retained [2, 6]; the empty receptor drives again to the cell membrane surface. Lysosomes / nuclear membrane and DNA have an average distance of 8 up to max 12 μm [7]. This obviously means that DNA lies within the destroying *R*95=5.94 mm β^- particle range of yttrium-90 (*R*95 being the distance within which the β-particle transfers 95% of its energy to the target tissue), the 2 mm β^- particle range of lutetium-177 and the 0.02-10 μm range of Auger and the 200-550 μm of Internal Conversion electrons [8] of indium-111. Taking into account that in each ^{111}In decay, a spontaneous emission of about 8 Auger electrons results, enabling it to destroy few numbers of cells, only micro-metastases and small (≤ 20 mm) sized nodules could be candidates of this type of therapy [9]. On the other hand, in every ^{90}Y or ^{177}Lu decay, about 200 and 50 cells respectively, are expected to be killed, meaning that larger nodes (≥ 20 mm) are the most suitable candidates for the latter radionuclides for treatment. The effectiveness of these emissions (β^-, Auger and Internal Conversion electrons) is very high due to their high efflux and energy deposition, which depends on the atomic binding energies (Eb).

In 1993, ^{111}In—DTPA^{0} - Phe^{1}-Octreotide was used for the treatment of these types of tumours [5, 10], *via antecubital intravenous infusions*, exploiting the Auger and Internal Conversion Electron emission of ^{111}Indium [5, 11]. This treatment modality aimed at destroying the tumour tissue none-invasively through the linear energy transfer (LET) delivered from these electrons [12]. The disadvantage of the procedure was the increased accumulation of the radiopeptides in the kidneys, considered to be the critical organs [13, 14].

In order to maximize the highest possible activity absorption onto the metastatic *liver lesions*, achieving larger possible destruction with the lowest delivered dose to the kidneys, we decided to modify the route of administration by applying radioactivity as close as possible to the malignancy after *selective catheterization of the hepatic artery* [15]. Furthermore, because of the catheterization procedure discomfort, since repetitions for ^{111}In were necessary to arise the 12 folds in order to deliver an effective absorbed dose to the tumour, a temporal port installation was always positioned after patients' written consent (Fig. **1**). The implantable port system obviously offers a stable connection mechanism at port chamber/catheter junction, the high flow rate in thin catheters, secure placement of the puncture needle in the chamber septum, easy location of the puncture site, and the most important, quality of life [7].

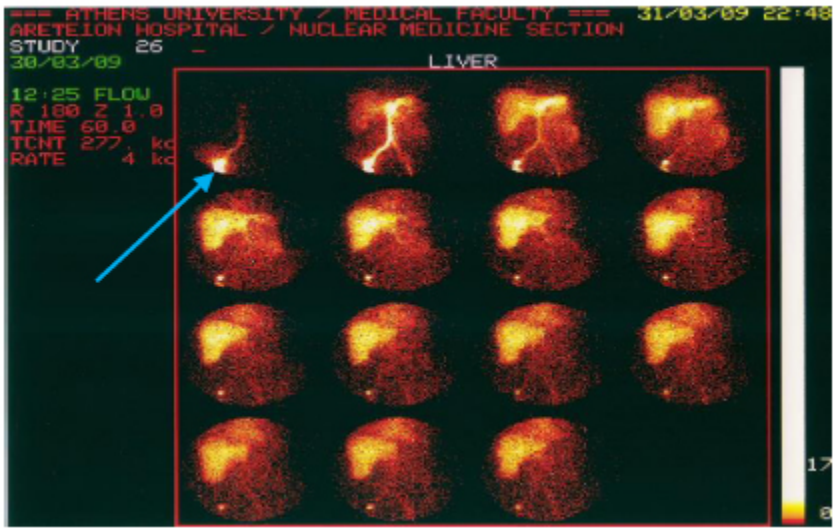

Fig. (1). Intra-arterial infusion *via* implanted port system.

MATERIALS AND METHODS

Patients

A cohort of 21 patients with *un-resectable* neuroendocrine liver metastases, confirmed by biopsy, previously managed with high doses of ^{111}In-DTPA^{0}-Phe^{1}-Pentetreotide [6.3±0.3 GBq per session, in monthly intervals] was planned to be further treated using two radio-labelled somatostatin analogues, ^{90}Y-DOTA TOC, 3 folds in total, in a dosage of 4.1± 0.2 GBq per session and /or n.c.a. ^{177}Lu-DOTA TATE, 4-6 folds in total in a dosage of 7.0 ± 0.4 GBq per session. All pts present in *advanced stage* and *progressive disease*, without having any other conventional treatment option (*chemotherapy and/or radiotherapy).* The protocol followed was

CHAPTER 17

Theranostics in Japan

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Abstract: Frankly, Japan is at the end of the line of current clinical theranostics such as PRRT and PSMA. Many patients go abroad for PRRT and PSMA treatment. This lamentable situation has been caused mainly by the strict regulations as well as the limited number of isolation rooms available for these purposes in this country. But despite this, Japanese scientists are developing several unique activities in theranostics, including ^{211}At[NaAt] for ^{131}I radioiodine refractory thyroid cancer and meta-^{211}At-astato-benzyl guanidine (^{211}At-MABG) for ^{131}I-MIBG refractory pheochromocytoma/ paraganglioma, which are currently ready for investigator-initiated trial. There are several other developments in this field. Such information is described in this short article.

Keywords: ^{131}I-MIBG, ^{211}At[NaAt], ^{225}Ac-fibroblast activation protein inhibitor (FAPI), ^{64}Cu-diacetyl-bis (N4-methylthiosemicarbazone) (^{64}Cu-ATSM), Mmeta-^{211}At-astato-benzylguanidine (^{211}At-MABG).

INTRODUCTION

It is no wonder that theranostics has become one of the major current keywords in nuclear medicine. When I joined the Department of Nuclear Medicine, Kanazawa University in 1986, radioiodine therapy for thyroid diseases was the only available therapeutic option. In those years, radioimmunodetection and radio-immunotherapy (RIT) were being vigorously researched globally. For instance, programs of annual meetings of the Society of Nuclear Medicine were full of sessions on these topics through the conferences. Researchers, including myself, were trying hard to introduce them into daily clinical practice too. However, we had to wait until technologies of producing chimeric or humanized antibodies and stable radiolabeling were established. Moreover, it took a long time for the first

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RIT to be approved. ^{90}Y-Ibritumomab tiuxetan(Zevalin®)for CD-20 positive B-cell malignant lymphoma was approved by the US FDA at last in 2002. Japanese patients had to wait to undergo this treatment until 2008.

One of the disadvantages of antibodies as carriers for radionuclides is their long biological half-life. Therefore, the use of fragments or engineered small antibody-like moieties has been attempted. Small moieties, typically somatostatin analogues that bind somatostatin receptors (SSTR), have been choices preferable to antibodies. Efforts for 20 years in STTR targeting were finally realized as Peptide Receptor Radionuclide Therapy (PRRT) with ^{177}Lu-DOTATATE (Lutathera®) which was approved in Europe in 2017 and in the United States in 2018. In Japan, ^{177}Lu-DOTATATE was submitted for approval in August 2020 and will hopefully be approved in mid-2021.

As you may know from the examples of ^{90}Y-Ibritumomab tiuxetan and ^{177}Lu-DOTATATE, Japan is one of the most underdeveloped countries in theranostics. Clinical studies of ^{68}Ga/^{18}F-PSMA for prostate cancer have only just been initiated. No Japanese patients have yet been able to undergo ^{177}Lu-PSMA therapy in their own country so far, but rather have had to go abroad mainly to Australia to receive it [1]. A number of patients went to Switzerland and Germany to be treated with ^{177}Lu-DOTATATE for many years. This has been a matter of shame for the Japanese medical community. But despite this, Japanese scientists are developing several unique activities in theranostics. I would like to introduce some of them in this article.

^{131}I-MIBG FOR MALIGNANT PHEOCHROMOCYTOMA /PARAGANGLIOMA

This historical radiopharmaceutical was first introduced in Japan in the late 80's for compassionate use. I participated in the treatment of a few patients during my postgraduate student days. However, due to its unstable supply, its use was ceased after a few years. Treatment was resumed in 2000 independently in 4 institutions including my hospital. The data indicated that multiple treatments at 150-200 mCi doses could improve the prognosis (Fig. **1**) [2, 3].

In 2016, a phase 1 investigator-initiated trial (IIT) was carried out in these hospitals in the Japanese Ministry of Health, Labour and Welfare (MHLW)'s Study Group program on unapproved and off label drugs of high medical need. The best overall response rate based on RECIST was 10% (2/20) in complete response (CR), 65% (13/20) in stable disease (SD), 15% (3/20) in progressive disease (PD), and 10% (2/20) in not evaluated (NE) [4]. An industry-sponsored phase 2 trial succeeded it (data not published yet). The results were submitted all

together to the MHLW on January 28, 2021. This is specified as an orphan drug, and was approved just on Sept. 29, 2021.

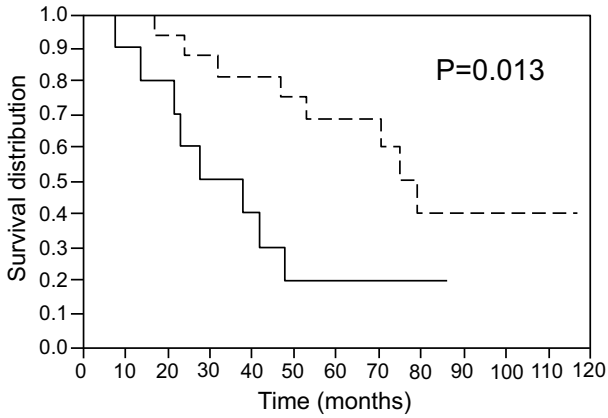

Fig. (1). Kaplan–Meier curves of overall survival after first ^{131}I-MIBG therapy: multiple-time ^{131}I-MIBG therapy (dashed line) and control group (solid line). Reproduced from ref. 2 with permission.

^{131}I-MIBG FOR HIGH-RISK NEUROBLASTOMA

This was also initiated like the treatment of pheochromocytoma/paraganglioma. Because of the difficulty of treating children due to radiation safety concerns [5], Kanazawa University Hospital has been the only institution performing this since 2001. It was initiated as non-myeloablative therapy with a fixed dose of 100 mCi. Due to its limited effectiveness, treatment was switched to a myeloablative dose at 15-18 mCi/kg followed by high dose chemotherapy and bone marrow transplantation. Treatment response in 19 advanced patients was either complete (CR) or partial (PR) in three and two cases, respectively. The EFS and OS rates at 1 year following ^{131}I-MIBG therapy were 42% and 58%, and those at 5 years following ^{131}I-MIBG therapy were 16% and 42%, which were comparable to the historically reported results [6].

In patients who attained CR on ^{123}I-MIBG scintigraphy after induction therapy and relapsed after that, we applied myeloablative ^{131}I-MIBG therapy similar to the protocol as mentioned earlier in 6 patients. Three patients showed no signs of disease relapse during the observation period. The 5-year PFS and OS were 44% and 67%, respectively, which were better than the previous results, indicating that ^{131}I-MIBG therapy would be more likely to improve survival in patients with minimal tumor burden. Currently, the IIT is on-going as the consolidation treatment in patients with CR to induction therapy as determined by ^{123}I-MIBG scintigraphy [7]. We are planning to submit the data to MHLW for approval after the end of this IIT.

CHAPTER 18

Theragnostics in Austria

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Abstract: Over the past decades, Professor Kalevi Kairemo has been a well-known and dear colleague with whom we have excellently cooperated, especially *via* the international organisations IAEA (International Atomic Energy Agency) and The WARMTH (World Association of Radiopharmaceutical and Molecular Therapy). The work resulted in the construction of radiotracers using different modal systems, including a variety of radiolabelled peptide analogues such as somatostatin, cholecystokinin (CCK-2/gastrin), or prostate-specific membrane antigen (PSMA) ligand for specific tumour targeting. Radiopharmaceuticals are produced at clinical grade in dedicated laboratories for use in SPECT/CT or PET/CT studies. Patients evaluated by SPECT/CT dosimetry studies are treated with high dose thera(g)nostics. Radioiodine ablation therapy of thyroid cancer remnants, peptide receptor radionuclide therapy (PRRT) of NET patients, and peptide ligand radionuclide therapy (PLRT) of PC patients are today the most important therapeutic tools.

Keywords: Peptide Receptor Radionuclide Therapy, Peptide ligand Radionuclide Therapy, Radioiodine Refractory Thyroid Cancer, Hormone Refractory Prostate Cancer, Neuroendocrine Tumours, Thera(g)nostics.

INTRODUCTION

The Department of Nuclear Medicine at the Medical University of Innsbruck is best known for its work with radiolabelled peptides, both for diagnostic and therapeutic purposes, a theme that we have systematically explored over the last 3 decades (www.nuklearmedizin- innsbruck.com). We are developing a variety of radiopharmaceuticals for different targets for clinical use. Our goal is to engineer more effective ligands/peptides/antibodies - "thera(g)nostics" - for individualized treatment, mainly in the area of oncology. Over the past decades, Professor Kalevi Kairemo has been a well-known and dear colleague with whom we have excellently cooperated, especially *via* the international organisations IAEA (International Atomic Energy Agency) and The WARMTH (World Association of Radiopharmaceutical and Molecular Therapy). Our extensive research discussions

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in the fields of neuroendocrine tumours (NETs) and prostate cancer (PC) were intensified during exhaustive meetings and social dinners in conjunction with ICRT`s (International Conferences on Radiopharmaceutical Therapy) of The WARMTH. Some impressions we leave in the addendum showing Professor Kalevi Kairemo as an active colleague and friend, not sparing to drink one or the other glass of good red wine at gatherings such as the WARMTH Oenophiles dinner (www.WARMTH.org).

The Department of Nuclear Medicine at the Medical University of Innsbruck, similar to the work performed at the Docrates Institution of Professor Kalevi in Helsinki, accelerates the translation of preclinical radiopharmaceutical research development into clinical applications towards imaging of biomarkers used for cancer treatment (70% of clinical routine), treatment of neurological impairment (20% of clinical routine) or cardiac disease (10% of clinical routine). The structure of the departments at both sites is based on a creative, productive, well-funded and internationally respected Preclinical Research & Development group. Their work results in the construction of radiotracers using different modal systems, including a variety of radiolabelled peptide analogues such as somatostatin, vasoactive intestinal peptide (VIP), cholecystokinin (CCK-2/gastrin), or prostate-specific membrane antigen (PSMA) ligand for specific tumour targeting. Other important developments are based on Arg-Gly-Asp (RGD) for imaging of angiogenesis in tumour lesions or hepatic binding protein imaging with galactosylated albumin (NGA) for functional liver reserve estimation. Radiopharmaceuticals are produced at clinical grade in dedicated laboratories for use in SPECT/CT or PET/CT studies. Patients evaluated by SPECT/CT dosimetry studies are treated at the Nuclear Medicine therapy ward with high dose thera(g)nostics. Radioiodine ablation therapy of thyroid cancer remnants, peptide receptor radionuclide therapy (PRRT) of NET patients, and peptide ligand radionuclide therapy (PLRT) of PC patients are today the most important therapeutic tools.

Nuclear Medicine is not only involved in clinical studies with radiolabelled thera(g)nostics, particularly industry-sponsored Phase I/IIa trials, but also in academic Phase I trials with radiopharmaceuticals developed in-house.

Thera(g)nostics

The research activities focus on preclinical research dedicated to the optimization and improvement of radiolabelling procedures for established radiopharmaceuticals, the in-house preparation of new radiopharmaceuticals for clinical studies, as well as the preclinical development of new radioligands for molecular imaging and therapeutic purposes. Different research projects illustrate the

activities in this field. Some of the thera(g)nostics developed at the Department of Nuclear Medicine in Innsbruck have already entered larger clinical Phase I/II trials.

Siderophores for Molecular Imaging and Therapy

Nuclear Medicine can play a vital role in the field of infection by molecular imaging and thera(g)nostics. Siderophores are low-molecular-mass, Fe^{3+}-specific chelators secreted by bacteria and fungi. The use of siderophores labelled with gallium-68 for PET has been a focus of preclinical research for many years. In a current preclinical project triacetylfusarinine C (TAFC) the main extracellular siderophore of Aspergillus fumigatus (AFU), and responsible for severe invasive fungal infections, is modified for novel applications. The main objective is to develop and characterize novel analogues of TAFC targeting AFU *in vivo* and to establish a novel table concept for thera(g)nostics of invasive aspergillosis. One example is the chemical modification of TAFC with fluorescent dyes. This allows "hybrid imaging" by combining optical imaging (650-800 nm excitation wavelength) with PET. An example of microscopy of such a compound and *in vivo* imaging in a rat model infected with AFU in the lung by PET/CT and optical imaging is shown in Fig. (**1a**) [1]. Therapeutic applications, modifying siderophores with antifungal molecules, are currently under investigation leading to thera(g)nostic compounds. This work was financed by the Austrian Science Fund (FWF project number 30924-B26). Other research topics are the use of radiolabelled siderophores for bacterial infections, including a variety of preclinical approaches.

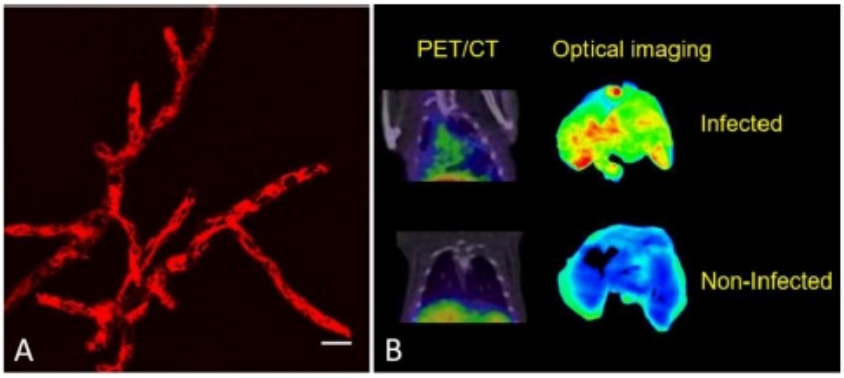

Fig. (1a). Hybrid imaging of aspergillus fumigatus (AFU). (A) Live-cell image of AFU hyphae with [Fe]DAFC-Cy5 after 15 min, highlighting intracellular mitochondria. Scale bar 10 µm. (B) Left column: Coronal µPET/CT slices of AFU infected (top) and non-infected animals (bottom) 45 min p.i. in immunocompromised Lewis rats (approx. 5– 10 MBq injected dose) Right column: Fluorescence images of corresponding lungs excised from infected and non-infected rats 1.5 h after injection. Images reproduced from Pfister *et al.* [1].

CHAPTER 19

Precision Oncology Through Radiating Bullets: What All We Have Conquered and What All We Have To

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Abstract: Precision oncology refers to personalized or precise oncological care for each patient based on their biomarkers, gene sequencing profile, and disease /receptor-specific imaging status. Precision oncology through theranostics is derived from a diagnostic tool that helps identify a therapeutic tool for a specific disease. In Nuclear Medicine, a radioisotope with suitable imaging characteristics or a tracer labeled ligand is fired to a particular target on a cancer cell. After identification of the target, it is labeled with a tracer having therapeutic characteristics labeled with the same ligand to target the disease. The theragnostic concept was first used in 1964 to treat thyroid cancer with radioiodine I-131 (RAI). With the passage of time, this concept has been refined, and more theragnostic pairs have been added successfully for clinical use.

The growth of the theragnostic in India is parallel to the west with the availability of indigenous radiotracers like Lu-177 and others, available from the reactors of Bhabha Atomic Research Centre (BARC). The peptides like DOTATATE and PSMA are also available in a ready-to-use labeled form with an excellent tradesmanship by BARC and Board of Radiation and Isotope Technology (BRIT) We, in India, perform radionuclide therapies for neuroendocrine tumors (NET) and metastatic castration-resistant prostate cancer (mCRPC) regularly. The main constraints about this concept are the cost of treatment and awareness among the clinicians. These are gradually being taken care of by the private health insurance and our participation in disease management group and tumor board meetings. The theragnostic concept has become quite popular over the years and has the potential for further and rapid sustained growth. This article is a living tribute to Prof Kalevi Kairemo, who has a tremendous research interest in radio-targeting and molecular radiotherapy.

Keywords: Constraints, Current Status, History, India, Prof Kalevi Kairemo, Theragnostics.

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INTRODUCTION

My first introduction with Prof Kalevi Kairemo was in 2012 when he organized the International Conference on Radiopharmaceutical Therapy (ICRT), the annual meeting of the World Association of Radiopharmaceutical and Molecular Therapy (WARMTH) at Levi in Finland. It was a very well-organized meeting with excellent scientific deliberations and multiple recreational programs and sightseeing. What impressed me most was his astute scientific knowledge about radionuclide therapy, his published work, along with his organizing capabilities and friendliness. This article summarizes our contributions to precision oncology through theragnostic nuclear medicine and some of the contributions to literature in this aspect from India, which will contribute to the collection of writings published in honor of a scholar like him. Precision and personalized oncology enable diagnostic and screening methods to manage the individual patient's disease or predisposition towards illness better. It helps in treating each individual with the same disease separately and sometimes differently based on certain advanced genomic features, risk stratification and gene mutation studies which could be targeted to the person's particular phenotype. This helps in achieving a better outcome both in the form of disease control and better quality of life. The term theragnostic combines a diagnostic modality to predict a specific therapeutic modality for the specific person's disease type and clears the path for personalized and precision management. In the case of radionuclide, a target is identified and imaging is performed after labeling the target with the diagnostic tracer. In case the disease sites show the expression of that particular target, it is labeled to a tracer with therapeutic characteristics and the therapy is carried out. The concept of "we treat what we see and see what we treat" holds true in such cases. In radionuclide therapy, since the same vector is used for both diagnosis and therapy, it can just be done by changing the tracer as one for diagnosis and the other for treatment. This facilitates specific concentration at the disease sites and spares normal tissue (which has no target expression), achieving a highly absorbed tumor dose. Theragnostic concepts in neuroendocrine tumor and prostate cancer are currently used world over including India [1].

NUCLEAR MEDICINE JOURNEY OF INDIA

The successful practice of the theragnostic concept in India owes significantly to its step-by-step journey in this country which we owe to our world-renowned scientists and mentors. It all started in the mid 20th century after India's independence in 1947. The Atomic Energy Establishment Trombay (AEET) was first established in 1954 to spearhead India's nuclear journey. The first research reactor was commissioned in 1954 and the name given was APSARA, followed by the second one named CIRUS in the year 1960. The indigenous production of

radionuclides for medical use began gradually with the production of isotopes like radioiodine (RAI), P-32, Cr-51 and many more. The AEET was rechristened as Bhabha Atomic Research Centre (BARC) in 1967 named after nuclear scientist Dr. Homi Jehangir Bhabha, who took India's nuclear journey to the world platform. Since the early 1960's BARC was engaged in the production of medical radioisotopes which was supplied to institutes in India and neighbouring countries for patient's use. This continues even today and has exponentially grown over the years. With the passage of time we built institutions and infrastructure along with the technological advancement in instrumentation, making the specialty an integral part of patient care. We started imaging with the rectilinear scanner in the early 1960's moving on to Gamma camera, SPECT-CT gamma camera, PET scanner, medical cyclotron and PET–CT scanner over the next four decades. Training of qualified human resources like physicians, technologists, radiochemists and physicists went on parallelly till we became a complete Nuclear Medicine friendly country. With this gradual exponential transition, the molecular imaging facilities in India stands parallel to the global facilities in the production, usage of radioisotopes, and training of personnel in postgraduate degrees and fellowships [2].

JOURNEY OF THERAGNOSTICS IN INDIA

The theragnostic application in India is going on since 1964, which started with the therapeutic application of RAI followed by treatment of NET with Lu-177 DOTATATE and prostate cancer with Lu-177-PSMA. I-131-MIBG therapy for Neuroblastoma and malignant pheochromocytoma is also being practiced. There is a discrepancy, of the centers performing molecular imaging, which has grown exponentially over the years, compared to the facilities for radionuclide therapies which have not kept pace with it due to the regulatory requirements laid down by the Atomic Energy Regulatory Board (AERB), which is the authority, functioning under the government's department of atomic energy, regulating the radiation safety aspects of radionuclide therapies. The main among these is the requirement of a large capacity delay and decay tank for the toilets in the therapy ward, which becomes a challenge to comply in an already functioning organization. At present, there are 92 institutions in India having such treatment facilities with 200+ bed capacity. We have three such beds in our institution and have been practicing theragnostics for the last 25 years [2].

AVAILABILITY OF THERAGNOSTIC RADIOISOTOPES AND RADIOPHARMACEUTICALS

Gradually, the scientists from different divisions of BARC were successful in developing theragnostic radiopharmaceuticals for clinical use which was utilized

CHAPTER 20

Current Status of PSMA Targeted Alpha Therapy in Prostate Cancer Patients

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Abstract: Despite multiple new agents having been available routinely for men with metastatic castration-resistant prostate cancer (mCRPC), the diagnosis remains fatal, with these agents contributing minimally to over-all survival. Targeting the prostate-specific membrane antigen (PSMA) has been attractive because it is overly expressed in prostate cancer cells with upregulation of the over-expression related to tumour grade, castration status and metastatic disease. To this end novel agents have been developed targeting the PSMA antigen not only for imaging but also for therapy. Actinium-225 (^{225}Ac), an alpha emitter, has been labelled to PSMA ligands as ^{225}Ac-PSMA for targeted alpha therapy (TAT). ^{225}Ac deposits high energy, resulting in irreparable double strand DNA destruction while sparing surrounding normal tissue, making it an attractive anti-tumour agent. Clinical application of ^{225}Ac-PSMA TAT as the last line of therapy in patients with mCRPC has demonstrated an excellent response, especially in the setting of chemotherapy-naive patients. Widespread application of ^{225}Ac-PSMA TAT, though remains hampered by its salivary gland toxicity.

Keywords: ^{225}Ac-PSMA, mCRPC, Prostate Cancer, Targeted Alpha Therapy, Theranostics.

INTRODUCTION

Prostate cancer remains the leading cancer diagnosed in men worldwide, with its incidence varying throughout the world [1, 2]. Prostate cancer treated while still confined to the prostate gland may have an expected 5 year survival of nearly 100% whilst the 5 year survival of metastatic prostatic cancer is only 33% [3]. Approximately 20% of patients with prostate cancer will develop metastatic disease which is androgen deprivation therapy refractory, so called metastatic castration-resistant prostate cancer (mCRPC), a lethal form [4].

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Chemotherapy (docetaxel and cabazitaxel), androgen axis targeting agents (abiraterone and enzalutamide), Sipuleucel-T®, and the bone metastases targeting $^{223}RaCl_2$ have been the standard therapy in mCRPC [5 - 10]. Despite this range of treatment options available for mCRPC, there has been minimal impact on overall survival, with mortality from mCRPC approximating 100% [11].

Prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein, is highly expressed in prostate cancer with increasing expression correlating with tumour grade, hormone resistance, and metastatic disease [12]. This increased expression of PSMA in prostate cancer cells as compared to normal tissue made PSMA an attractive antigen for targeted imaging and therapy. To this effect, PSMA-617 and PSMA-I&T gained traction as the leading molecules for PSMA radioligand therapy (PRLT) with ^{177}Lu-PSMA [13].

PRLT with ^{177}Lu-PSMA is now commonly administered as the last line of therapy in patients with mCRPC in centers worldwide. A prospective phase II study of PRLT with ^{177}Lu-PMSA in patients with mCRPC who had failed standard therapy demonstrated a ≥50% PSA decline in 57% of the patients, with 82% of patients demonstrating a response in soft tissue disease [14]. In a meta-analysis on ^{177}Lu-PSMA PRLT a ≥50% PSA decline was noted in 307 (45%) of the 681 patients included [15]. This highlights the significant number of patients who may not have appropriate disease control after ^{177}Lu-PSMA PRLT. Furthermore, the β particle tissue range of ^{177}Lu of up to 2mm precludes its use in patients with diffuse widespread marrow disease as these patients risk severe haematological toxicity secondary to PRLT [16].

^{225}Ac has a half-life of 9.9 days and decays to produce 4 alpha particles with an energy of 5.8 – 8.4 MeV, with a tissue range of up to 85μm [17]. Alpha particles are attractive anti-tumour agents as they have a high LET and relatively short tissue length and are able to produce double-strand DNA damage whilst minimizing toxicity to adjacent tissue; this is a far more favourable cytotoxic agent as compared to β particle emission, which mainly results in single strand DNA breaks and a relatively long tissue path length which contributes to its toxicity profile [18].

Clinical Experience in ^{225}Ac-PSMA

In a study with the first-in-human use of ^{225}Ac-PSMA-617 Kratochwil *et al*. reported complete response in two patients with mCRPC who had failed multiple lines of previous therapy, one had widespread marrow disease making him ineligible for ^{177}Lu-PSMA therapy whilst the other patient had progressed from ^{177}Lu-PSMA therapy presenting with diffuse abdominal and liver disease [19]. A subsequent study on dosimetry determined a recommended treatment activity of

100kBq/kg administered every 8 weeks as appropriate, balancing between tumour lethality and adverse toxic effects of ^{225}A-PSMA-617 [20].

Kratochwil *et al*. reviewed the efficacy of ^{225}Ac-PSMA-617 in a large cohort of 40 patients with advanced disease [21]. All patients had mCRPC and failed or were ineligible for conventional therapy; 70%, 85% and 60% of the cohort had had prior docetaxel, abiraterone and enzalutamide, respectively [21]. ^{68}Ga-PSMA PET/CT and ^{99m}Tc-PSMA SPECT/CT imaging were used for patient selection with patients with a limited disease selected for ^{177}Lu-PSMA radioligand therapy whilst those with diffuse uptake on imaging were treated with ^{225}Ac-PSMA, those patients who demonstrated no tumour uptake on imaging were declined target alpha therapy (TAT) [21]. An activity of 100kBq/kg ^{225}Ac-PSMA-617 was administered 8 weekly for a minimum 3 and up to 5 cycles, the protocol would later be amended to reduce the administered activity should the patient demonstrate a reduction in PSA of >60% [21]. This was done in an attempt to take advantage of the tumour sink effect and reduce radioligand toxicity as the tumour load reduced as a response to therapy, making more radioligand available to non-target uptake in the salivary glands and bone marrow [22]. Of the 40 patients enrolled 38 survived at least 8 weeks, with 63% of these patients demonstrating a PSA response >50% and 87% demonstrating any PSA response, a median overall survival and progression-free survival of >12 and 7.0 months was demonstrated [21]. This compares with an absolute overall survival in comparison to placebo of 3.4 months, 2.2 months and 3.6 months for arbiterone, enzalutamide and ^{223}Ra respectively [8, 10, 23]. Xerostomia was the most frequently reported side effect, with 10% of the enrolled patients refusing any further treatment due to severe xerostomia [21].

Feuerecker *et al*. investigated ^{225}Ac-PSMA-617 TAT in 26 patients who had failed a median 6 lines of previous therapy for mCRPC; all had progressed after ^{177}Lu-PSMA therapy [24]. A PSA decline of >50% was demonstrated in 65% of the patients whilst 88% of the patients demonstrated any PSA reduction, however, no complete response was seen in the population [24]. The median overall survival was 7.7 months (95%CI 4.5-12.1) [25]. Mild irreversible xerostomia was seen in all patients, with 23% of patients refusing any further treatment due to severe xerostomia, 8% of the patients had to have their treatment discontinued to prevent further deterioration of marrow toxicity had been pre-existing [24]. Poor prognosticators that were noted in the patients who had failed the previous ^{177}Lu-PSMA included the presence of liver metastases and higher ECOG status [24].

Similar findings were described by Yadav *et al*. where 28 patients with mCRPC were enrolled to receive ^{225}Ac-PSMA-617 TAT; of these patients, 54% had failed ^{177}Lu-PSMA therapy whilst 46% were ^{177}Lu-PSMA therapy naïve [25]. A

CHAPTER 21

Nanotheranostics: A Dream Coming True

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Abstract: This chapter discusses how nanoparticles and multimodal nano-imaging are bringing closer to the moment where imaging and therapy converge. This means that the diagnosed illnesses can be treated *in situ* based on the imaging result allowing personalized Nano-medicine. There are already theranostic nano-medicines that can do precise drug delivery only to the targets that are seen and approved by radiology and nuclear medicine tools. In this chapter, we also discuss the already existing emerging techniques and their challenges and implications on the traditional pharma industry and startup-driven biobusiness.

Keywords: Drug delivery, Multimodal Imaging, Nanoimaging, Nanomedicine, Theranostic.

Since Hippocrates, the father of modern medicine, imaging has developed tremendously, starting with visualization with bare eyes at daylight. Inventions like quantum mechanics in physics, organic ring structure from Kekule's dream, Curie's table drawer images, and Fourier transformation calculations in mathematics are significant steps needed before modern 3D-imaging could be born. At the moment, tracer development and nanotechnology have brought theranostic imaging to a state where radiologists can make diagnoses and make therapeutic interventions critical to the patient. Still, we are not jet in the stage where silver nanoparticles are silver bullets and gold nanoparticles are gold standard in imaging [1]. We are living in a dream but is it sweet, ^{18}F-FDG alone can not tell.

The success of nanotechnology in medicine can only be fully realized when laboratory innovations can be translated into pharmaceutical or medical products

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[2]. This requires the strategic collaboration of different disciplines from surgeons, radiologists, material sciences, engineering and instrumentation, physicist, chemist, analytical chemist, and biologists to fulfill regulatory affairs' needs and have a successful translation. Parallel advancements in these disciplines will surely accelerate the progress of the next generation of Nanocarriers from bench to bedside. Small animal imaging speeds up the process and opens up the creation of a totally new class of tools to be used in intraoperative settings. Theranostic imaging fuses imaging and the therapy component.

Nanotechnology-based delivery systems radically change the biodistribution of the drug. If the metaphor of a human body is a sieve, it is an enormously complicated one. There are multiple barriers for nanoparticles like the Blood-brain-barrier and blood-testis that limits nanoparticles capability to transport themselves from one side to another [3,4]. However, our knowledge of these borders has increased lately, and we can now say that the barrier is the machine. The natural barriers in the body change their permeability in diseases. This can be beneficial to target nanoparticles only in the location it is needed, like when using enhanced permeability and retention (EPR) effect of certain tumors to be targeted nanocarrier based chemotherapeutics to the tumor. The body's natural barriers can be circumvented by manipulating the nanoparticle's size, charge, or softness. Liposomes and micelles are widely developed and used to promote the efficacy of drug treatment. By preferentially enhancing the localization of pharmaceutical activity in the organ/tissue of interest, their use can reduce the required systemic drug doses, thus minimizing the risks of adverse side effects while increasing treatment efficacy. Liposomes have been generated in multiple settings and in different formulations for clinical use, and they are generally well tolerated. Most of the liposomes used in clinical trials are used to solubilize drug molecules and prolong the blood half-life. Some of the liposomes accumulate close to the tumors because of the EPR enhanced permeation and retention effect (EPR). Even though this effect increases the amount of drugs on the site of the tumor, it does not necessarily increase the number of drugs biologically available because the drugs can get trapped inside the liposomal envelope. Molecular imaging is critical to the development and success of targeted molecular medicine, since it allows the detection of diseases and monitoring therapeutic efficacy [3,4]. In pre-clinical experimental animal models, a multiplicity of modalities is established and used for much more precise monitoring of therapeutic effects compared to “historical” end-point measurements like tumor weight or cancer-related death of animals.

When I started my post-doc period, professor Kalevi Kairemo mentioned that the human being is a complicated sieve where different particles are separated in different compartments. I have been practicing this view in my studies. It is indeed peculiar that small nanoparticles smaller than 7-8 nm can pass through the

kidney threshold and end in the urine, whereas larger particles are either stored in the body indefinitely or secreted through the liver to hepato-biliary excretion. We used this finding to bring the first small silica particle targeted with phage display peptide containing radioactive iodine and fluorescence label to the clinic in MSKCC. Before that, there were years of development with me and Kairemo in CTT Cancer Targeting Technologies Finland, where we compared different coupling and labeling strategies in order to make the most efficient phage display peptide targeted liposomal nanoparticle possible. At the time, using synthetic phage display-derived peptides for nanoparticle targeting and tacking its success by using nuclear imaging techniques was way ahead of its time. Nanoparticle-based delivery was not known as a concept nor combining imaging tracer and therapy, now called theranostics. The funding of the company withered in Finnland, but luckily the information gathered was not lost and is now after several successful clinical trials utilized by several pharmaceutical companies like Elucida Oncology New York. Elucida Oncology uses Phage display peptide RGD for targeting silica nanoparticle that is radiolabeled and carries optical tracer. This general strategy and labeling strategy is exactly the same as was used in the CTT Cancer Targeting Technologies Finland ten years before [2].

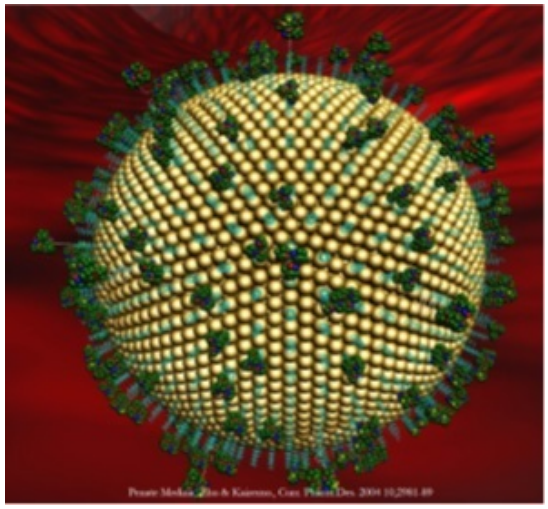

Fig. (1). Phage-display petide targeted liposome in the early 2000´s [1].

At the moment, Elucida Oncology is mentioned to be one of the most successful nanoparticle companies. It has products in the clinics in imaging as well as in theranostic therapeutics. It has raised almost 100 M$ investment money from private as well as public sources. It has top executives like Geno Germano from Pfizer's where he was the leader of Global Innovative Pharmaceutical Business, cultivating a $14 billion operation. However, in the core, it is a kind of brainchild

CHAPTER 22

"Fit for Purpose" ^{64}Cu Labeled Liposome Formulations Specialized for Enriched Targeting to 1) Bone Marrow Spleen; 2) lymph Nodes; or 3) Tumor

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Abstract: Upon intravenous injection, liposomal particles are rapidly cleared from the blood by fixed macrophages in the liver, spleen, bone marrow and lymph nodes *i.e*. specialized cells of the innate immune system. By reducing the affinity for these fixed macrophages, therapeutic liposomes containing drugs have been used to target tumor by the Enhanced Permeability and Retention (EPR) effect. In this communication, we report minor modifications of lipid compositions that result in the production of 3 classes of liposomes, each suitable for enhanced selectivity of uptake in 1) Bone Marrow/Spleen (SBMT Lipo); 2) Lymph Nodes (LNT Lipo); and 3) Tumor (TT Lipo).

Keywords: Bone Marrow Imaging, Copper-64, Endothelial Macrophages, Lymph Node Imaging, Nanoparticles, PET, Reticuloendothelial System, Tumor Imaging.

INTRODUCTION

For many years nuclear medicine has exploited the cells of the fixed macrophage system for imaging purposes by using microscopic particles as radiaotracers. Initially, Au-198 colloid and succeeded by Tc-99m colloid were used to imaging liver, for detection of metastatic tumors, as well as bone marrow to identify sites for biopsy. More recently, a variety of simple radiolabeled particles are used for lymphatic imaging upon subcutaneous injection, *i.e.* sentinel lymph node imaging for breast cancer and melanoma staging. These have also included a variety of nanoparticles of various materials and sizes.

In the current manuscript, by modulating the size and surface lipid composition,

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we have developed liposomal formulations that allow for enhanced targeting to organ-specific cells of the fixed macrophage system (aka Reticuloendothelial System (RES), after parenteral administration. Liposomes in the size range of ~90 nanometers in diameter with varying degrees of pegylation and surface charge were developed for specific targeting purposes. For example, SBMT Lipo preferentially accumulates in the phagocytic cells lining the bone marrow and spleen sinusoids [1]. SBMT Lipo formulation was used to provide enhanced delivery of radioprotector drug γ-tocotrienol (GT3), or GT3-Nano for short, to the spleen and bone marrow, to mitigate bone marrow radiation damage from external beam radiation or targeted radionuclide therapy (TRT). Fig. (**1**) shows the biodistribution profile of different "fit for purpose" liposomal formulations that can be used for distinct purposes, including imaging, drug delivery.

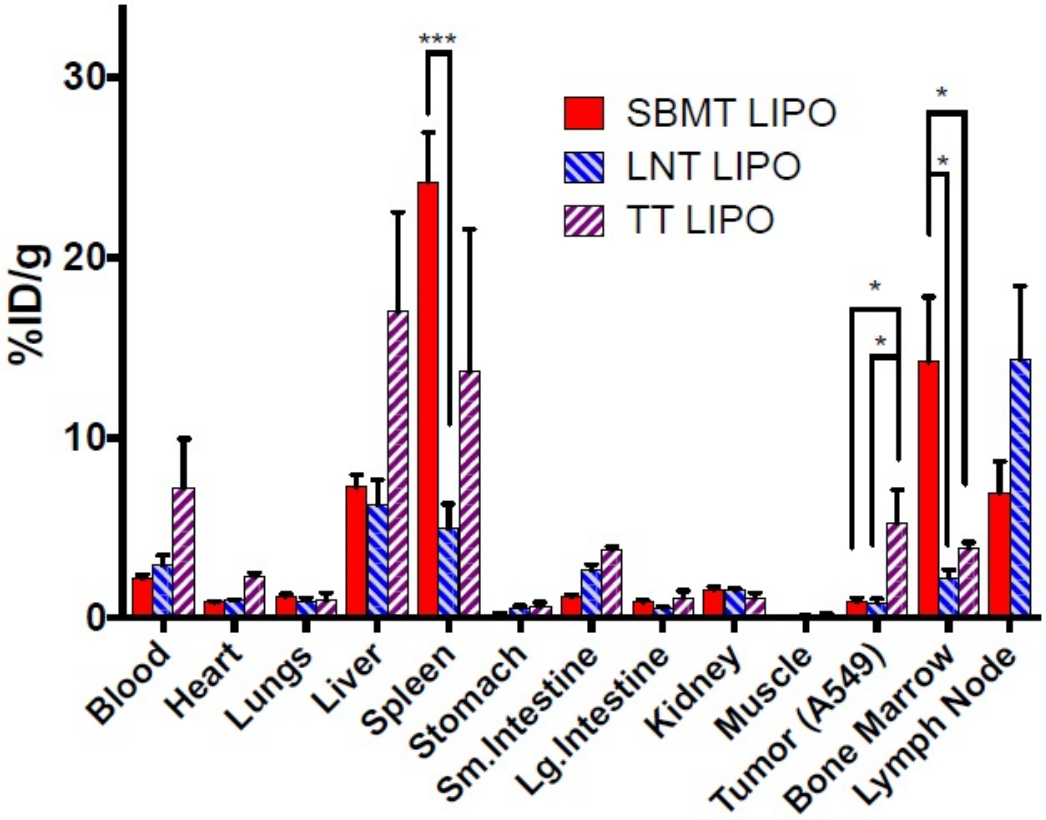

Fig. (1). Biodistribution of ^{64}Cu labeled selective targeting liposomes at 24 h post-injection. Athymic nude mice bearing A549 tumor were injected with ~140 μCi (5.18 MBq) of ^{64}Cu labeled liposomes. 1.4 mg (2 μmoles) of lipid was injected each mouse through tail vein injection and it is corresponding to approximately 6 x 10^{12} liposome particles per mouse. Mice were euthanized at 24 h post-injection and organs were harvested in pre-weighed tubes to measure organ weight and γ-counting. Data were presented as mean and SEM. n=5 per group. * $p < 0.05$, *** $p < 0.001$.

METHODS

The compositions of each liposome are as follows; SBMT Lipo. Phosphatidylcholine (PC), cholesterol, succinyl phosphoethanolamine (SuPE) and mPEG2k-DSPE (6:3:1:0.1). LNT Lipo. The ratio was adjusted to 6:3:1:0.7. TT Lipo, the ratio between PC, cholesterol, and mPEG2k-DSPE are 7:3:0.5. Tumor targeting no SPE MPEG 5%. All liposomes were manufactured by the standard extrusion method at 65 ^{o}C and the sizes of liposomes are 90 nm. The formulation was stable for 2 years at 4 ^{o}C in size and ^{64}Cu labeling to the liposomes. Labeling was performed with ^{64}Cu chelation to DOTA-bn- DSPE doped liposomes after incubation of [^{64}Cu] $CuCl_2$ at 37 C for 1 hour. ITLC was used for quality control, and yield was quantitative [2].

Animal studies. Mice were injected intravenously by tail vein and *ex-vivo* biodistribution was performed at 24 hours post-injection. Mice were imaged 24 h post liposome administration using Focus 120 microPET or Inveon PET/CT scanner.

RESULTS AND DISCUSSION

Using 3 different formulations, mice were sacrificed, and biodistribution was performed at 24 hours after injection of approximately $6x10^{12}$ particles (60 pmoles), of liposomal preparations of approximated 90 nm in diameter of 3 stable formulation types: SBMT Lipo, LNT Lipo, and TT Lipo. ^{64}Cu, a positron emitter, provides a convenient radiotracer for gamma counting and/or PET imaging. (1) A comparison of the biodistribution results from independent studies is shown in Fig. (1). All 3 formulations target the spleen, bone marrow, liver and lymph nodes. However, by altering the surface charge and/or pegylation fraction, major changes in relative biodistribution occur. As is clear from Fig. (**1**), there are statistically significant distribution differences between the tissues, and this translates into major differences in PET imaging appearance. In Fig. (**1**), in one case, a tumor was targeted and comparison, in this case, is between the SBMT Lipo and the TT Lipo. Tumor uptake is most favorable in this TT Lipo formulation, with a mean change greater than 5 times the uptake in tumors seen with the SBMT LIPO.

The LNT Lipo steers liposomes to the lymph node, as shown in Fig. (**2A**). The SBMT Lipo formulation steers the liposome to the spleen and bone marrow at the expense of the liver uptake Fig. (**2B**). The preparation was developed to deliver cargo as selectively as possible to the spleen and bone marrow, wherein stem cells reside that are important for the regeneration of bone marrow, damaged by radiation effects. A recent publication in the JNMMI [2] describes a newly developed radioprotector drug liposomal formulation GT3-Nano based on SBM

CHAPTER 23

Theranostics at the Crossroads of Precision Health and Precision Medicine

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Abstract: There have been major recent advances in multiple disciplines that have culminated into the underpinnings of precision health and precision medicine. The advances include but are not limited to new insights into human biology in health and disease, innovations in computation technology capable of storing and processing massive amounts of multidimensional data (big data), improvements in imaging technology, and developments such as sophisticated radiomics, and incorporation of artificial intelligence and deep learning. Theranostics, which is an integration of targeted diagnostics and therapeutics, is emerging rapidly and is positioned strategically to link precision health and precision medicine.

Keywords: Cancer, Health, Medicine, Precision, Theranostics.

There have been major recent advances in multiple disciplines that have culminated into the underpinnings of precision health and precision medicate. The advances include but are not limited to new insights into human biology in health and disease, innovations in computation technology capable of storing and processing massive amounts of multidimensional data (big data), improvements in imaging technology, and developments such as sophisticated radiomics, and incorporation of artificial intelligence and deep learning.

PRECISION HEALTH

Precision health is defined as approaches that integrate the complex interactions

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of biological, behavioral, environmental and social systems that affect human health. The goal of precision health is to achieve a deep understanding of the state of human health. Such knowledge allows an improved grasp of how health may transition into disease, with the hope to discover highly accurate predictors and devise effective interventions to either prevent or markedly delay the transition. The Project Baseline Health Study (PBHS) is a prospective, multicenter, longitudinal cohort study with the aim to establish a health state reference using "big data" obtained from thousands of participants with diverse backgrounds [1]. The enrolled individuals will be evaluated serially in order to collect measurements across spectra of clinical, molecular ("-omics"), imaging, sensor, behavioral, psychological and social domains. This major undertaking started in 2017 with the intention to follow participants for at least 4 years. The objectives of the PBHS are described as follows: 1) to develop a set of tools and technologies to collect, organize and analyze multi-dimensional health-related data, 2) to evaluate the utility of sensor technologies for the collection of accurate continuous health information, 3) develop and assess the diversity of a multi-phenotype measurement database as it relates to health status and potential transition into disease, 4) share the big data with qualified investigators and promote open science. The PBHS effort is anticipated to fill the gap in our deep understanding of how various multi-dimensional parameters maintain the state of health in humans and what perturbations lead to the state of disease.

PRECISION MEDICINE

Precision medicine is a more familiar term that has been coined recently to refer to personalized or patient-specific management decisions and care. The former U.S. President Barack Obama introduced his Precision Medicine Initiative as "to pioneer a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients" [2]. The ever-increasing advances in the understanding of the biology of disease, particularly cancer, and new sophisticated technologies including liquid biopsy, imaging biomarkers and systems, computational innovations in amalgamating and analyzing diverse data, and new therapy regimens (*e.g.*, targeted, immunotherapy) have all contributed to approach the primary goal of precision medicine [3 - 12]. This goal simply states that not all disease phenotypes are the same in that, for example, 2 patients with the "same" diagnosis may need entirely different approaches for their disease management. In the clinical setting of cancer medicine, precision oncology has made major recent strides which received a major boost through the Cancer Moonshot Initiative by the President Obama administration with the allocation of US$2 billion of funding through the 21st Century Cures Act in the USA. A Blue Ribbon Panel was formed to lay out a

roadmap to identify priority areas in exploiting new developments in cancer prevention, diagnosis, and treatment [13, 14]. The priority areas included medical oncology, radiation oncology, surgical oncology, imaging, theranostics, health disparities, regulatory and financing systems, and public policy.

THERANOSTICS

Theranostics is the systemic integration of targeted diagnostics and theranostics [15]. As outlined above, theranostics was considered a priority area in precision oncology by the Cancer Moonshot Initiative Blue Ribbon Panel. While there are various forms of theranostics (*e.g.*, opto-theranostics, magneto-theranostics), the scheme that has received the most attention is radiotheranostics which refers to the use of radionuclides for paired imaging and therapy agents for use in appropriate clinical settings [16 - 19]. Radiotheranostics was born about 75 years ago with the use of radioiodine in the imaging and treatment of thyroid diseases. Therefore, while the concept is not new, it has undergone a renaissance with the development of novel agents for imaging and targeted radionuclide therapy of cancer (*e.g.*, ^{68}Ga- or ^{64}Cu-DOTATATE for imaging with PET and ^{177}Lu-DOTATATE for treatment of somatostatin receptor-expressing neuroendocrine tumors;). Other agents are anticipated in the near future that are targeted to prostate-specific membrane antigen, chemokine receptors, and fibroblast activation protein. This list will likely expand as further biological insights and biomarker developments continue.

Kalevi Kairemo, yoga teacher and Hossein Jadvar in Kochin, India at ICRT in November 2016, after a morning yoga lession.

CHAPTER 24

Oncolytic Immunotherapy: From Spontaneous Regression to Development of Armed Gene Modified Viruses

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Abstract: Spontaneous regression of tumors, meaning the disappearance of clinically diagnosed tumors without treatment, is a relatively rare but well-established phenomenon. Many explanatory theories have been proposed, but currently, the strongest data support a role for microbial infection in inducing antitumor immunity, which then eradicates the tumor. For at least 4600 years, physicians have been attempting to take advantage of this phenomenon. Initially, bacteria or bacterial products were used for infecting tumors or cancer patients. Then, about a hundred years ago, the focus shifted to viruses. Initially, virulent wild-type (unmodified) viruses were used, but these caused many side effects. In the late 20th century, the generation of modified (recombinant) viruses became possible. Oncolytic viruses are replication-competent only in tumors. Initial modifications of the respective wild-type viruses focused on making them safer for clinical use, and the next step was increasing efficacy by arming with transgenes. The field of immunotherapy evolved to take advantage of immune cells directly in approaches such as dendritic cell therapy and adoptive T-cell therapy. It was also discovered that many T-cells are inhibited by tumors, and that they could be reactivated with checkpoint inhibitors. An unexpected finding relating to the gut microbiome ties together microbes, diet and the immune system. Cancer immunotherapy can already cure some patients, and rapid steps forward are expected to continue. Learnings from attempts of recreation of spontaneous regression have contributed to these developments in an important manner.

Keywords: Adenovirus, Adoptive Cell Therapy, Checkpoint Inhibitor, Gene Therapy, Immuno-oncology, Immunotherapy, Microbiome, Oncolytic Virus, Spontaneous Regression, Spontaneous Remission, Virotherapy.

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INTRODUCTION

The disappearance of tumors without treatment is a rare but well-established phenomenon in medicine, as demonstrated by more than 4000 case reports found in PubMed. Once detected, cancer typically behaves quite predictably, progressing until successfully treated or until the patient dies. This is because genetic changes, which have accumulated in cells over years or decades, have allowed the tumor to escape the defense mechanisms of the body. As the outcome of cancer diagnosis is typically inevitable, if not treated in time, those few cases that behave differently are noteworthy.

Putative explanations for spontaneous regression (solid tumors) or spontaneous remission (hematological malignancies) have ranged from divine intervention to diet, herbs, supplements and psychological factors. However, from the scientific point of view, the most likely explanation is clinical (with symptoms) or subclinical (without symptoms) microbial infection, which leads to inflammation, stimulation of pathogen-associated molecular pattern (PAMP) recognition signaling and subsequent induction of an immune response against the tumor.

Indeed, many tumors are infested with microbes [1]. On one hand, this demonstrates how the immune-suppressed nature of tumors allows microbial growth. On the other, it could also indicate antitumor activities of microbes. The mechanisms of infection leading to immunity have been worked out in molecular detail and proven in a randomized setting [2], while the same cannot be said for the other mechanisms proposed for spontaneous regression.

Estimates on the frequency of complete spontaneous regression vary wildly and there appears to be a lack of reliable data. While numbers between 1:100 and 1:100 000 have been suggested, these could be under or overestimations; almost all reports are retrospective case studies. It is possible that some spontaneously regressing cancers were initially diagnosed incorrectly, and were in fact some other process. There is some thinking that partial or complete spontaneous regression, might be especially common and seen in several percent of certain "immunogenic" tumor types, such as melanoma and renal cell cancer [3, 4].

However, the clinical experience of most oncologists is that complete regression of advanced tumors, which have been confirmed by a pathologist but not treated in any way, is exceedingly rare. Part of the reason could be that some treatment is usually attempted, and thus, the response would be attributed to the attempt. As defined, most cases of spontaneous regression are indeed spontaneous, but there is a long history of trying to understand and facilitate the process. The ability to make advanced or metastatic tumors disappear without unacceptable damage to the body remains the holy grail of oncology.

INDUCING SPONTANEOUS REGRESSION

The earliest reports of engineering of a spontaneous regression date back to Egyptian pharaoh Imhotep (2600 BC) [5]. In his time, inoperable tumors could be nicked with a knife to ensure microbial access, followed by the application of a poultice on the wound (Table **1**). No doubt many types of microbes were able to enter the tumor from the poultice.

Table 1. Timeline for engineering "spontaneous regression" of tumors, *i.e.* induction of anti-tumor immunity.

Time	Intervention
2600 BCE	Imhotep poultice + incision
1320	case reports, *e.g.* St Peregrine Laziosi
1700's	purposeful infection of tumors
1813	Vautier: clostridium perfringens. perfringens gangrene treats tumors
1891	Coley's toxin
1896	Tumor reductions in "flu patients."
1910-30	Purposeful contraction of cancer patients with different viruses
1950	Adenovirus injections into cervical tumors
1977	Bacillus Calmette Guerin for bladder cancer
2005	Oncolytic virus approved in China: Oncorine (R)
2010	Cell therapy approved in US, EU: Sipuleucel-T
2011	Checkpoint inhibitor approved in US, EU: ipilimumab
2015	First oncolytic virus approved in US, EU: Imlygic
2017	First CAR-T cell therapy approved

St. Peregrine Laziosi constitutes a notable spontaneous regression case example from 1320 [5]. Divine intervention was proposed as the mechanism for a tumor first reddening, becoming inflamed, and then disappearing. However, these findings would be quite compatible with a microbial infection.

USING BACTERIA AGAINST CANCER

By the 18th century, the association of microbial infection and tumor disappearance was becoming increasingly established. This led physicians to attempt purposeful infection of tumors, and in 1813, Dr. Vautier was experimenting with *Clostridium perfringens* gangrene as a treatment method [6]. One notable scientist was Dr. William B Coley, who in the late 19th century did ground-breaking work in optimizing "Coley's toxin", a mixture of bacterial

CHAPTER 25

Boron Neutron Capture Therapy and Targeted Alpha Therapy for Intractable Cancers Combined with Positron Emission Tomography/Computed Tomography

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Abstract: The boron neutron capture therapy (BNCT) is based on the cell-killing effect of α-particle and lithium-particle produced in the body by ^{10}B (n, α) ^{7}Li nuclear transmutation reaction after ^{10}B delivery to target cancer cells and local irradiation of neutron. Neutron source was initially a nuclear reactor, and recently in-house accelerator. ^{10}B delivery molecule was ^{10}B-boronophenylalanine (^{10}B-BPA), which was transported into cancer cells through L-type amino acid transporter 1 (LAT1) predominantly expressed on the membrane of cancer cells. ^{18}F-fluor--boronophenylalanine (^{18}F-FBPA) was a PET probe to estimate ^{10}B-BPA accumulation in the target tumor and surrounding normal tissue. The BNCT was recently approved as a treatment of head and neck cancer in Japan. The targeted α therapy (TAT) employed α-particle emitting radioisotopes mainly to metastatic cancers. The element 85, ^{211}At with physical half-life of 7.2 hours, belongs to halogen family in the Periodic Table. Its distribution was similar to ^{131}I. We are now trying to apply ^{211}At to treat intractable thyroid cancers and other types of advanced cancers. Preclinical studies with ^{211}At labeled LAT1 compounds including ^{211}At-phenylalanine (^{211}At-Phe) and ^{211}At-α-methyl tyrosine (^{211}At-AAMT) demonstrated their tumor growth suppression effect on the xenograft model of glioblastoma and pancreatic cancer in rats, respectively. ^{18}F-fluor--phenylalanine (^{18}F-FPhe) and ^{18}F-fluoro-α-methyl-tyrosine (^{18}F-FAMT) are PET probes to study their accumulation to cancers, respectively. The BNCT and the TAT combined with PET/CT imaging may provide effective treatment of intractable and/or metastatic cancers.

Keywords: BNCT, High Linear Energy Transfer, Pancreatic Cancer, PET tracer, Targeted α Therapy.

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INTRODUCTION

Radiotherapy has utilized external radiation of high energy X-ray with a linear accelerator, electron beam, gamma-ray of ^{60}Co, proton beam, and heavy-ion beam and internal radiation with β-emitting radioisotopes for a long time. Recently neutron irradiation and α-particle emitting radioisotopes are employed to treat intractable cancers. The former is boron neutron capture therapy (BNCT), and the latter is targeted α therapy (TAT) by means of ^{223}Ra, ^{225}Ac, ^{211}At, and others.

Boron Neutron Capture Therapy (BNCT)

Chadwick of Cambridge University discovered the neutron in 1932 [1]. Among intensive studies on the biological effects of neutron irradiation, Locher proposed a possibility of cancer treatment by neutron [2]. Irradiation of neutron to non-radioactive element ^{10}B resulted in the production of high linear energy transfer (LET) α particle and recoiling ^{7}Li by ^{10}B(n, α)^{7}Li nuclear reaction. The path lengths of these particles were within 10 μm. Therefore, their biological effects may occur within single ^{10}B-containing cancer cells. This is the principle of BNCT (Fig. **1**).

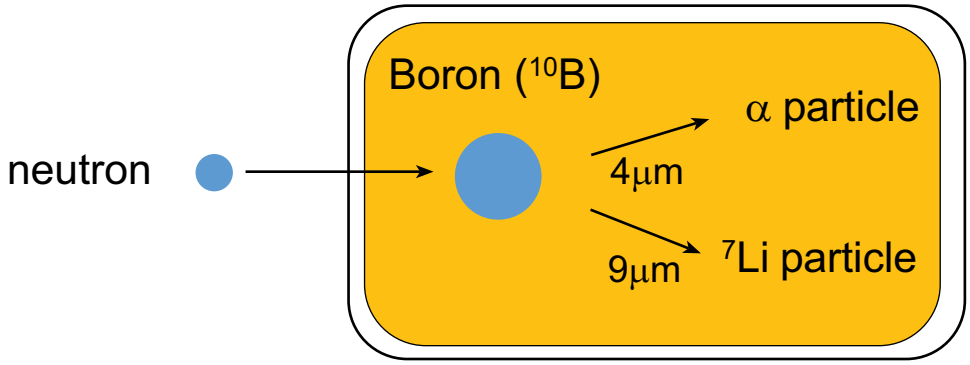

Fig. (1). Epithermal neutron beam irradiates 10 B-containing cells. Within the cell, nuclear transmutation reaction of ^{10}B (n, α) ^{7}Li may occur, resulting in α and ^{7}Li particle. Since the travel length of these particles is less than 10μm, a radiation effect would be limited within a single cancer cell.

In 1951, initial clinical studies of BNCT were carried out for malignant brain tumors by using nuclear reactors at Brookhaven National Laboratory [3] and the Massachusetts Institute of Technology (MIT)/the Massachusetts General Hospital (MGH) [4]. Thermal neutron was irradiated in both studies. The ^{10}B carriers were inorganic boron-containing compounds, borax or sodium pentaborane, or sodium borocaptate ($Na_2B_{12}H_{11}SH$, BSH). These initial studies were followed by Nakagawa and Hatanaka by using thermal neutron in five nuclear reactors in Japan using BSH as ^{10}B carrier combined with surgical removal of tumors [5].

Slatkin summarized that inadequate outcome was primarily attributable to (a) inadequate tumor specificity of the inorganic boron chemicals that had been used as capture agents, (b) insufficient tissue-penetrating properties of the thermal neutron beams, and (c) high blood boron concentrations that resulted in excessive damage to normal brain vasculature and the scalp [6]. These initial experiences facilitated a transition of neutron source from the nuclear reactor to an in-house accelerator and developed compounds with higher tumor specificity such as ^{10}B-borono-phenylalanine (^{10}B-BPA) [7]. ^{10}B-BPA was transported through L-type amino acid transporter 1 (LAT1), which was predominantly expressed on the membrane of cancer cells [8]. In addition, positron emission tomography (PET) has been utilized to estimate ^{10}B concentrations in target tumors and surrounding normal tissue before the BNCT. When ^{10}B-BPA was utilized as ^{10}B carrier, ^{18}F-fluoro-boronophenylalanine (^{18}F-FBPA) was employed as a LAT1 PET tracer [9] in order to monitor ^{10}B concentration in tumors and normal surrounding tissue because of the similar pharmacokinetic behavior of ^{10}B-BPA and ^{18}F-FBPA [10, 11] (Fig. **2**).

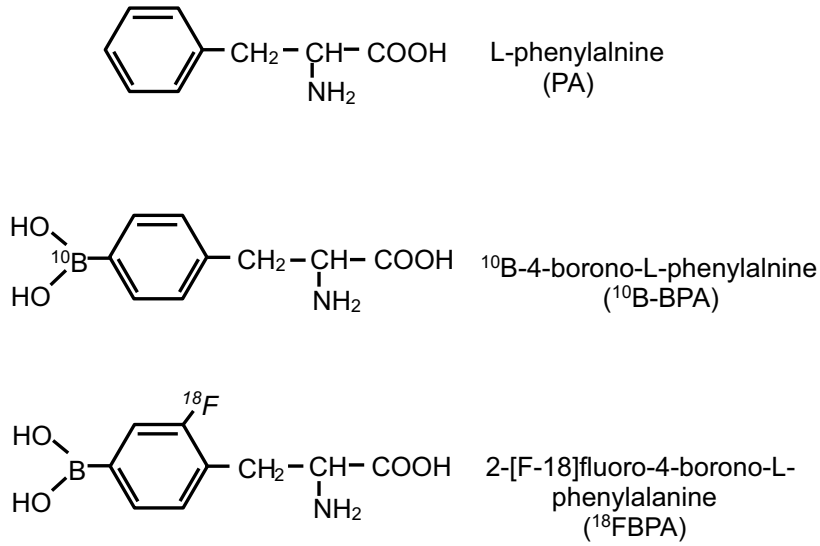

Fig. (2). L-phenylalanine (top), L-phenylalanine labeled with ^{10}B (middle), and L-phenylalanine labeled with natural B and ^{18}F (bottom).

The similarity of *in vivo* distribution of ^{10}B-BPA-fructose and ^{18}F-FBPA, was tested by therapeutic dose administration of ^{10}B-BPA-fructose after tracer dose administration of ^{18}F-FBPA and PET/CT imaging., The absolute concentration of ^{10}B, was measured in an autopsied tissue sample through ICP-OES. Fig. (**3**) showed a linear correlation between ^{10}B-BPA-fructose and ^{18}F-FBPA (Fig. **3**).

CHAPTER 26

Targeting Imaging Brain Lesions with PET/CT: F18-CH and F-18-FLT

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Abstract: Passing to the era of molecular imaging and precision oncology, the radiopharmaceuticals may play an incremental role in further revealing the nature of the evaluated lesion. FLT, a radiolabeled thymidine analogue, and FCH, a radiolabeled substance of the cell membrane phospholipids, have been more or less investigated in the imaging, identification, and evaluation of brain tumor lesions. In our study, using a Siemens Biograph LSO PET/CT 16 slices device, a Siemens multimodality workplace (MMWP) system for brain analysis, and qualitative and semiquantitative analysis (SUVmax, SUVpeak, T/B ratio), we investigated the role of these two radiopharmaceuticals in primary and metastatic brain lesions, lymphomas as well as in investigating neurological symptoms with inconclusive/indefinite evidence in the conducted MRI. Using F-18-CH for PET/CT imaging, we found that there was FCH uptake by active tumor sites, with no statistical significance in SUVmax, SUVpeak and T/B ratio for the discrimination of the lesions between primary, metastatic and lymphomas, ($p > 0.05$). However, recurrent primary lesions exhibited lower T/B and SUVmax compared to the respective mean values of the metastatic ones. With the utilization of F-18-FLT we concluded that it could discriminate between active from non-active foci, while mean values of T/B and SUVmax were statistically significantly higher for NHL compared to primary and metastatic tumors ($p<0,001$). There was a tendency for significance for SUVmax and T/B between low and high-grade recurrent primary tumors ($p=0.08$ and $p=0.06$, respectively) when excluding the outliers. However, further investigation is required for definite conclusions.

Keywords: Brain Lesion, Brain Tumor, FCH, FLT, PET/CT.

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Antti Jekunen (Ed.)

F-18-CH: A LESS INVESTIGATED RADIOPHARMACEUTICAL IN BRAIN TUMORS

Identification and verification of brain lesions is a challenging process, starting from the clinical evidence and expression of the disease to the proof through surgery and biopsy. Imaging is an important step in the intermediate process of identification the brain lesion, aiming to provide as much information as possible about the nature of the lesion, and why not, characterizing it. Moreover, as research reveals more and more about the pathogenesis and the specific characteristics of the brain lesions, classification of primary brain tumors is tilting from histopathological categorization towards genetic and epigenetic modification as well as molecular individualization. The MRI plays a key role in the above procedure, being the examination of choice for investigating the initial presentation of the symptoms, the imaging of the primary and metastatic tumors, during follow up, for the assessment of response to treatment and investigation of relapse. The role of MRI for brain tumors evaluations has increased not only with the introduction of newer technics, such as diffusion weighted imaging (DWI), Perfusion-weighted magnetic resonance imaging (PW-MRI), Magnetic Resonance Spectroscopy (MRS) and the use of apparent diffusion coefficient (ADC), but also with the establishment of clear criteria for assessing response to treatment in clinical practice and clinical trials with the usage of updated RANO criteria. PET imaging is currently used for brain tumors investigation as well as for evaluation of treatment response and tumor recurrence, with PET imaging with amino acids outweighing the rest of radiopharmaceuticals.

Choline is a substance of the phospholipids of the cell membrane. Tissues with increased metabolism express increased uptake of choline [1 - 3]. Accordingly, cancer cells may have increased needs for choline uptake and utilization, while in slowly multiplying tumors the high levels of phospholipid metabolites may be correlated to alterations in the transport, incorporation, or the usage of choline [1, 4]. Choline is radiolabeled with F-18 or C-11, thus allowing PET imaging and serving as a marker of lipogenesis and biosynthesis of the membranes [3, 5]. It is widely investigated and used in prostate cancer [6] and less investigated in other cancers *i.e*. renal, liver, and lung [7 - 9]. A few studies, mostly with a small sample, have evaluated radiolabeled choline in brain tumors.

In our pilot study, we investigated the F-18-choline (FCH) uptake in brain lesions. In total, eleven PET/CT examinations were performed (twenty lesions). Patients' age ranged 6-74 yo. Three were investigated for metastatic lesions, 4 for primary brain tumor recurrence, 2 for Non-Hodgkin Lymphoma (NHL), and two for neurological symptomatology. All patients, but two, had received prior therapy according to their disease. Imaging started 55±5 min after the iv injection of the

radiopharmaceutical in a Siemens Biograph LSO PET/CT 16 slices device and analysis took place in Siemens multimodality workplace (MMWP) system for brain analysis. For the semiquantitative analysis, we measured SUVmax, SUVpeak, T/B ratio. PET/CT examinations were performed in Hygeia Hospital Athens Greece and our results in detail have been demonstrated in the thesis "Investigation of space-occupying lesions of the Central Nervous System (CNS) with Positron Emission Tomography (PET): use of newer radiopharmaceutical" (translated from the Greek title), University of Thessaly [10].

18F-FCH-PET/CT was positive in 2/4 cases of recurrent brain tumor, 2/3 primary tumor, 2/2 cases of investigation of neurological symptoms, and ½ cases of NHL. All these patients received treatment. 18F-FCH-PET/CT was negative in 2/4 cases of recurrent primary tumor and in one case of NHL, and equivocal in 1 metastatic case. From the lesion analysis, no statistical significance was found in SUVmax, SUVpeak, and T/B ratio for the discrimination of the lesions between primary, metastatic and lymphomas, ($p > 0.05$), however, they could discriminate between positive and negative lesions. Using paired t-test, there was a significant difference between SUVmax and T/B for the metastatic and recurrent primary tumors ($p < 0.05$). Table **1** shows the mean semiquantitative values of the positive lesions.

Table 1. Mean values of SUVmax, SUVpeak and T/B of positive lesions.

	SUVmax	**SUVpeak**	**T/B**
Number of lesions (N=20)	-	-	-
Mean (SD) – POSITIVE LESIONS		-	-
LYMPHOMA (N=5)	3.07 (2.05)	1.89 (2.21)	14.9 (8.8)
PRIMARY (N=3)	**2.58 (1.08)**	**1.68 (0.7)**	**14.3 (4.2)**
METASTATIC (N=5)	**3.24 (3.26)**	**2.11 (1.91)**	**24.2 (20.2)**
p-value (ANOVA)	0,93	0,95	0,52

As in the bibliography, recurrent primary tumors received radiopharmaceutical. The reported sensitivity and specificity between recurrence and necrosis is 92.3% and 87.5% *vs.* 87.2% and 81.3% for MRI [11]. What is worth mentioning is that high-grade gliomas in our study had similar values of SUVmax and T/B as in the bibliography, while metastatic lesions have higher mean SUVmax and T/B values compared to the respective mean values of the recurrent primary lesions. Although not statistically significant in our study (probably at least partially due to the small sample), this is in respect to the Kwee *et al*. study, which mentions the significant difference between metastatic and primary tumors and higher SUVmax T/B values for the metastatic tumors [12]. These observations could be

CHAPTER 27

FDG Uptake by Brown Adipose Tissue in Paediatric and Adolescent Hodgkin Lymphoma, Visualised on PET/CT Performed at Diagnosis

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Abstract: We aimed to shed some light on the relation between brown adipose tissue (BAT) visualisation on FDG PET/CT at diagnosis in children with Hodgkin lymphoma (HL) and the main determinants reported in adult HL, outside temperature, gender, age, but also with the metabolic activity of HL lesions and of some organs that did not look to be invaded by HL.

Pre therapeutic FDG PET/CT was performed in 135 children or adolescents suffering from HL and was centrally blind read, in search for BAT visualisation, determination of SUVmax of the liver, the bone marrow at the iliac crest and the spinal cord at Th12, providing those sites did not show focal uptake evocative of HL. The maximum SUVmax, total metabolic tumour volume, and total lesion glycolysis of HL were also determined.

The visualisation of BAT as foci of FDG uptake in those patients with paediatric HL was not significantly associated with gender, age, the outside temperature on the day of PET/CT, the intensity of FDG in non-invaded organs and maximum SUVmax of HL tumours. There was a trend for an association with lower tumour volume and lower total lesion glycolysis of HL that did not reach the statistical significance level.

Our study confirms, in 135 paediatric HL patients at diagnosis, *i.e*. a homogeneous clinical status, previous evidence derived from heterogeneous conditions, that the epidemiology of BAT activation is quite different between paediatric patients and adults. In relation to HL, BAT activation was not linked with the metabolic activation of the liver, the bone marrow, and the spinal cord, which may be observed as a conse-

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quence of HL presence in the patient. Nevertheless, our results suggest that BAT visualisation could be associated with a lower HL tumour mass.

Keywords: Bone Marrow, Brown Adipose Tissue (BAT), Child, FDG PET/CT, Liver, Lymphoma, Outside Temperature, Paediatric Hodkgin's Lymphoma, Spinal Cord, SUVmax, Total Lesion Glycolysis (TLG), Total Metabolic Tumour Volume (TMTV).

INTRODUCTION

Brown adipose tissue (BAT) takes up FDG when metabolically activated [1]. The resulting FDG foci or masses constitute a well-recognised source of pitfalls in the evaluation of cancer extent [2], in particular in the cervical region. FDG uptake in supraclavicular area fat was originally called "USA-Fat" [3]. As early as 2003, Cohade *et al*. [3] reported that the incidence of activated BAT was highest, at 38/278 =13.7%, in January through March, while outside temperatures were low and was significantly lower, at 30/739 = 4.1%, during the rest of the year, and greater in females (53/504=10.5% than in males 15/513=2.9%). Furthermore, patients with activated BAT were younger than non-affected patients (46.9±15 y *vs*. 58.9 ± 15 y), and its incidence was 10/42 = 23.8% in FDG PET/CTs of patients aged 18 y or less *vs*. 58/975 = 5.9% in patients older than 18 y. In another study published in the same year [2], FDG PET showed activated BAT neck significantly more frequently in the paediatric population (4/26 = 15%) than in the adult population (16/837 = 1.9%).

In the subsequent study of Ouellet *et al*. [4], FDG showed activated BAT in 328 of the 4842 adult patients (6.8%). The mass and glucose-uptake activity of FDG-detected BAT decreased with increasing outdoor temperature, age, and body mass index. They were lower in men than in women and in diabetic than in non-diabetic adult patients.

Recently Brendle *et al*. [5] studied FDG uptake by BAT in adult lymphoma patients, PET/CT is performed at different steps of disease evolution. Of all types of lymphomas, HL had the highest frequency of BAT visualisation, 36/206 =17%. The lymphoma disease was identified as active if vital manifestations with FDG uptake above the mean liver uptake were present. No association between BAT and lymphoma metabolic activity was found.

Focusing on paediatric BAT, Drubach *et al*. [6] analysed the FDG PET/CTs of 172 patients aged 5-21 years and found that the epidemiology of BAT was different between paediatric patients and adults. In contrast with the results confirmed by several teams in adults, the authors reported a very high prevalence

of BAT visualisation (76/172 = 44.2%), which was not significantly different between boys (42/97 = 43.3%) and girls (34/75 = 45.3%) and the BAT activity did not correlate with outdoor temperature.

Gilsanz *et al*. [7] studied a shorter but more homogeneous paediatric series: the FDG PET/CTs studies of 31 paediatric patients (age range: 3.7- 18.2 y), 21 with Hodgkin lymphoma (HL) and 10 with non-Hodgkin lymphoma (NHL), were analysed. The aim was to compare the prevalence of metabolically active BAT at diagnosis and its prevalence when there was no evidence of disease after effective treatment in the same cohort of patients. The overall prevalence of BAT visualisation on FDG PET/CT was 3/31=10% at diagnosis *vs*. 24/31=77% without evidence of active lymphoma. In the group with HL the corresponding prevalence values were 3/21= 14% *vs*. 18/21= 86%.

Our pilot study [8], published in 2016, included 30 paediatric patients, all diagnosed with HL (15 male and 15 female, age range 3–17 y). Its aim was to evaluate the FDG uptake by non-HL invaded structures as a potential determinant for HL activity and prognosis. Activation of BAT was noted on FDG PET/CT at diagnosis in 2 patients only (2/30=7%), compatible with the prevalence reported by Gilsanz *et al*. [7]: 3/31.

We aimed to shed more light on the relation between BAT visualisation on FDG PET/CT at diagnosis in children with HL and the main determinants reported in adults, outside temperature, gender, age, but also with the metabolic activity of HL lesions and of some organs apparently non-invaded by HL. With this objective, we gathered a larger series including more than 120 HL paediatric patients, 4-fold larger than our pilot cohort.

MATERIAL AND METHODS

Patients

The study includes data of 135 children or adolescents, 62 boys, and 73 girls, suffering from HL who underwent FDG PET/CT at diagnosis. Their mean age at FDG PET/CT was 13.6 years, median=14.3, range 4.5-17.9. Patients have been referred to FDG PET/CT by paediatric oncology departments of various hospitals, most frequently (n>10) Hôpital Trousseau (n=26), Institut Gustave Roussy (n=26), Hôpital Robert Debré (n=22) or Institut Curie (n=14).

FDG PET/CT Practice

The common way of performing FDG PET/CT was similar to that of our pilot study and may be summarised as follows: after fasting for at least 4 h, well-

CHAPTER 28

[^{99m}Tc]Tc – MIBI as Oncologic Radiotracer

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Abstract: Latest advances in PET imaging, the growing importance of the theragnostic approach and the inclusion of 18F-FDG in the staging guidelines of many oncological situations put in shadow the research on SPECT radiopharmaceuticals, including those considered classic as having oncological tropism. However, there are studies, some of them very recent, that highlight an important role of MIBI in cancer imaging and management. The dynamics of uptake and the wash-out process differ depending on the cellular metabolism and can be used for various indications, one of them being differentiation of malignant processes or predict chemotherapy resistance. In this paper, we will review the literature and present most important actual and potential application of 99m-Tc-MIBI scan in oncologic diseases.

Keywords: Chemoresistance, Malignancies, Metabolic Imaging, Nuclear Medicine, Oncology, Radiotracers, 99m-Tc-MIBI.

A long time before FDG PET-CT having entered current practice and oncology guidelines, nuclear medicine specialists tried to develop a lot of radiotracers for tumor imaging. Most widely used were represented by 201-Thallium and 99m-T--SESTAMIBI/MIBI (Hexakis-2-methoxy-2-methyl propyl-isontrile), both tracers being initially developed for myocardial perfusion imaging.

The physical properties of 99m-Technetium were more favorable for imaging in terms of energy and half-life. Therefore, it was preferred, with the advantage of higher doses administration, higher photon density, and better target/background ratio.

The unprecedented advancement of PET imaging, the development of new radiotracer for diagnosis and treatment, the growing importance of the theragnostic approach, and the inclusion of 18F-FDG in the staging guidelines of many oncological situations - put in shadow the research on SPECT radiopharma-

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ceuticals, including those considered classic as having oncological tropism.

However, there are studies, some of them very recent, that highlight an important role of MIBI in cancer imaging and management. The dynamics of uptake and of the wash-out process differ depending on the cellular metabolism and can be used for various indications, one of them being differentiation of malignant processes - lung, musculoskeletal, breast, thyroid, for thyroid even if there is an inconclusive result at FNA [1 - 4].

MIBI is an important indicator of the activity of the disease in multiple myeloma [5, 6], can differentiate tumor recurrences from post-therapeutic changes in brain tumors [7] and - very importantly - can predict resistance to chemotherapy [8 - 10], which cannot be visualized which cannot be visualized by any other imaging method.

99mTc MIBI is a cationic and lipophilic substance that enters the cell passively, following the electrical gradient. Once in the cell, MIBI is located in the mitochondria. Increased uptake in (malignant) tumor cells is due to an increase in the mitochondrial membrane potential, which is thought to facilitate tumor progression [11, 12].

MIBI uptake in tumor cells is therefore proportional to the level of perfusion and energy metabolic consumption, being related to viability and the degree of cell proliferation.

The physical properties of 99m-Technetium are very favorable for scintigraphic imaging, with much lower costs than a PET-CT exam. However, the limitations are represented by the hepatobiliary and intestinal excretion of MIBI with intense abdominal uptake. For this reason, abdominal masses can be very difficult to differentiate from the background.

However, many authors have reported the use of MIBI with particularly good results primarily in differentiating malignant from benign processes in many types of tumor pathologies. Especially it is worth mentioning a good negative predictive value in many pathological situations [1].

But the use of MIBI in oncology seems to have another reason, other than differentiating malignancies (which, of course, may not always be possible). MIBI is a substrate for P-glycoprotein encoded by the polychemotherapy resistance gene (MDR-1). PGP is responsible for the rapid outflow of MIBI from the cell through the same mechanism by which chemotherapeutic agents are removed from the cell. For this reason, reduced uptake or a rapid wash out of MIBI may predict resistance to chemotherapeutic treatment.

This property was initially seen as a source of false negative results but recently, research was focused on this potential of prediction of the chemoresistance and eventually of factors able to modulate this property. In a very recent publication on cell biology Parker et al found that in cancer cells with low MDR1 expression MIBI uptake is largely dependent on mitochondrial membrane potential; if high level of MDR1 expression - low baseline ^{99m}Tc-MIBI uptake can be markedly increased in the presence of verapamil [11].

In order to prevent false negative studies, it is generally recommended an early acquisition 10 min post-injection, eventually with delayed imaging – for studying wash-out [10].

99m-Tc-MIBI – PHYSIOLOGIC DISTRIBUTION

After intravenous administration, MIBI is distributed in the body proportionally to the blood flow, mainly in the heart and the thyroid, parathyroid, choroid plexus, and the salivary glands - generally in structures with intense metabolic (or secretory) activity. The bone and the hematopoietic marrow cannot be visualized on the scintigraphic image in normal conditions - the reason why many authors have reported very good results in multiple myeloma, where there is medullary pathologic involvement and bone destruction – (Fig. **1**).

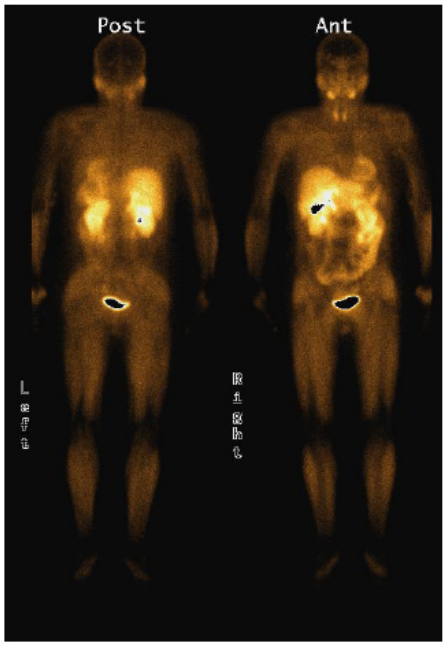

Fig. (1). Physiologic 99m-Tc MIBI distribution.

CHAPTER 29

The Actual Role of Nuclear Molecular Imaging in the Follow-up of Chemotherapy-Induced Cardiac Dysfunction

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Abstract: The increase in life expectancy due to the increase in cancer treatment success has made the follow-up of the acute, short and long-term cardiac side effects of chemotherapeutic drugs more important today. Although chemotherapy-induced cardiac dysfunction is one of the major problems, there is still a need for an accurate and readily available non-invasive monitoring technique. In the present article, we tried to evaluate past and present nuclear molecular imaging techniques from the perspective of chemotherapy-induced cardiotoxicity monitoring.

Today neither nuclear imaging methods nor other techniques are sufficiently accurate/readily available to use in clinical routine to show cardiotoxic effects of chemotherapeutics at an early stage. However, nuclear molecular imaging can detect biological processes at the molecular level that precede the structural changes and pathological consequences of chemotherapy-induced cardiotoxicity.

Until today, many molecules to use with a conventional gamma camera or positron emission tomography have been tried for this clinic pathology. Many of them have been shown to have prognostic value in the early stages of the disease, but relatively in small patient groups. However, sometimes due to difficulty in procuring, the lack of comparative studies seems to prevent their value from coming to light. There is a need for additional studies to clarify the role of nuclear imaging of cardiac damage in chemotherapy-induced carditoxicity.

Keywords: Cardiac Dysfunction, Chemotherapy-Induced Cardiotoxicity, Molecular Imaging.

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INTRODUCTION

The cardiotoxic effects of chemotherapeutics have been known since the '60s. For the follow-up of chemotherapy-induced cardiac side effects, first-pass radionuclide ventriculography, which was the newest and best non-invasive imaging technique in the '80s, and multigated equilibrium radionuclide ventriculography (MUGA) since '90s, were successfully used in the follow-up of ventricular functions, especially monitoring of left ventricular ejection fraction (LVEF).

21 years ago, together with Dr. Kairemo, we studied the subclinical cardiotoxic effects of doxorubicin with In-111 Antimyosin scintigraphy in breast cancer patients in the framework of different treatment protocols [1]. None of the patients had any known previous cardiac disease history, medication for cardiac disease, or signs of cardiac dysfunction in the clinical examination. However, it was possible to discriminate with antimyosin scintigraphy which patient had been exposed to a high dose of doxorubicin. Unfortunately, the antimyosin kit was out of the market shortly after our study. Since then, studies on many molecules, such as meta-iodobenzylguanidine (MIBG) and Annexin, or others used with SPECT or PET have continued and many reports have been published in the literature. The problem is that no scintigraphic examination shows cardiac damage in the cardio-oncology guidelines today, relating to chemotherapy-induced cardiotoxicity follow-up.

Today, cardiotoxicity may be monitored by several non-invasive and non-ionizing modalities, for example, echocardiographic assessment of ejection fraction (EF), fractional shortening, or diastolic dysfunction parameters, tissue characterization with MRI, *etc.* In addition to non-invasive imaging methods, there are also biochemical monitoring parameters. One of them is troponin, which is in the discussion arena for a long time and already takes place in clinical routine and the clinical guidelines.

All these modalities are generally regarded as suboptimal since they predict relatively advanced stages of cardiotoxicity rather than the earlier one in a patient base [2]. Preferably, while toxicity is still in a subclinical stage, there is a need for reliable, non-invasive techniques that can accurately predict the cardiac adverse effect of relating chemotherapy regimens. Here, the physician's task is not to produce a ready-made solution for patient follow-up but to make tailor-made clothes, and even this dress should be haute-couture. The non-invasive method used to monitor early toxic effects should not give a false positive result reducing the effectiveness of the chemotherapy or a false negative result, ending with heart failure.

In this article, firstly the related problem is briefly outlined, and the monitoring techniques were summarized. Then, we tried to look over the actual role of nuclear molecular imaging in the follow-up of chemotherapy-induced cardiac dysfunction.

Clinical Features of Cardiotoxicity

Today, thanks to chemotherapy, very successful results are obtained in many oncological diseases. With recent advances in cancer management, the number of cancer survivors has doubled in the last 3 decades. Nevertheless, while life expectancy is prolonged in oncology patients, the cardiotoxic effects of some of the chemotherapeutics threaten the expected quality of life and duration. Cardiotoxicity is one of the most serious adverse effects of chemotherapy, resulting in a rise in morbidity and mortality. The European Society of Cardiology defines cardiovascular toxicity as any heart injury, either functional or structural related to cancer treatment [3]. Many cardiovascular problems occur in patients receiving chemotherapy; some of them start right after the treatment, some may take place at a later stage. As an example, hypertension may also be associated with anthracycline-based chemotherapy [4].

The cardiotoxic effects of antineoplastic drugs are classified in several ways in the literature; Early/Late or Functional/Structural or Type I/Type II [5]. Cardiac manifestations may appear within a week[early) following the chemotherapy, as is the case in anthracycline treatment or within a year of treatment (delayed). The cardiotoxic effects of conventional antineoplastic drugs, for example, anthracyclines, and high doses of cyclophosphamide, are described as Type I. This type of cardiotoxicity is cumulative dose-dependent and there is vacuolization of the cytoplasm of cardiomyocytes and loss of myofibrils, which is largely irreversible. The cardiotoxic effect caused by biological molecules such as monoclonal antibody trastuzumab is classified as Type II and its important difference from Type I is there is no ultrastructural damage and is usually reversible on discontinuation [6]. Another classification proposed was the reversibility degree of LVEF; if improvement in LVEF occurs within 5% of baseline, then the cardiotoxic effect is considered to be reversible if improvement of LVEF >10% from nadir but remaining >5% below baseline then, it shows partial reversibility, but if improvement in LVEF is <10% from the nadir and remaining>5% below baseline then it is classified as irreversible [7].

Whatever the classification of cardiotoxic effect, the result would be serious, and heart failure may even be seen years after the treatment, without any acute effects of chemotherapy-induced cardiotoxicity. In short, the term used as “cardiotoxicity” means a wide spectrum of cardiac dysfunctions that may appear

CHAPTER 30

Quantitation of Myocardial Perfusion using ^{15}O-Water PET: From a Research Tool to Clinical Routine

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Abstract: The application of ^{15}O-water for cardiac PET perfusion imaging was one of the main goals when this tracer was developed. However, the development of a method from basic research to routine tool in clinical work takes a long time. With the case of cardiac ^{15}O-water PET it took 22-27 years from the initial plans to clinically accepted tool. This is likely not unusual as the validation of new method and demonstrating the clinical impact requires many studies and a long time. Eventually, the method has been now included in the European clinical guidelines of chronic coronary syndromes as an accepted clinical tool. This paper illustrates the development of the cardiac ^{15}O-water PET at Turku PET Centre, one of the pioneers in developing the method from bench to bedside. Despite the current success, there are still many open issues, which warrant further development and studies.

Keywords: Coronary artery disease, Cyclotron, Diabetes, Fractional flow reserve, Heart, Hypertension, Myocardium, Oxygen-15, Perfusion, Positron emission tomography, Quantitation.

EARLY YEARS OF ^{15}OXYGEN PET IMAGING

Coronary artery disease (CAD) was one of the main target of cardiac PET research already in 1980'ties. Most publications focused on using ^{13}N-ammonia or ^{82}Rubidium for myocardial perfusion imaging. ^{15}O-water was mainly used for brain perfusion, but Bergmann *et al*. [1, 2] published encouraging results about quantitation of myocardial perfusion using ^{15}O-water. Heinrich Schelbert [3] wrote in his review already in 1987 that "*These (^{15}oxygen) radiopharmaceuticals hold considerable promise for routine clinical use*".

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The application of ^{15}O-water for perfusion imaging was facilitated soon by two main publications about the mathematical approaches: Iida *et al*. [4] and Herrero *et al*. [5]. The former study measured absolute myocardial blood flow, and the tissue fraction in 15 subjects with a kinetic technique. The results were found to be consistent with their coronary angiographic findings. The mean value of the measured absolute myocardial blood flows in normal subjects at rest was 0.95 +/- 0.09 ml/min/g. The study by Herrero *et al*. [5] found that the implemented mathematical approach provided accurate quantitation of regional MBF in absolute terms.

There were two further critical advancements in the method that helped significantly. The first one was the method to estimate myocardial tissue fraction to correct partial volume effects [6]. The second reported that the input function for quantitation could be reliably derived from images, and blood sampling was not needed [7].

The early clinical studies were focused on a variety of patient groups. Yamamoto *et al*. [8] published a case in which ^{15}O-water was used to quantitate myocardial perfusion in a patient with reperfusion therapy for acute myocardial infarction. Agostini *et al*. [9] used ^{15}O-water PET to quantitate myocardial perfusion in a patient with stunned myocardium. Their results showed preserved myocardial blood flow and perfuseable tissue density in this patient.

One of the most interesting early studies was published in 1994 by DeBruyne *et al*. [10]. In this study, invasive measurement of fractional flow reserve (FFR) was validated against quantitative ^{15}O-water PET perfusion imaging in 22 patients with single vessel CAD. They found a close correlation between relative myocardial flow reserve, defined by PET and invasive FFR while the correlation was weaker between PET results and anatomical degree of stenosis. The study validated the use of FFR as an index of the physiological consequences of given coronary artery stenosis. Interestingly, the very same FFR has been used as a reference standard for physiological assessments of CAD and also applied to validate quantitative ^{15}O-water PET perfusion imaging in clinical trials [11].

Early Cardiac ^{15}O-water PET Studies in Turku PET Centre

I wrote my own doctoral thesis plan in 1989 "*to develop a clinically feasible method for quantifying myocardial perfusion using ^{82}Rubiudium and PET*." However, these plans were never realized. The director of the Turku PET Centre at that time, Prof Uno Wegelius decided to purchase a dedicated baby cyclotron (IBA Cyclon-3, Belgium) for ^{15}O-water instead of ^{82}Rb generators. This purchase was realized in 1992 (Fig. **1**), and my plans were revised to start the projects to apply ^{15}oxygen studies for cardiac applications in Turku.

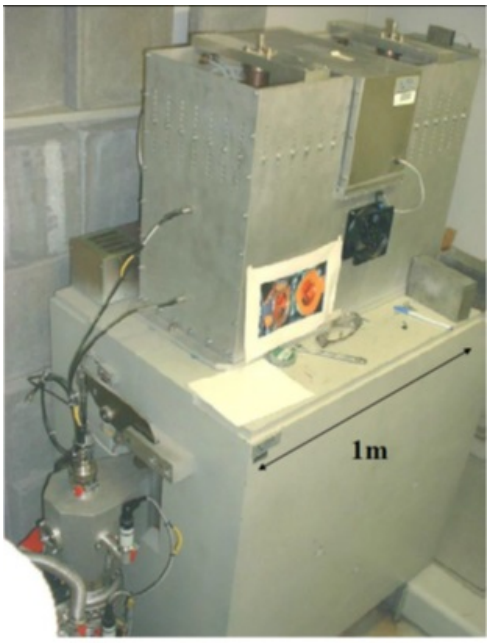

Fig. (1). IBA Cyclon-3 after installation at Turku PET Centre in 1992.

Fig. (2). GMP compatible ^{15}O-water delivery system components. The single use module with 2 semipermeable membranes is plugged in to the lead-shielded delivery system that is controlled remotely from the scanner control room by technicians. The device automatically delivers required bolus of ^{15}O-water to patient.

CHAPTER 31

Bone Targeted Radionuclide Therapy in Russia From Beta- to Alpha- Emitters

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Abstract: Treatment of patients with painful multiple bone metastases is a complicated clinical task. Radionuclide therapy is one of the solutions, which is used to achieve the long reduction of pain syndrome and to significantly improve the quality of life. However, the mechanism of action of bone-seeking radiopharmaceuticals suggests not only pain control but the antitumor effect as well. In early clinical studies of safety and efficacy, single administrations of the most common bone-seeking radiopharmaceuticals did not demonstrate any benefit in overall survival, but individual extraordinary tumor regressions were reported. Repeated administrations and combination with other treatment modalities can help to gain a statistically significant increase in overall survival. In this chapter, the history of bone-targeted radionuclide therapy in Russia is reviewed.

Keywords: ^{89}Sr-chloride, ^{153}Sm-EDTMP, ^{153}Sm-Oxabifor, ^{188}Re-HEDP, ^{188}Re-zoledronic acid, ^{223}Ra-chloride, Bone Metastases, Bone Pain Palliation, Bone-Targeted Radionuclide Therapy.

INTRODUCTION

Metastatic bone lesion is one of the most common and severe manifestations of cancer diseases. The lesion is more frequently developed in patients with prostate cancer (33-85%) and breast (47- 85%) cancer. The bone lesion occurs less frequently in patients with lung (30 - 66%), kidney (33-40%),) thyroid (28-60%) cancers [1]. Metastatic bone lesions most commonly present as multiple lesions accompanied by different complications. The pain syndrome is usually the primary complication, pathological fractures, hypercalcemia and spinal cord compression syndrome; other complications frequently occur as well. Advanced clinical syndromes sharply decline the quality of life, restrict a patient's activity and often lead to his/her disability.

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In the absence of current methods for complete recovery of patients with multiple bone metastases, the aim of the therapy approach is to prevent patients' quality of life decline or possibly improve it. Historically, bone-seeking agents were first used only to control pain [2, 3]. Later it became known about the antitumor effects and the effect on survival [4, 5].

A mode of bone-seeking radiopharmaceuticals (RPh) action is based on their ability to accumulate in sites with increased mineralization of the bone tissue, typically caused by osteoblastic and mixed metastases. The lesions are exposed to "internal" irradiators, β- or α- particles, resulting in prolonged anesthesia. Due to the use of repeated treatments anticancer effect achieves. The highest effectiveness is achieved in the treatment of patients with prostate and breast cancers. The wide range of RPhs with different physicochemical properties of β-emitting radionuclides is widely used: ^{153}Sm, ^{89}Sr, ^{32}P, ^{186}Re, ^{188}Re, ^{117m}Sn, ^{177}Lu, and others and α-emitter ^{223}Ra.

Two domestic bone-seeking therapeutic RPhs – short-lived ^{153}Sm-Oxabifor® and long-lived ^{89}Sr-chloride and Bayer's Xofigo®, ^{223}Ra chloride, are registered in Russia

SHORT HISTORY OF THE BONE-SEEKING RADIOPHARMACEUTICALS USE IN RUSSIA

The world history of the use of radionuclide therapy (RNT) with bone-seeking RPhs began in 1941 when Dr. Ch. Pecher made the first injection of Strontium-89 chloride for the patient with prostate cancer, bone metastases and pain syndrome [6].

In Russia, the bone-seeking RPh was first used at A.M. Granov Russian Research Center for Radiology and Surgical Technologies (Sankt-Peterburg) in1995. At first, Amersham's Metastron®, ^{89}Sr chloride was used. The domestic Strontium-89 chloride production was started later.

It is notable that ^{89}Sr radionuclide for production of the Metastron was produced in Russia. Then, studies with Sm-153-EDTMP and Russian analogue – Oxabifor were started. The first injection of Oxabifor was made at the Medical Radiological Research Centre (MRRC), Obninsk, in December 1997 [7, 8].

In Russia, the ^{188}Re-based radiopharmaceuticals obtained from ^{188}W/^{188}Re generators were first used at MRRC in 2012-2015. The first RPh was ^{188}Re-HEDP (Phosphoren®) [9]. The next RPh was ^{188}Re-zoledronic acid (Zoleren®). Zoleren has no world analogues. The first injection of this therapeutic RPh to a patient was done in July 2013 [10, 11].

The use of ^{223}Ra chloride in Russia began in 2014 in MRRC, firstly it was used within frames of the international clinical trials; after the RPh registration in 2017, it is used routinely for the treatment of castration resistant prostate cancer (CRPC) patients with bone metastases. ^{223}Ra chloride is currently widely used in Russia.

At the same time as studies of the new RPh, the new treatment schedules of bone-targeted therapy were studied. The aims of bone-targeted therapy remarkably changed: not to reduce severe pain syndrome, but to prolong life. Table **1** presents the list of bone-seeking radiopharmaceuticals are used in Russia.

Table 1. Bone seeking radiopharmaceuticals in Russia.

Radiopharmaceutical	t1/2	Dose	Emission	First use in RF
$^{89}Sr\ Cl_2$	50 days	150 MBq	β	1996
^{153}Sm-EDTMP (Oxabifor)	48 hours	37 MBq/kg	β, γ	1997
^{188}Re-HEDP (Phosphoren)	17 hours	37 MBq/kg	β, γ	2012
^{188}Re Zoledronic acid (Zoleren)	17 hours	45 MBq/kg	β, γ	2013
$^{223}Ra\ Cl_2$ (Xofigo)	11 days	55 kBq/kg	α	2014

Strontium-89 Chloride

Strontium 89 is a radioactive isotope, a pure β-emitter (maximum energy is 1,46 MeV, average energy is 0.58 MeV), its half-life is 50,5 days. The average range of β-particles in bone tissue is 2.4mm, maximum range is close to 8mm. Strontium is chemically equivalent to calcium, but Strontium -89 affinity for metabolically active bone tissue, especially for osteoblastic skeletal metastases, is higher. During the 90-days treatment period, the isotope's content in a body varies from 10 to 80% of its administered amount. For a long time time, ^{89}Strontium chloride has been the most common radiopharmaceutical for bone metastases therapy in Russia. This is due to the radioisotope long half-life and convenient delivery. However, ^{89}Strontium long half-life and high energy of β-particles cause relatively high hemotoxicity. Recommended standard dosage of 150 MBq was suitable for use, however, the recommendations do not take into account patients' personal characteristics.

In many publications, authors informed that ^{89}Sr is the effective remedy to relieve pain syndrome. O.P. Modnikov *et al*. reported about the effectiveness of ^{89}Sr-chloride in 43 patients, mainly with breast (29, 67.4%), and prostate (10, 23.3%) cancers. The standard activity of the radioisotope, 150 MBq, was administered to patients. The 89 Sr chloride therapy was combined with radiation,- chemo- and hormone- therapies, some patients only took radionuclide therapy with ^{89}Sr

CHAPTER 32

Role of Beta-Emitter Sm-153 in Combined and Complex Therapy of Skeletal Metastases

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Abstract: In spite of significant progress in the diagnosis and management of solid tumors, the incidence of bone metastasis is still high, and the use of bone-targeted agents does not prevent the development of their complications such a skeletal related events. While the most current bone targeting medications act on the bone micro-environment and the osteolytic bone metastasis. The beta-emitters radiopharmaceuticals such as Samarium-153-ethylene diamine tetramethylene phosphonate and Sm-153 oxabifore target osteoblastic bone lesions by irradiating nerve fibers that innervate the skeleton and cancer cells which may lead to the termination of growth factorsthat stimulates cancer cell dissemination to the skeleton.

However, their role usually is limited by palliative treatment for painful bone metastases. Recently it is demonstrated that the combination of radionuclide therapy with bisphosphonates or chemotherapy is potentially more effective as compared to use in isolation. The synergetic approach of bone metastasis therapy is perspective; however, chemotherapy is generally contraindicated in combination with radionuclide therapy due to possible synergetic myelotoxicity. Vertebral fracture and impending cord compression are other contraindications for radionuclide therapy.

In this book chapter, we presented possible combined/complex therapy approach including best timing of radionuclide/bisphosphonate administration, combined therapy with monoclonal antibody Denosumab its effectiveness and metabolic response, radionuclide therapy in combination with percutaneous vertebroplasty, possibility to use Sm-153 therapy in combination with bisphosphonates, hormonal therapy, chemotherapy and targeted therapy in breast cancer patients, side effects, survival rate and incidence of SRE in patients who received combined/complex therapy and the possibility to use of lactate dehydrogenase level as an indicator of disease progression.

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Keywords: Beta Emitter, Bisphosphonates, Bone Metastases, Breast Cancer, Combined Therapy, Complex Therapy, Chemotherapy, Denosumab, Hormonal Therapy, Impeding Cord Compression, Lactate Dehydrogenase, Monoclonal Antibody, Percutaneous Vertebroplasty, Prostate Cancer, Samarium-153-ethylene Diamine Tetramethylene Phosphonate (153Sm-EDTMP), Sm-153 Oxabifore, Skeletal related events, Survival Rate, Vertebral Fracture, Vicious Circle.

INTRODUCTION

Despite the significant progress in the diagnosis and management of solid tumors [1], the incidence of bone metastases still remains high. Common cancers that metastasize in the skeletal are prostate cancer showing metastases up to 89.6%, lung cancer [2], and advanced stages of breast cancer (up to 75% of patients develop bone metastases) [3]. Even extensive use of bone-targeted agents does not prevent skeletal related events (SREs) [4].

High incidence of bone metastases and SRE are explained by the presence of an effective, complex, multistep, cascade mechanism of cancer cell migration which starts with the detachment of cancer cells from the primary tumor, entrance into the circulation, and survival there, followed by adherence to specific endothelium. Activated cancer cells disrupt the balance between bone resorption and bone formation by secreting growth factors that stimulate the activity of osteoclasts and/or osteoblasts. The bone-derived growth factors from the bone matrix reciprocally enhance the survival and proliferation of tumor cells, creating a so-called "Vicious Cycle" that finally leads to the formation of osteoblastic, osteolytic, or mixed bone metastases [5].

The heterogeneity of bone metastases serves as an additional concern for the management of skeletal metastases [6]. Most of the bone targeting medications such as bisphosphonates and denosumab act on the bone micro-environment and the osteolytic bone metastases, while beta-emitting radiopharmaceuticals such as samarium-153-ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), strontium-89 chloride ($^{89}SrCl_2$), and Re-186-etidronate are overall used for osteoblastic skeletal metastases, although their role is limited mainly to palliative therapy. Alpha-emitter Radium-223-Dichloride has been approved for Castration-Resistant Metastatic Prostate Cancer, and it is demonstrated to increase the survival rate [7]. Previously, Kalevi Kairemo and co-authors have shown good response of painful bone micro-metastases with the negative bone scan but with bone marrow involvement seen on ^{18}FDG PET/CT in a patient treated with ^{153}Sm-EDTMP. A possible mechanism of pain relief was suggested by the "vicious circle" disruption by the β-particles, the nerve fibers' irradiation, as well as the

irradiation of cancer cells, leading possibly consequently to the termination of VEGF or other growth factors' production [8].

The combination of radionuclide therapy with bisphosphonates may be more effective compared to either one alone. However, to our knowledge, studies about the timing of bisphosphonate administration to reach more effective pain relief are at least scarce if not absent [9, 10]. In addition, when referring to combined and complex therapy, chemotherapy combined with radionuclide therapy is generally contraindicated due to possible synergetic myelotoxicity. Vertebral fracture and impeding cord compression are other contraindications for radionuclide therapy [11]. However, there may be synergetic benefits from combined chemotherapy, and radionuclide therapy since patients with vertebral fractures usually have widespread bone metastases and intolerable bone pain.

The purpose of our work was to create effective approaches for combined and complex therapy of bone metastases and to find ways to make combined/complex therapy possible with minimal side effects.

MATERIAL AND METHODS

In total, 300 patients (190 breast cancer, 68 prostate cancer, 20 kidney cancer,12 lung cancer and 10 other tumors) with multiple bone metastases received Sm-153 oxabifore therapy (998 therapies) for treatment of skeletal metastases either as monotherapy or in combination with bisphosphonates, monoclonal antibody denosumab, chemo-, hormone therapy and vertebroplasty (VP). Duration, efficacy and metabolic response were estimated in monotherapy and in combined therapy. Furthermore, we evaluated the relationship between pain-free period and tumor activity, frequency and appearance of SRE in patients who received different schemes of combined and complex therapy, and finally, for breast cancer patients, the 5-years survival rate and possible side effects. Inclusion criteria for therapy with Sm-153 oxabifore were according to general recommendations. Sm-15--oxabifore was administered at the standard dose of 37 MBq/kg body weight unless creatinine clearance level was between 30-50 ml/min, in which case the activity of Sm-153 was reduced to 50%. Before therapy, all patients received both written and verbal information about the whole procedure in detail and all signed written consent and agreement for receiving therapy.

RESULTS

Analyzing the appearance of pathological fracture among patients who received combined /complex therapy including Sm-153 oxabifore for bone metastases (300 patients) during afollow-up period 40 months, only 7 patients developed pathological fractures within 9-21 months (mean period 14,1±4,8 months).

CHAPTER 33

Molecular Radiobiology and Radionuclides Therapy Concepts

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Abstract: Radionuclides therapy (RNT) development is a multidisciplinary endeavor. It requires expertise in radiochemistry, radiobiology, oncology, pharmacology, medical physics, and nuclear medicine. Many pharmaceutical companies are not familiar with the aspects of radiation and radionuclide therapy, and the deployment of RNT agents for cancer therapy is also unfamiliar to the oncology community. When compared with almost all other systemic cancer treatment options, RNT has shown efficacy with minimal toxicity. Moreover, molecular radiobiology needs to be further explored to gain knowledge of the bystander's radiation effect. It can lead to updating for systemic radionuclide therapy concept. This paper aims to review radiation biology and radionuclides concepts to better understand the importance of basic concepts of ionizing radiation, particularly for a systemic cancer treatment option.

Keywords: Alpha particle, Auger electrons, Beta particle, Radionuclide induced bystander effects, Radionuclide targeted therapy, The abscopal effect.

INTRODUCTION

Cancer is the second-highest cause of death following cardiovascular disease, and 15%, 30%, 23% cause death in low, middle, and high-income countries, respectively [1]. It would be an estimated 18.1 million new cancer and 9.6 million cancer deaths in 2018. Lung cancer is the most common disease (11.6% of the total cases) in both sexes and the most frequent leading cause of death (18.4% of the total deaths) among males. It is followed by breast cancer (11.6%), the most common cancer disease and the leading cause of death among females [2]. Cancer disease varies across countries and within each county depending on the degree of economic development and associated social and lifestyle factors [1, 2]. Avoiding

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and eliminating risk factors exposure can reduce one-third to two-fifths of new cancer cases [2 - 5]. So, it is needed to understand the disease process and translated it into prevention and effective therapies.

To understand the process of carcinogenesis, from a normal cell is transformed into a cancer cell, we have to know the intricacies of cell function and the molecular pathways that underline it. In modern cancer management, genetic information is used to guide decisions on therapy [6]. The treatment strategy combines diagnostics and therapy called theranostics, becoming famous. It starts with a holistic characterization of the patients, including disease staging and molecular profiling, optimizing radionuclides therapy (RNT) [6 - 8]. Theranostics' advantage is identifying patients most likely to benefit or be harmed by particular medication [8, 9]. Nuclear medicine uses unsealed radionuclides to provide information on organs' physiology and biochemical condition at the cellular and molecular level for diagnostic and therapy. The use of radionuclides in therapy has been recognized for many decades, such as iodine-131 (^{131}I), phosphorous-32 (^{32}P), strontium-89 (^{89}Sr), and yttrium-90 (^{90}Y). They have been used for the treatment of benign and malignant diseases [10]. This review discusses the basic principles of radiation biology, molecular targeted therapy, and radionuclides' therapeutic application.

Basic Concepts of Radiation Biology

Traditional radiation biology concepts stated that any immature, undifferentiated, and actively dividing cells are radiosensitive. They exhibit effects of radiation exposure, such as cell injury or death. Mature, differentiated, and not actively dividing cells are more radioresistant than non-diving cells after exposure to ionizing radiation [11, 12]. Mitosis is a type of cell division that reproduces a cell into two daughter cells. In the cell cycle process, deoxyribonucleic acid (DNA) is split into two identical chromosomes. The cell cycle is consist of four stages: G1, in which cells prepare for DNA replication (gap 1); S phase in which DNA doubles by replication; G2, in which cells prepare for mitosis (gap 2) and M phase, in which the chromosomes are condensed and paired, cells divide into two and cytokinesis. G1, S, and G2 make up the part of the cycle called interphase. The genetic material is replicated in the S phase (DNA synthesis) [11 - 13]. M phase involves the cell's partitioning to produce two daughter cells and the most radiosensitive phase [11]. Furthermore before the experiments showed ionizing effect depends on total dose and exposure rate. A higher dose is given in a short period of time is more damaging than the same accumulation doses are given over a more extended time [11].

A paradigm shift in understanding radiation's effect on biological systems from

DNA-centric dogma to radiation effects involving multiple cellular targets. They included a membrane, mitochondria, and extracellular microenvironment, exosomes, *etc*. The radiation damage manifested in a target cell may extend to non-targeted cells [14 - 17]. Ionizing radiation-induced DNA damage and activated p53-related additional pathway of exosome formation. Exosomes may transfer more complex information such as apoptosis, survival, division, growth, differentiation signals to non-targeting cells [15] (Fig. **1**). The evolution of radiobiological concepts also needs to be understood in radionuclides therapy (RNT) application. The interaction of ionizing radiation with cells will risk cell death. However, cellular repair usually occurs, and permanent damage will not necessarily result from ionizing radiation with the cell. Two types of interaction between ionizing radiation with the cell are direct or indirect interactions [11].

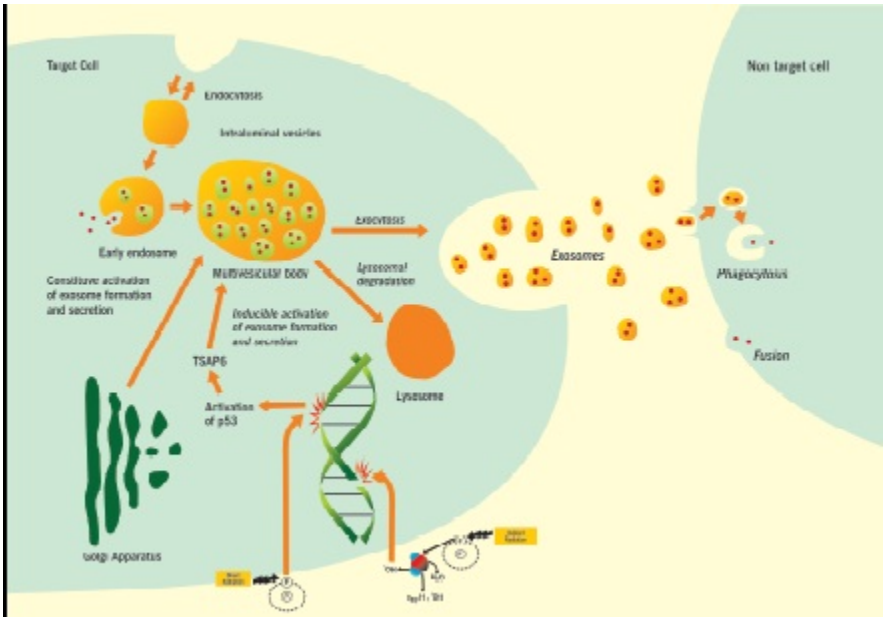

Fig. (1). Interaction between ionizing radiation and cell are direct and indirect interactions. A direct interaction causes a break in the DNA or permanent damage, leading to death immediately or eventually. Radiation-induced DNA damage and activated p53-related exosome formation. Exosomes may transfer more complex information such as apoptosis, survival, division, growth, differentiation signals to non-targeting cells. An indirect interaction is between radiation with water molecules inside the cell, causing water-derived radicals. The radicals react with adjacent molecules quickly, which results in the breakage of chemical bonds or oxidation of the affected molecules.

Direct Interaction

The ionizing radiation (alpha (α), beta (β), gamma (γ) or X-ray) hits intracellular or extracellular targets. The effect on the cell's macromolecules, such as proteins or DNA, leads to critical endpoints, including chromosome aberrations and cell

CHAPTER 34

War and Peace Inside - imaging Immune Attack in Blood Vessels

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Abstract: During evolution, immunity has been developed to protect against invading organisms and remove unwanted structures, like malignant cells. Yet, in extreme cases the organisms, like bacteria or parasites, find their way through tissues and can survive even in blood, which contains most elements of the immune system. A drastic example is parasitic *Schistosoma mansoni* worms that can live within blood vessels for years. Imaging studies have helped us to visualize ways how *Schistosoma* parasites can escape immune attacks inside circulation. Parasites often escape the immune system by hijacking soluble inhibitors of the blood complement inhibitors. By molecular radioimaging it is also possible to trace the accumulation of these inhibitors to their targets. Specifically, our collaborative work has been able to demonstrate the acquisition of immunoglobulins by adult *S. mansoni* worms and show the distribution of the complement inhibitor factor H in live animals. Radioimaging can thus be applied not only to detection of tumors and their metastases but to analysis of immune reactions against endogenous and exogenous targets *in vivo*.

Keywords: aHUS, C3, C3GN, Complement, DDD, Factor H, Glycosaminoglycans, Immune Escape, Metastasis, Radio Imaging, Schistosomes.

INTRODUCTION

Blood should be a toxic environment to foreign organisms as well as to tumor cells originating from distant sites but living in the wrong place. Yet, many types of organisms, like bacteria and parasites, can survive in blood and cause serious infections, and tumor cells can send their metastases *via* blood. Blood-dwelling microorganisms have multiple mechanisms of immune escape. They can block an attack by antibodies and complement or by phagocytic cells, prevent blood coagulation or hide inside cells, like malaria parasites. Although we know a great deal of mechanisms of immune escape by tumor cells and microorganisms from

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studies *in vitro*, there is a wide gap in relating these molecular mechanisms to how they actually operate *in vivo* at the level of a whole vertebrate organism. The present special review discusses the escape mechanisms and possibilities to observe them by radioimaging.

Immune Escape by Microbes and Tumor Cells

Radioimmunoimaging provides useful investigational tools for analysis of tumors and their response to therapy [1,2]. However, they have not been fully exploited for fundamental studies on microbe-host or tumor-host interactions from an immunological point of view. We know how metastatic tumor cells spread, but we know less well how immune cells trace them in circulation and tissues and how tumor cells avoid being recognized and destroyed. Studies on microbial escape mechanisms educate us on the mechanisms that tumor cells use to avoid immune attacks. The best ways microbes use are to mimic our own escape mechanisms. The mechanisms that the tumor cells use are largely the same as those of normal healthy cells but tuned to be more efficient. A good general example of how microbes escape killing in human blood and tissues is to bind the complement system factor H. Factor H is a master inhibitor of complement attack that binds to complement C3b, wherever it has become bound as a result of innate or adaptive immune recognition. Together C3 and factor H constitute a robust and fundamental basic recognition system to distinguish between non activating and activating structures, i.e., self and nonself [3].

Many bacteria have learned to produce specific proteins that bind factor H. Human tumor cells produce their own membrane-bound complement inhibitor proteins much like normal cells. In exceptional situations, tumor cells can also secrete soluble complement inhibitors, like factor H, which for the major part are the products of the liver or leukocytes [4]. In addition, and probably to a larger extent than normal cells, the tumor cells exploit a spectrum of polyanionic surface molecules for the binding of factor H. These include sialic acids, various glycosaminoglycans, mucins, and anionic phospholipids.

In a way, tumor cells also represent unwanted “parasites” in victims of cancer attacks. The tumor cells have undergone genetic changes to escape the normal regulation of cell growth and settlement within tissues. In blood, body fluids and tissues, the tumor cells are exposed to various components of the immune system. It is likely that a proportion of the tumor cells are eliminated because they are in a hostile environment. Part of our protection against tumors could be by antibodies. Antibodies contribute to immunity in three ways: neutralization, opsonization, and complement-mediated direct killing. Once bound to the target cells, they can activate the classical complement pathway. Complement attack can lead to

opsonization by deposition of complement proteins on the target cell surface. This also helps to recruit phagocytic cells to the site of the attack and sensitize the cells to killing by leukocytes (neutrophils, macrophages, NK-cells). Activation of the membrane attack complex (MAC) of complement can directly kill target cells by forming pores with a diameter of ≈10 nm on their membranes. These are standard responses in microbial infections but for tumors; however, the activity of complement is not that effective. Malignant cells, in general, have protective mechanisms against complement attack and MAC-mediated destruction.

Complement and its Regulators

Already during early life, the human embryos are facing contact with the maternal complement system. This can lead to the deposition of complement on both the membranes of the embryonic cells as well as on the protective zona pellucida layer surrounding the embryo [5]. The embryos, however, like healthy and *via*ble normal cells in general as well as malignant cells, are protected from complement attack by multiple mechanisms. Factor H binds to surface-associated C3b. If the surface is rich in polyanions, they assist in factor H binding, which subsequently acts as a cofactor for factor I in degrading C3b to iC3b. This will stop complement activation efficiently on blood cells, endothelial cells and other cells in contact with human plasma proteins. Additional mechanisms include binding of the classical pathway inhibitor C4bp and expression of membrane inhibitors CD46 and CD55 that also regulate complement at the C3 step [6, 7]. In the terminal pathway, CD59 (protectin) inhibits the formation of the membrane attack complexes [8]. Although most of these mechanisms operate on the surfaces of malignant tumor cells, for some metastatic tumor cells, blood can be a toxic environment.

Dysfunction of Complement

Deficiencies in the complement system can predispose individuals to severe infections or an inability to remove cellular waste products. No generally increased risk for tumors has, however, been described. Classical pathway complement deficiencies cause an abnormality to clear apoptotic or injured cells or their components. This can lead to a systemic lupus-like (SLE) disease as a consequence. Disturbances in complement regulation often cause damage to endogenous cells and tissues [3]. Factor H protects cells and *e.g.*, vascular walls [9] against complement attack, but when protection fails, the complement will get activated and may cause vascular damage [10], membranoproliferative glomerulonephritis, or atypical hemolytic uremic syndrome (aHUS) [11, 12]. Membranoproliferative glomerulonephritis is currently divided into immune complex-mediated disease (IC-MPGN) and C3 glomerulopathy (C3G) [13]. C3G

CHAPTER 35

Observations on Russia's COVID-19 Politics

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Abstract: Russia's Sputnik V vaccine has become for various reasons, a topic of geopolitical struggle, a source of vaccine nationalism and Russia's soft power, and conversely, a source of Western vaccine nationalism also. Global competition over the souls and minds of low-resource countries will continue since 80 percent of their population will not receive a vaccine this year. In this context, Sputnik V is not only a medical achievement and a step towards overcoming the pandemic, but it has also interpreted a political victory for the Russian regime. Politicization and suspicions over the vaccine, the lack of transparency and deep distrust of the Russian authorities' actions against COVID-19, and the impact of the pandemic, as well as several factors related to Russian political culture, have caused problems for the regime. The general lack of trust and the public belief in conspiracy theories, as well as widespread vaccine skepticism, have had a significant influence on Russians' attitude towards vaccination and restrictions. A significant portion of populace is skeptical about COVID-19, and the vaccine and vaccinations have not progressed very well so far. The biggest challenge of regime seems to be gain the trust of the population to achieve adequate vaccine coverage and herd immunity.

Keywords: Conspiracy theories, Geopolitics, Putin, Russia, Russia's regime, Societal trust, Sputnik V, Vaccine nationalism, Vaccine skepticism.

More than a year before the COVID-19 era, I discussed our common history with my third cousin Kalevi Kairemo in a family meeting in Tampere. Our common first ancestor, Henrik Wilhelm Tuomaanpoika Trapp [1], was born in Liuksiala estate in Kangasala in 1825, not far from Tampere. Trapp was a farmhand like most Finns at that time, but when he turned 30 years old, he was recruited to the ranks of tenement soldiers as a sniper. The reason for upgrading his social status was the Crimean War in 1855-56 for which the Empire of Russia recruited soldiers and military units also from the Grand Duchy of Finland. The task of a sniper tenement soldier was to defend Finland's coastal cities against artillery fire

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from the British fleet. We do not know which fights Henrik Trapp took part in, if any, during his six-month war service. However, as far as is known, he is not only our first ancestor but also the first of our common relatives who has awarded a Russian medal. He received a bronze medal for his service in the Crimean War, and in the army, he was also given the family name Trapp. It was a common practice to receive a name for service, and the name Trapp was a typical army name at that time. After four years' service in Russia's army, Henrik moved back to the Liuksiala Estate, married for the second time and worked there as a farmhand. He had four children.

Some of these children saw the Russian revolutions, the collapse of the Empire in 1917 and the declaration of Finland's independence on December 6th, 1917. Finland gained a new neighbour, the Soviet Union and the Eastern border of Finland was drawn in the Tartu Peace Treaty of 1920. Kalevi's father was born in 1930 on the Karelian Isthmus, in the village of Valkjärvi, about 100 km from St Petersburg. During World War II, he and about 400 000 other inhabitants of Karelian Isthmus, the whole population of the area, were evacuated to different cities in Finland to keep out of the way of the advancing Red Army. In the Peace Treaty, the area was ceded to the Soviet Union.

Life had to continue, and after the collapse of the Soviet Union, Kalevi visited Russia many times, saw his father's home place in Valkjärvi, and established wide, professional cooperation with Russian colleagues.

Kalevi has been a keynote speaker in several scientific conferences in Russia. There he encountered a number of respected scholars, and his friendship with them was warmly recalled in our discussions. All academic work also includes social life. Kalevi once took part in a cross-country skiing race with his Russian colleagues, which ended with him winning a medal. Thus Kalevi and his ancestor Trapp had the honour of both winning medals.

A sign of Kalevi's tough condition and his reputation as a skier is the fact that he was invited to the competition as far as is known by the organizers. Afterward, Kalevi modestly wondered whether his success might have been influenced to some extent by the hospitality of the colleagues. However, this is unlikely, as the competitions of the Winter Cross-Country World Cup of this winter have shown that Russian cross-country skiers have little mercy on the racetracks and not always even afterward.

Conferences have moved online, and in-person meetings have been largely halted by the pandemic, and countries hardest hit by the pandemic have been ordered to lockdown.

At the same time, a medical race to find a vaccine against COVID-19 has also begun. However, the competition has not just been a matter of the disease and medicine alone, for vaccine nationalism and geopolitics came to the fore almost from the beginning. The ongoing geopolitical struggle between the United States and China acquired a new dimension manifested in harsh mutual accusations and incitement to suspicion, including outright lies, about the disease.

The tension between the EU and its member states also arose, particularly from the lack of adequate international assistance, supply of masks, and medical protective equipment to Italy, which was one of the worst affected by the pandemic. After a long period of globalization and European integration, the stream changed direction and the role of nation-states as guarantors of the security of their citizens became central. States started to limit the spread of the pandemic by various national restrictions and by restricting movement across and within state borders. Financial support for business has so far been allocated mainly through national governments, and each country has applied the strategy it considers best to protect the health of its citizens and keep the economy running.

From the beginning, it has been clear that without an effective vaccine it is not possible to stop the pandemic. This led to a race against time by different countries, drug giants and the research community. The research community developed vaccines in an unprecedentedly fast time and with extensive collaboration. There was also a huge competition between states and companies to make a workable and safe vaccine available.

Due to global demand and the insufficient supply of vaccines, vaccines have also become a soft power tool for states.

The COVID-19 policy of different governments has also had a wide range of policy implications starting from the postponement of elections and the granting of emergency powers to governments and restricting the basic democratic rights of people. The successful response to the pandemic has also benefited some governments. Previous research has shown that usually external shocks may lead to a temporary consolidation of political support for the government. At first glance, that seems to be the case, at least in some societies like South Korea, England and Finland. After the first shock over the pandemic, disputes concerning pandemic politics have returned, and the possible “rally round the flag” effect has started to fade away.

One factor in this development has been Russia’s Sputnik that for various reasons, became a topic of geopolitical struggle, a source of vaccine nationalism and Russia’s soft power, and also conversely, a source of Western vaccine nationalism. It is safe to expect that the discussion over Sputnik V and other

CHAPTER 36

Radiomics Analysis of ^{177}Lu-PSMA I&T Radioligand Therapy Dosimetry in a Castration Resistant Metastatic Prostate Cancer Patient

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Abstract: ^{177}Lu-DOTAGA-(l-y)fk(Sub-KuE) (^{177}Lu-PSMA I&T) is currently used for radioligand therapy (RLT) of metastatic castration-resistant prostate cancer (mCRPC) in several centers in Europe. It was launched in Tallinn, Estonia, in December 2018. As an additional project, a model of dosimetric analysis was created, utilizing voxel-based dosimetry and intra-lesion radiomics to assess their practicality in routine dosimetry [1]. This was a successful project, and the work is summarized in this chapter.

Keywords: ^{177}Lu isotope, Dosimetry, Positron emission tomography, Prostate cancer, PSMA, Quantitative SPECT, Radiomics, Radionuclide therapy, Voxel-based dosimetry.

In 2020 a radiomics analysis for ^{177}Lu-DOTAGA-(l-y)fk(Sub-KuE) targeted radioligand therapy (RLT) dosimetry in castration resistant metastatic prostate cancer (mCRPC) was performed in co-operation of nuclear medicine team of Ida-Tallinna Keskhaigla, Estonia (nuclear medicine physicians Eve Kelk and Anne Poksi together with physicists Priit Ruuge and Kristi Rohtla) and professor Kalevi Kairemo from Finland [1]. The following is a short summary of this work.

The last decade has brought new promising prostate specific membrane antigen (PSMA) related diagnostic and therapeutic tools to the management of prostate cancer [2, 3]. As PSMA demonstrates, the stronger expression on cancer cells, the more aggressive the cancer is [4, 5]; it performs especially well in the cases where all other therapy options are exhausted.

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Antti Jekunen (Ed.)

After launching RLT in our hospital in December 2018, we witnessed very different patterns of the clinical effectiveness of RLT. This made us seek an optimal quantitative tool to assess the distribution of radioactivity which could aid to predict the outcome of RLT already after the first cycle of RLT [1]. As the effect on radionuclide therapy depends on accumulation of the radiopharmaceutical and its residence time in the lesion, voxel-based dosimetric analysis could aid in better planning of Lu-PSMA therapies – selection of patients and predicting how much disease is possible to eradicate in a certain case [1].

Voxel-based dosimetry is not commonly used in RLT. Our aim was to evaluate if this labor- and time-consuming method would add an extra value in predicting the response to radioligand therapy already after the first cycle of RLT. Driven by the interest in single lesion kinetics at voxel level, *i.e*. intra-lesion radiomics, we performed an extensive quantitative analysis of a series of ^{177}Lu-PSMA I&T (Lu-PSMA) of one mCRPC patient. The series consisted of four cycles, 6934–7722 MBq administered with 7–10 weeks intervals (Fig. **1**) [1]. We performed accurate 3D measurements on pre- and post-RLT PET/CT scans and also on quantitative SPECT/CT scans at three times (4, 24, and 48 hours after injection of Lu-PSMA) of all four therapy cycles. Both voxel-based and organ-based dosimetry with DRT were performed from the quantitative SPECT/CT images, and the voxel-based dosimetry data about different types of metastases, acquired with the Dosimetry Research Tool (DRT, a software by Siemens Healthineers) were compared with standardized uptake values (SUV), acquired on quantitative SPECT/CT system [1].

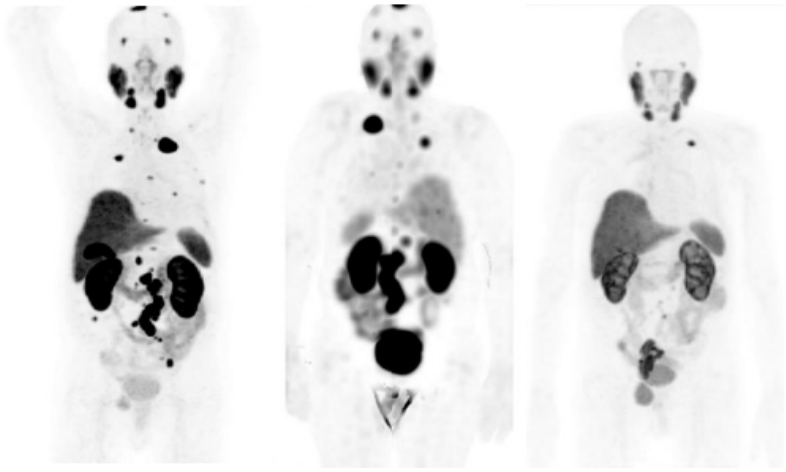

Fig. (1). From the left to the right: 18F-PSMA-1007 PET/CT baseline scan; ^{177}Lu-PSMA I&T scan during the 1st RLT cycle; 18F-PSMA-1007 PET/CT scan 6 weeks after the 4th cycle of RLT.

Absorbed-dose map for voxel-based dosimetry was created with matrix size 64 and mono-exponential fit between time points (Fig. **2**). While large organ segmentation is created automatically by DRT, the small organs and metastatic lesions need manual segmentation with spherical VOI large enough to cover visually high-dose regions. To compensate for registration errors and partial volume effect, the following equation was used:

$$D(Gy) = \frac{Mean(Gy) * Volume\_of\_VOI(ml)}{Volume\_of\_Organ(ml)},$$

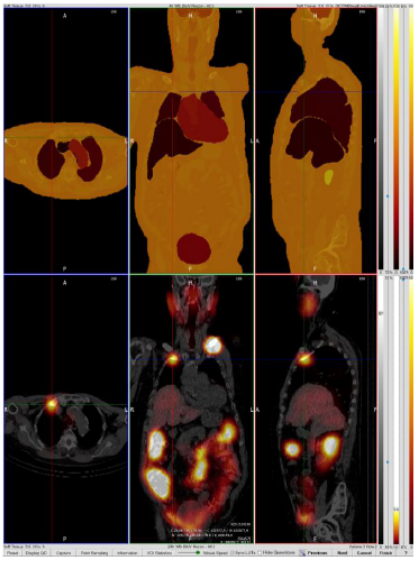

Fig. (2). Automatic segmentation of the organs (at the top) and Absorbed-dose map (at the bottom) with DRT.

Where ***D*** is absorbed dose in organ, ***Mean*** is mean dose in spherical VOI, ***Volume_of_Organ*** is the volume of organ or tumor lesion measured on computed tomography (CT). Voxel size is 1.95 mm x 1.95 mm x 1.95 mm [1].

We observed a systematical decrease of both the absorbed radiation doses in tumor lesions and their SUVmax values in the course of RLT cycles. Also, the volume of all analysed lesions decreases in the result of RLT. In later cycles, when the tumor size remains constant, the activity concentration is still decreased [1].

There exist considerable limitations in our study. The precision of measuring absorbed radiation dose in smaller lesions is poor due to the partial volume effect.

CHAPTER 37

Dancing in the Rain. Cancer as a Personal Experience

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Abstract: A discussion on the experience of cancer and how it affects one's personal life Many authors think that cancer is in the last instance a positive learning experience. At least it is seen as necessary to emphasize the positive attitudes towards cancer when trying to overcome its effects and recover. Hope is seen as the essential ingredient of adapting to cancer. Or fighting it. I also compare having cancer to corona or getting to know of your spouse's unfaithfulness.

Keywords: Adaptation to Cancer, Cancer Diagnosis, Cancer Experience, Fighting Cancer, Survivor.

INTRODUCTION

I am a 75 years old, healthy man. In Finnish we say perusterve, *i.e.* basically healthy, but it is not quite the same in translation, perusterve means a person without any serious illnesses. Yet I was born premature and almost died in the early summer 1945, when conditions for taking care of the premature babies were in many ways not ideal. My mother used to tell me that after two months in the hospital, her doctor came and said, the boy has gained 10 grams, he'll survive (I may remember the grams wrong, I weighed 1800 g when I was born). Only later did I understand that I spent two months in a premature box (keskoskaappi), which affected me in many ways I begin to understand only now.

I have survived many diseases: tuberculosis at a very early age (it was only found out much later), polio, against which I got a vaccine, all the childhood illnesses, which you nowadays get vaccinated against.

There have been lots of threats which have touched me only remotely, when I visited India, or most generally, when they have been in the news: AIDS, SARS, ebola, malaria. And now we have the coronavirus, COV-19, which I have already

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Antti Jekunen (Ed.)

been tested against several times and once believed having caught for sure (I remember going to bed and thinking that this was my last healthy day). There is a parallel with cancer and the coronavirus: it is actually relatively rare and mostly not lethal but still much feared and thought of. The big difference is of course that cancer is not contagious whereas the coronavirus is.

Ten years ago I was diagnosed with melanoma. It was discovered at an early stage, thanks to an observant doctor and the happy coincidence that she asked me to remove my shirt when checking my lungs and heart. My only time at a hospital (until recently) was the removal of the appendicitis at the point of bursting open.

I don't remember being worried about cancer when I was young. It was not a very common cause to die in the 50's. It was sure to kill you, but it was rare. And it hit older people who would die anyway. So it was almost unthinkable, but terrible. And it was very painful. Most terrible was of course if a child got cancer, which is still true [1, 2].

Now all that has changed. Cancer is not what it used to be [3]. Of course part of it is that I have grown older, as has my friend Kalevi Kairemo (congratulations!). People in our age CAN and will have cancer. But cancer has also become much more common. And for people in my age, it also carries the label "deadly", but slowly. Yet the most important thing to know is that most cancers are curable or can be tamed, so to say.

I know many people in my work, neighbour and friendship circles who have had cancer. And especially in my close family! My siblings have both had cancer. My eldest daughter has had cancer. My wife died of cancer. My mother-in-law has had cancer. There are also many survivors' tales. My old friend Bill Aron, a survivor, has collected 120 of them in an impressive book [2]. He himself is a survivor, since 1993. The big thing is that you have to adapt: "Life isn't about waiting for the storm to pass, it is about learning to dance in the rain" [2]. Only a few cancers are still really dangerous, those which give little if any symptoms, until it is too late, like cancer of the pancreas. Most of them are nowadays treatable illnesses, especially if discovered early.

And there is a lot of literature about survival, more than about death. So now I'll tell some stories of how to have cancer and survive, or die in cancer, from a friend's or relative's perspective.

My Own Cancer Experience

First, my own story, which is easy and has a happy ending, yet not atypical. I went to a doctor (I still remember her name, Marina von Ungern-Sternberg! She

had a - for me - very well known surname, as one of her distant relatives had shortly been a military ruler in Mongolia and I had actually chosen her because of the name) to complain about high blood pressure. She did not think it was serious but did all the motions and finally asked me to remove my shirt to listen to my heart and lungs. Then she said that here is a wart I would check if I were you. It might be melanoma. Just like that, in a very offhand way. So, after a time I did so, I had a piece of my skin taken and forgot about it. One month afterwards, when I was in the Jura mountains with my family and we were driving in the car to go cross-country skiing a bit higher up in the mountains, there was a telephone call from an unknown number. I was driving and answered. A brisk voice told me that the cancer test was positive. I had cancer and I should get in touch with the Helsinki skin cancer hospital as soon as possible for an operation. I said thanks and the call ended. There was a stunned silence in the car. We had just minutes before been talking and having fun. Because of the children, I took it very lightly and assured that there was nothing to worry about. But for me, it always takes time to digest bad news, much more than good news. So when my wife told me she was having an affair and had fallen in love with somebody else, it took me a month to really understand what it meant. The cancer news hit me a bit faster, but not much. When I came back to Finland, I called the hospital and they gave me a time to come there. Once there, I was operated on (they cut out a rather large bit around the cancerous skin and it took quite a long time to heal. Now I could not automatically place it, but i think it was on the right side). After a month or so, I was checked and they told me that everything was OK, but I should check myself regularly. It is funny that in this case there is no automatic invitation for checkups. One is expected to do everything yourself. Which means that the careless ones will be punished, mostly. So I have been careful, and all suspicious warts have been removed. The cancer has not renewed, yet. But it still lurks in my mind, from time to time. On the other hand I often notice, when thinking or talking about somebody else's (much worse) cancer that yes, I have had cancer, too. So it is really not something I feel I have actually had. It has just touched me lightly. But with all the cancers around me, my siblings, my daughter, it seems that it is just a question of time when it hits me.

Getting To Know That You Have Cancer

This is something that you find in the literature: typically cancer is discovered by accident, not via regular and well directed controls.

As in all descriptions of rather tragic and fatal events, there are (men) who want to make fun of it. My examples here are Colm Toibin [4] and Martti Mäkelä [5]. Toibin tells how he thought it funny that he should go and see an oncologist when

CHAPTER 38

The Flat Earth: Working with Patients and Patient Advocates in our Connected World

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Abstract: Abstract: This is a patient´s journey after a diagnosis of rare cancer in the US and multiple treatments in Europe who became active in the cancer support community, communicating and networking with each other, patient to patient, provider to provider, and provider to patient. In addition of being active in their patient networks, this is a prime example of how patients can contribute to the scientific community by actively participating in social networks and global scientific conferences.

Keywords: Cancer diagnosis, Cancer experience, Cancer survivor, Cancer support community, Metastatic pancreatic neuroendocrine tumors, PNET, Social networks, Thera(g)nostics, WARMTH.

Many things have changed since I was first diagnosed with a Metastatic Pancreatic Neuroendocrine tumor(PNETs) in 2007. Treatments and life expectancy have improved for those with PNETs as well as many other diseases. Nuclear Medicine has seen approvals for several drugs for the diagnostics and therapeutics for NETs as well as other diseases. As we move closer to the promise of Thera(g)nostics in Nuclear Medicine across many diseases, we as a community have moved closer together thanks to the innovations in communications. Coincidentally, the first iPhone was debuted by Steve Jobs, a fellow PNET patient, in 2007, which helped kicked off a telecommunication revolution.

When I was initially diagnosed in the late summer of 2007, I knew no one who had received my diagnosis. After four months living with a PNET, I had yet to have a conversation with another person who had a similar diagnosis. In many ways, I was very fortunate to live in a region of the United States with two resear-

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ch institutions within 45 minutes of each other and have departments that have specialized departments for NETS.

At the end of 2007, thanks to an introduction by a friend to the Cancer Support Community, I found a newly formed Neuroendocrine support group that encouraged me to learn more about my disease and attend the educational conference, which at the time were held yearly in the US and Canada. Towards the end of 2008, I was able to attend my first Neuroendocrine Tumor Conference held in Toronto, Canada, where I heard lectures and had the opportunity to meet Dr. Sandy McEwan, and Prof.Dr. Richard Baum MD.

In 2008, the Earth was still round for Neuroendocrine tumor patients, and I need to travel over 3,000 miles from my home to learn about nuclear medicine. After the conference, I would travel to Germany to be evaluated and subsequently treated several times over the last eleven years.

Much has changed since I first visited Europe for Ga68 dota scan. There are now several approved dota scans for the diagnosis and management of NETs in the US and in Europe. The pivotal NETTER-1 study was conducted and reported on in the New England Journal of Medicine which lead to the subsequent registration of Lutathera in the US, Europe, and other countries. There have been several follow on well-designed phase II and III studies for Nuclear Medicine therapies for Neuroendocrine Tumors and Metastatic Prostate Cancer.

Perhaps the most significant change in the 14 years since I was first diagnosed and the introduction of the iPhone is our ability to communicate and network with each other, patient to patient, provider to provider, and provider to patient. In these 14 years, the Earth is now flat.

An advancement that happens in Australia is sent as a Twitter message, viewed on a flat-screen in Los Angeles and London, and immediately commented on or collaborated with in real-time. The Earth is no longer round; we are no longer required to fly around the world or across a country to learn about new advancements; we are able to do this from our home or office.

In a little over a decade, there are dedicated sites for patients to network with each other on platforms such as SmartPatients or Inspire. There are dedicated private Facebook groups for NET patients with many thousands of members each. There is even a dedicated patient group for PRRT with over two thousand members. These groups generate hundreds if not thousands of messages a day.

I first met Dr.Kalevi Kairemo at the first Theranostics World Congress in 2011; I was but one of a handful of patients invited to the conference of several hundred

in Bad Berka, Germany. I had just launched a website PRRTINFO.org that was to serve as an information hub of sorts about PRRT for NET patients for years to come. In an average month, PRRTInfo.org has nearly 30,000 visitors seeking information on PRRT.

In the years since the site first launched, our ability to access information online and to the network has increased exponentially. In 2018, by the time I had the pleasure to work with Dr. Kairemo on WARMTH's ISRT in Helsinki, Finland. The capability to record and/or live stream was within reach, enabling even relatively modest budgeted conferences like ICRT 2018 could be recorded and shared with much larger audiences (https://vimeo.com/showcase/5564813) [1]. In 2020 virtually every conference, meeting, or networking was done virtually. WARMTH's 2020 conference, originally planned to be held in Bangladesh, was held virtually with speakers recording their presentation from around the world and accessible to all on the flat screen of their choosing (https://warmth.org/videos/62-videos-from-the-15th-icrt) [2].

WARMTH, while being a global nuclear therapy medical society, has embraced the use of Theragnostics for the benefit of humanity and has included the patient voice in nearly all of its congresses and symposia, and the 2018 ISRT was no exception.

While we know the Earth is not really flat, the flat screen earth has presented some opportunities as well as challenges in working with the patient and patient advocate community.

Information is available to all patients nearly immediately from a multitude of sources. This can be advantageous when information is coming from vetted sources, but it can be challenging for both patient and provider when the information comes from unvetted sources or is misunderstood by patients and passed on to others. Your patient will pass on whatever you say to a community of other patients for better or worse.

The flat-screen Earth has also allowed patients to be more involved in advocacy, especially in countries where previously patients had to travel several hours by plane in order to make their voices heard. Many regulators and government officials have changed from an in-person meeting model to virtual meetings or fly-in enabling voices that were not commonly heard by regulators or government officials.

The 2018 ICRT meeting in Helsinki that was hosted and chaired by Dr.Kairemo was part of a turning point for WARMTH, we were still on the round Earth, but we started preparing ourselves for a time when the Earth became flat. [1, 2].

APPENDIX: KALEVI KAIREMO'S LIFE

In Health Care During Seven Decades

Kalevi Kairemo

I was born in 1955, in downtown Helsinki (Tehtaankatu). My late Father Aulis was born in Karelia in 1930 and worked as teacher in mathematical sciences in Secondary schools. My mother Pirkko was born in Central Finland in 1930 and she worked as a pharmacist mainly in the pharmaceutical industry. I have a younger brother Ari (b. 1956) who has been active in advertizing industry. I got married with my wife Ann-Christin (M.D.) in 1982 (June 19) and we have two children Eva-Stina (M.D.) and Johan M.Sc.(Econ.).

In the Tehtaankatu home in late 1950's.

Wife Ann-Christin in 1981

Education

I went to Primary School in 1962 (Tehtaankatu, 300 m from home) and to Secondary School in 1966 (Helsingin Normaalilyseo, 700 m from home). My first working place was at Maria Hospital where I worked as a messenger in the Clinical Laboratory in 1970. The following summer 1971 I worked in a storage of a

Pharmaceutical Company. In summer 1973, I won a scholarship by writing an essay in German; I spent a Short summer term in a Secondary School in Bremen, Germany which was the start of my education abroad.

Picnic in Bremen 1973

In 1974, I started my university career in the Department of Chemical Engineering at Helsinki University of Technology, resulting in MSc(Eng) degree in 1980. I had IAESTE internships in chemical industry in Athens, Greece 1975 and in Cairo, Egypt 1976. In 1977, I had student exchange in Warsaw, in Nencki Institute in the Department of Biochemistry (Academy of Poland). These were my training places abroad in chemical industry before undertaking medical training (MD, PhD) at the University of Helsinki (HU), Finland.

Technology student 1978

My first medical training abroad was in Brno, Csechoslovakia in 1979 where I worked in the University Hospital in the Departments of Physiology and Clinical Biochemistry. I completed my MD Degree in 1986, EU orientation internship phase in 1987, and got MD, PhD (D.Med. Sci) degree in 1993. Medical specialist training I took in Clinical Chemistry (examination in 1994, Nuclear Medicine (1996), Health Care Administration (2002) and Pharmaceutical Medicine (2006), all at HU (Central Hospital).

Academic Career

Guide in the Medical Exhibition for Science Center Heureka, Aamulehti Newspaper in 1985

My first academic exchange was between Academies of Finland and German Democratic Republic in 1988, related to experimental monoclonal antibody research and visit in East Berlin.

Then I had a post-doctoral research fellowship at Memorial Sloan-Kettering Cancer Center (MSKCC) from 1989-91 and again 1993 in New York. In 1994, I was appointed to a position of Associate Professor in Experimental Nuclear Medicine at HU. In 1999, this was upgraded to a clinical position, Associate Professor in Nuclear Medicine and Clinical Chemistry. Then I got a Professorship in Clinical Chemistry at the Norwegian University of Science and Technology (1998-9), Professor in Nuclear Medicine at Uppsala University Hospital in Sweden

(2001-5) and as Head of the Nuclear Medicine Division, Department of Oncology at Helsinki University Central Hospital (2004-9).

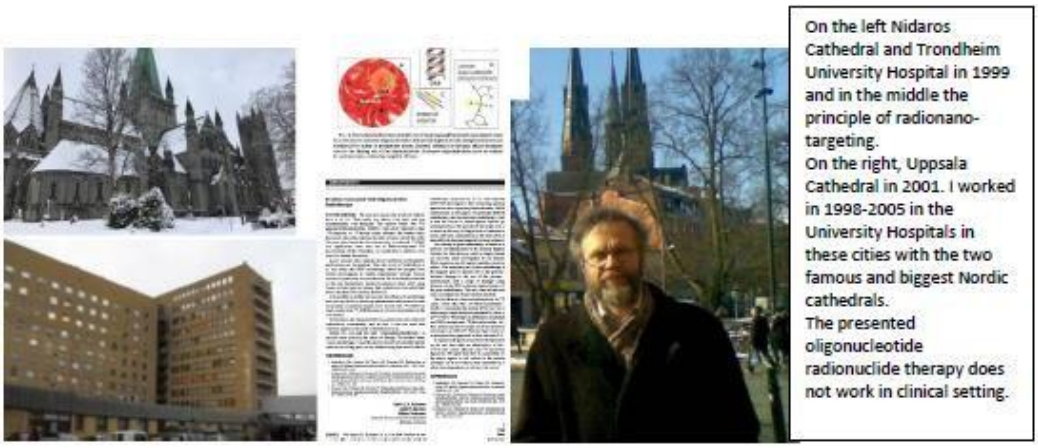
Daughter Eva-Stina and son Johan in 1993

In 2010-2018 I was the Chief of Nuclear Medicine and Molecular Radio therapy (Theragnostics) at the Docrates Cancer Center, in Helsinki. Since 2015 I have been as Visiting Professor in the Nuclear Medicine Department of The University of Texas MD Anderson Cancer Center.

Public transportation flyer to every home in Helsinki 1987, daughter Eva-Stina inside

Industrial Research

I have also held posts in industry, as Medical Director of CTT Cancer Targeting Technologies (2001-6), Medical Director of Imanext Ltd (2006-8) and Clinical Director at Advanced Accelerator.

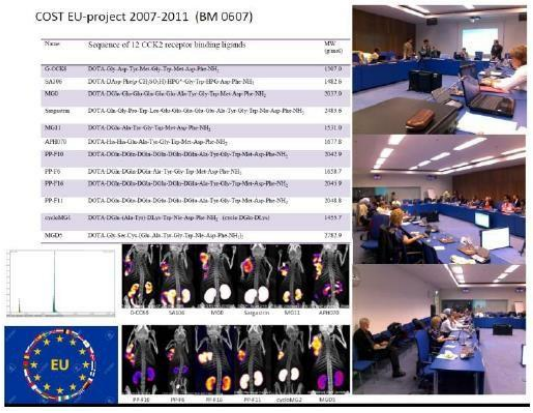


On the left Nidaros Cathedral and Trondheim University Hospital in 1999 and in the middle the principle of radionano-targeting.
On the right, Uppsala Cathedral in 2001. I worked in 1998-2005 in the University Hospitals in these cities with the two famous and biggest Nordic cathedrals.
The presented oligonucleotide radionuclide therapy does not work in clinical setting.

Applications SA (AAA), a joint French-Italian company. CTT was a Finnish biotech company focusing in targeted drug delivery with intelligent nanoparticles and phage display technology. Imanext was a Contract Research Organization focusing in tailored imaging services for pharmaceutical industry, having research

sites in 38 countries. AAA is now a Novartis Company, but in 2009 I was involved with initiating clinical services and designing phase I trials, such as LutaThera which in eight years became a blockbuster product. After retirement from the clinical work I have acting as Consultant in Curium Pharma.

I also acted as Chief Physician in the National Radiation and Nuclear Safety Authority (STUK) in 2000 by introducing national guidelines regarding the use radioactive compounds according to the EU Directive for Medical Radiation Safety.



In my research I have developed and investigated multiple tumour-seeking compounds, including monoclonal antibodies, specific phage-display peptides and cytotoxic drugs. I also have coordinated multiple EU Research Programme proposals in 1995-2004, and most important of these activities was the European Union COST Action Project (BM 0607, Targeted Radionuclide Therapy) where I was the National Coordinator and Management Committee Member for the from 2007-11.

For industry, I have been developing intelligent targeting nanoparticles which contained cytotoxic compounds and/or tracers (also for MRI, optical or ultrasound imaging). The key targets were MMP's and leukocyte integrins. I have been involved with *e.g.* radiation sensitizing, hypoxia, angiogenesis and apoptosis related targeting approaches. I also worked with gene therapy radionuclide applications (nanotargeting). In the clinic, I was developing PET-tracers for oncology, actually by introducing more than ten new tracers into clinical practice (compassionate use) in Finland. One of the foci, was early response evaluation in clinical cancer therapy.

Publications

For Scientific periodicals I have edited several special issues: 1) for *Current Radiopharmaceuticals* two Special issues, *i.e.* the very first issue vol.1 (1) in 2008

with a special emphasis on "The Role of Radiopharmaceuticals in Drug Discovery" and for the second time vol. 8 (1) in 2015 with special topics in "PET/CT in External Beam Radiation Therapy Dose Planning"; 2) for *Diagnostics (Basel)* three special issues in 2015-20: two of them dealt with early response evaluation; 3).

For *Current Pharmaceutical Design* two Special Issues, the last dealt with "Targeted Drug Delivery and Theragnostics"; 4) one for *International Journal of Molecular Sciences* entitled "Targeted Therapies in Cancer: Radionuclides, Multi-Omics and Nanomedicine"; 5) one for *Life*; 6) one for *Acta Oncology*.

Besides a few patents I have published more than 250 original articles in peer-reviewed journals (PubMed 170+, RG 250+). I also received the Lifetime Achievement Award from the World Association of Radiopharmaceutical and Molecular Therapy (WARMTH) in 2012.

WARMTH Award Winners 26.11.2012. Magne Aas (NOR), Anna-Liisa Brownell (FIN), Kalevi Kairemo (FIN), Sten Nilsson (SWE), Sven-Erik Strand (SWE), Roy Larsen (NOR), Sirkka-Liisa Karonen (FIN) and Oyvind Bruland (NOR). In the middle WARMTH President Ajit K. Padhy.

Career Highlights

Example of an International Congress flyer

I have arranged multiple international medical congresses in Finland, Sweden and Denmark. In Uppsala I arranged two In ternational Congresses in Nuclear Medicine (2002) and Radiobiology (2003). I acted as President of an International Conference for Pharmaceutical Development in Copenhagen in 2007. At Docrates Cancer I hosted four International Conferences about Nuclear Oncology, Nuclear Endocrinology and Emergency Oncology and Theragnostics (2012-2016). Most importantly, I was the President of the 7th International Conference on Radiopharmaceutical Therapy held in November 2012 in Levi in the Finnish Lapland. In 2014, I also hosted ISORBE Symposium and Workshop "Cell Labelling and Cell Therapies" in Helsinki. My latest contribution, was the arrangement of International Symposium on Radiopharmaceutical Therapy (WARMTH) in November 2018 in Helsinki.

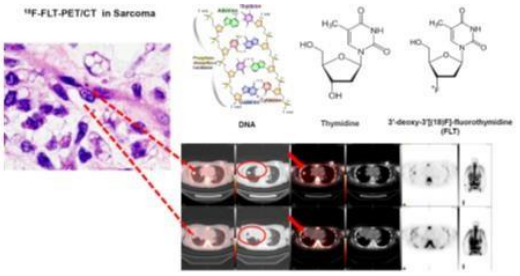
Examples of tabloid papers reporting radionuclide therapies.and therapy tourism
The front cover of Aftonbadet in Sweden. I am sitting with the patient who brought the journalist to Finland. (above)
On the left, another Swedish patient with me. Picture from the website of a Finnish tabloid newspaper (Iltasanomat)

My patient work has been mostly semiclinical mean ing that I have not met all of them when giving a diagnostic report. Patients whom I treated I have met at the time of administration, but I have not always been been able to follow them. My early clinical career was patient-oriented, I worked in Primary Health Care Centers in Helsinki regions and in Tuusula fore more than year. Most of the compulsory EU training I spent in surgery and internal medicine which I did in Tammisaari is Swedish. Most of my training in Nuclear Medicine and Clinical Chemistry took

place in Helsinki University Central Hospital (Central Laboratory, Radiology and Oncology departments), and in Helsinki City Hopitals (Laakso/ Maria) in 1985-1998. Then I went to Trondheim University Hospital in Norway (1998-1999) and to Uppsala University Hospital in Sweden (2001-2005). I also acted as Chief Physician in Kymenlaakso Central Hospital (Kotka) and South Karelia Central Hospital (Lappeenranta) in 2006-2010. Clinical highlights were multiple, but I never could imagine to end up on a front page of tabloids papers both in Sweden (Aftonbladet) and Finland (Iltasanomat) and only because of success in new patient treatments.

Science highlights were probably as follows: I had the priviledge to introduce approximately twenty monoclonal antibodies into clinical practice in late 1980´s and 1990´s in multiple indications [1]. SPECT imaging with Tc-99m, In-111, I-123 or I-131-labelled antibody fragments were used. Furthermore, I introduced radioimmunotherapy early 1990´s in Finland with Y-90- and I-131-labelled antibodies [2,3].

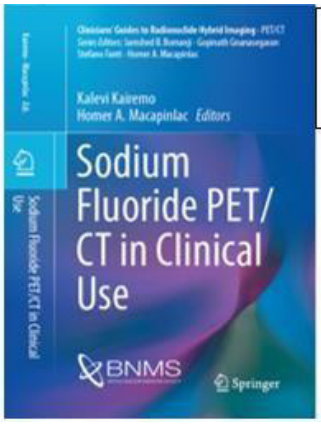
I worked with the theragnostic concept *in vitro, in vivo, ex vivo* (*e.g.* radioimmunochemistry), *in vivo* (Dx), *in vivo* (Tx), *in vivo* (Rx) ever since late 1980´s [4]. One of my initiatives was Auger-chemotherapy in the clinics. I also tested, oligonucleotide radionuc lide therapy (radionanotargeting) in theoretical setting and some *in vitro* experiments [5].



Graphical abstract and cover page of early response imaging in 2020

Phage display peptide were in use in preclinical setting. They were used to target nanoparticles, espec ially in the CTT Biotech Co. Then I got involved with commercial precision radio-molecular oncology using beta particles to target peptides at AAA in St Genis Pouilly, France; their first clinical thera gnostic product LutaThera got marketing approval in 2017.

I continued in 2010 at Docrates in Helsinki and introduced approximately 10 radiopharmaceuticals into clinical practice in Finland [6,7]. I was interested in early response criteria. I also developed response criteria for Alpha-emitter bone therapy (^{223}Ra). I continued this work at MDACC since 2015 and created *e.g.* own response criteria for metastasized osteosarcoma with NaF [8].



NaF-PET book cover (on the left). [9] NaFCIST criteria reference (below)

To cite: Kairemo K, Rohren EM, Anderson PM, *et al.* Development of sodium fluoride PET response criteria for solid tumours (NAFCIST) in a clinical trial of radium-223 in osteosarcoma: from RECIST to PERCIST to NAFCIST. *ESMO Open* 2019;**4**:e000439. doi:10.1136/esmoopen-2018-000439

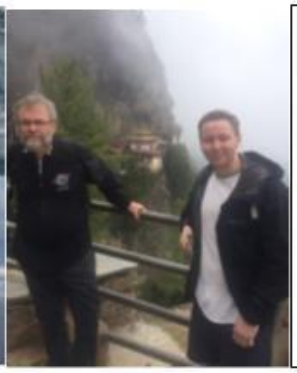
Nuclear Medicine Faculty at MD Anderson Cancer Center in 2017

Hobbies

Art has always been an important part of my life, this may be related to performing arts or visual arts. I have kept diary both about cultural and sports events where I have been participating. I have been active in visual arts. I have had one larger own exhibition (72 works) at my working place in 2013. I have made many illustrat-ions for own publications.

I have done extensive travelling. I am also a member of Maailmanmatkaajat (Globetrotters Finland) where the minimum requirement is 70 countries. I have visited more than 110 UN Member states, but I am not interested of travel itself or country count. There has to be several reasons for me to visit a new place. Very much of travelling has been due to participating in conferences. I have been given lectures in more than forty countries. I have been interested in nature (espec ially botany: Carl von Linne´s legacy in Uppsala), endangered species (peng uins) and regions (such as Antarctica and Arctica). I had early internships abroad and I have had work experience in eleven countries. I feel very priviledged with all these opportunities, and I have honestly visited very special regions, such as North Korea, Mongolia, Bhutan, Transnistria, Haiti, Antarctica *etc*.

Examples of big wall posters of guest lectures: Wuhan, China 2003 and St Louis, MO, USA 2016



Examples of extreme travelling: Antarctica 2008 (left panel) and Bhutan 2018 (right panel). In Antarctica I finished a marathon and then was swimming in the icy sea. In Bhutan I finished a high-altitude marathon and visited this remotely located monastery (Tigers Nest) together with my son Johan.

Sports has been an important part of my life since the early youth. Track & field (especially running and jumping) were important already at primary school. In the primary school we also skied. There was even a small jumping hill in the park (Kaivopuisto) where I used play soccer or basket ball daily in summers after school and ski in winters. In the secondary school I learned new disciplines, baseball, ice

hockey, handball and gymnastics. In the University I was interested of indoor soccer and running. After becoming veteran (M40+) I started to become interested of extreme running and skiing. I also started alpine skiing, because I could travel to the Alps and other higher mountain regions.

I have been a marathon enthusiast since my debut in mid-90´s up to five races per year. My marathon count is more than 100, and I have been running in more than 60 countries. Accidentally, I became the first Finn to become a member in Seven Continents Club in 2008.

Some data about marathon enthusiasm. Seven Continents Club (on the left). New York City Marathon in front of MSKCC in 2009 (in the middle). List of countries, where a full marathon was run (map not updated) (on the right).

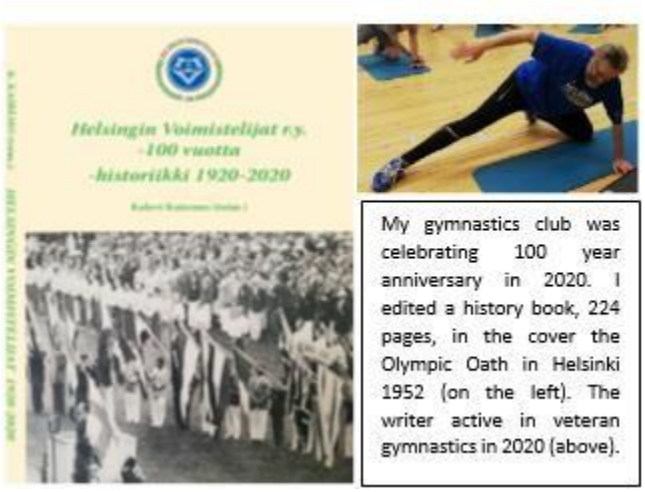
In sports I got a hamstring muscle rupture in floorball game in 2015; two broken muscles were rejoined in an operation meaning that I was unable to run for more than six months. But with progressive and continuous exercise I was able to finish a marathon in 2016. I also made success in running races in Texas in 2016 which I did not anticipate. I did not compete anymore after 2017, but exercise has been regular even during SARS-CoV-2 lockdowns in 2020.

Texas, Spring 2016. Highlights in veteran running competitions.. Award ceremonies, race medals of January, mascots and fans (on the left).
Four page coverage in a Finnish Runner´s Magazine (Juoksija 2007). Picture taken on Seurasaari bridge in Helsinki (on the right).

In skiing I have a very long history, 60+ years. But eventhough I am living in Helsinki, the skiing conditions may vary dramatically. Sometimes there is no winter at all, sometimes there is 40 cm snow, Anyway, I am fond of skiing, *i.e.* cross country skiing with free or classic style. I love alpine skiing, but for that purpose I have travelled (Andorra, Austria, Switzerland, Bulgaria, Chile, Canada *etc.*). In marathon cross country skiing I belong to Worldloppet Masters Finland; for a Master title 10 ski marathons in different coutries are required. I have got this Worldloppet Master title twice and Euroloppet Master once. Typically I travel to a ski race once in a year. I also did some ski jumping, but only in small hills (< 30 m). Nordic walking is good training for skiing when there is no snow or no indoor skiing facilities.

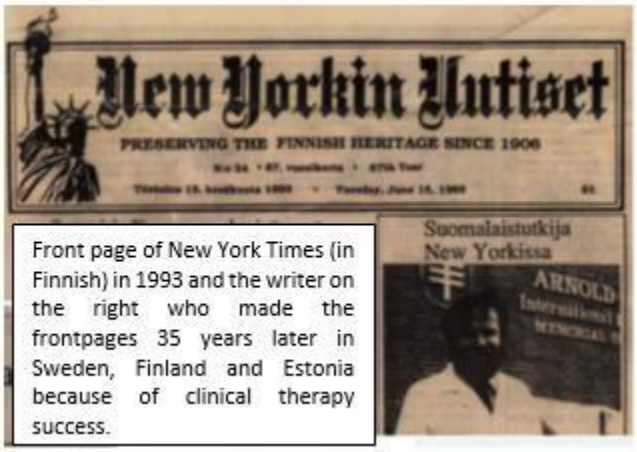
Skiing. In Italy at 67 km in 2005 (on the left) and in Lapland 2012 in the WARMTH Congress (on the right). In Lapland we demonstrated cross country skiing for congress particpants.

I am convinced that physical exercise is an essential part of good working performance. Gymnastics has belonged to basic education in Finland for more than 150 years. Senior gym-nastics has become important to me since 2016. I had the possibility to write a book about our team 100-year history [10]. Our team was earlier successful in the Olympics, nationally and had an interesting dramatic history reflecting even local turbulences.



My gymnastics club was celebrating 100 year anniversary in 2020. I edited a history book, 224 pages, in the cover the Olympic Oath in Helsinki 1952 (on the left). The writer active in veteran gymnastics in 2020 (above).

CONCLUSION



Front page of New York Times (in Finnish) in 1993 and the writer on the right who made the frontpages 35 years later in Sweden, Finland and Estonia because of clinical therapy success.

Retrospectively, I feel that I have had a visionary, systematic and productive trailblazer career in spite of limited local resources and remote Arctic location. I have always believed in education and resilient learning of new things. I am honored that I found my focus early and in order to accomplish something even the details matter. I am very thankful to my wife, children and grand children, without their support nothing would have happened. To the international community who created this book I can not verbally express my real gratitude.

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Memoirs from encounters with Kalevi Kairemo, edited by *Antti Jekunen*

Eve Kelk, Tallinn, Estonia

The first time I met Kalevi was in 1994 during my visit to Helsingin Yliopistollinen Keskussairaala. In Estonia, we were planning to start radionuclide therapies for thyroid cancer those days and the first place to look for an example and advice was self-evidently Finland. Kalevi had just arrived from the United States, where he performed his post-doctoral research at Memorial Sloan-Kettering Cancer Center. To me – a novice in nuclear medicine back then – he seemed a young professor floating somewhere high above clinical work. I remember Kalevi showed me his paper on radioimmunotherapy of ovarian cancer with monoclonal antibodies – it looked like science fiction to a physician coming from Estonia, a country which had recently escaped from the Soviet Union. Only after years of learning, I understood that nuclear medicine is always one step ahead of everyday clinical practice, molecular imaging and theragnostic concept being just a couple of examples here. And this is all thanks to professionals like Kalevi – not only compassionately doing his best fighting for the lives of his patients, but also generating new ideas changing the future, testing his hypotheses and sharing the results with the world-wide scientific community.

In Estonia, we are immensely grateful to professor Kalevi Kairemo for his firm support and friendly encouragement – not only in starting novel therapies with Lu-177, but also forcing us to examine and understand in depth the results acquired in this process.

Professor Kalevi Kairemo together with Eve Kelk (left) and Anne Poksi (right) after the 1st radioligand therapy with Lu177-PSMA was successfully administered in Ida-Tallinna Keskhaigla on 20.12.2018

Professor Kalevi Kairemo together with Eve Kelk (right) and Anne Poksi (left) after the 1st radioligand therapy with Lu177-PSMA was successfully administered in Ida-Tallinna Keskhaigla on 20.12.2018. The procedure was performed by nuclear medicine technicians Olga Marchuk and Artjom Matytsin.

Memoirs from the Badgastein Conferences *by Georgios S. Limouris*

In the decade 1990-2000, a small but very important conference of Nuclear Medicine took place immediately after the beginning of each New Year, around the 8th to the 12th of January. We are talking about 25 years back when we were 25 years younger. There, I had the opportunity to meet my esteemed colleague and later friend, Professor Kalevi Kairemo, to whom I dedicate with the utmost joy and honor an important topic of Nuclear Medicine dealing with the tumoricidal power of Auger and Internal Conversion electrons for which nowadays we celebrate the 100 years after their discovery by Lise Meitner and Pierre Auger. The winter conference in Badgastein had a special family atmosphere that allowed the development of closer relationships between colleagues. In fact, in a scientific competition among the three best manuscripts of Kairemo, Limouris and someone else (whose name I do not remember), Kalevi came third in the ranking, which I remember created him an explosive disappointment; he was right because his paper reported on a clinically applied basic scientific work, a topic rather unusual and easy to perform at that time. Those small winter conferences were unforgettable, and unrepeatable, and unfortunately, their spirit does not exist today because life has lost its quality due to “unscrupulous antagonism”.

My Collaboration with Kalevi by Akseli Hemminki, Helsinki, Finland

My first recollections of Kalevi are from around 2004 when I was specializing in oncology and radiotherapy, and Kalevi was the nuclear medicine physician at the Helsinki University Hospital Cancer Clinic. He immediately struck me as a development oriented independent thinker who very much wanted to improve the toolkit available for patient treatment and diagnosis. We had many interesting discussions where he also told me about his previous experiences in both academia and biotech. One memorable off duty experience was a rock concert at Ratina Stadion in Tampere, probably in 2004. I believe the band was Eppu Normaali. It was quite the trip sharing the minibus there and back. We continued to meet regularly at the clinic in the context of patient imaging, and our first scientific collaboration started around 2007, when he helped my research group preclinically test an oncolytic adenovirus coding for the hNIS iodide symporter. However, after 2010, when we were both working at Docrates Cancer Center, our collaboration intensified, resulting in 13 coauthorships. In addition to routine patient consultations, Kalevi was extremely useful in the experimental individualized treatment program running between 2007 and 2012, where 290 cancer patients were treated with oncolytic adenoviruses. He was always helpful, flexible, and ready to think outside of the box. It has been a wonderful experience collaborating with him and I wish him all the best for the future.

Raluca Mititelu, Bucharest, Romania:

I met Prof. Kairemo due to our participation in the activities organized by the World Association of Radiopharmaceutical Therapy (WARMTH). This respected international organization was found as a result of the initiative of respected Professor Ajit Padhy and brings together colleagues and friends from around the world - dedicated professionals in the field of Nuclear Medicine and who have promoted theragnostic methods in the personalized management of cancer.

Professor Kairemo has always been one of the most important promoters of our specialty, actively involved in training the youngest or least experienced. He never refused when asked for help. I remember 2010, when I participated in the organization of the third National Congress of Nuclear Medicine, as Secretary of Romanian Society of Nuclear Medicine, together with the president of the Society – Prof. Codorean and with my colleagues from Romania. Times were hard for nuclear medicine in Romania. We had many laboratories with extremely outdated equipment, and the PET-CT technique was hardly available which was only in a private system. Few of us had access to quality information, and our participation in international scientific events was possible with huge financial efforts. In this context, we appreciated the help of colleagues and friends from universities in developed countries, including Prof. Kairemo, who agreed to participate as guest speakers at our national events, bringing quality science and up to date information to those who at that time could not afford participation in events outside the country. Moreover, Prof. Kairemo managed to organize, in 2012, a meeting of the WARMTH association, an International Conference of Radiopharmaceutical Therapy, that brought together the participation of an impressive number of specialists from around the world, with many travel grants for young researchers that otherwise wouldn't have been able to attend the meeting.

Personally, I would like to thank Prof. Kairemo for all his efforts. Along with other professionals who have marked the field of Nuclear Medicine at the beginning of the 21st century - Prof. Kairemo is definitely a model.

I am honored to participate in the editing of this paper, and I want to be able to help dedicated professionals, with fewer or less experienced resources.

My Memory of Professor Kalevi by Marina Hodolic, Ljubljana, Slovenia

I first met Professor Kalevi when I was resident in nuclear medicine at the University Medical Centre Ljubljana, in Slovenia. He stopped by our department while travelling through Slovenia to see how nuclear medicine was in this small, former Yugoslavian country. After much discussion, mostly about fluorocholine, which was very popular at the time, we agreed to conduct a project on patients with prostate cancer in Helsinki and Ljubljana. I travelled several times to his wonderful country and department for research and to speak at his congresses, which were always perfectly organized.

During my first visit to Helsinki, he invited me for dinner in a typical local restaurant. I love all sorts of food and asked him to choose something Finnish for me. He chose meat with berries. It was tasty, well prepared and I enjoyed every last morsel. I asked what I had eaten and was told, “Reindeer”. I could scarcely catch my breath. “Reindeer? You mean the wonderful beast that brings Santa Claus with presents for the children in a golden carriage at Christmas?”. Yes, I still believe in him. I tried not to show my concern but I didn’t sleep at all that night, worrying if my 5 year old niece would ever forgive me for depriving her of her Christmas presents for years to come. Fortunately, I now know that Santa Claus keeps only the very best magical reindeer for himself and he has forgiven me.

Thanking you always for your professionalism, mentoring and friendship, Professor Kalevi.

Kalevi Kairemo and Marina Hodolic, Helsinki 2013

Alexandra Nikaki, Hämeenlinna, Finland/ Larisa, Greece

The moment I had the honor to meet Professor Kalevi Kairemo is still vivid in my mind and in my heart! It was 2016, when I had just moved to Finland, and participated in EANM congress as a Finnish citizen and employer with limited language skills, when, at a wine dinner offered during the congress, a man sitting right opposite me asked me where I was from, and then started saying words and phrases in Greek and narrated a story about his living and working time in Greece in his youth as a student— the period just after the dictatorship in Greece in a politically unstable environment and period. He also shared , the journeys he had in Crete, and finally his participation in several marathons across the world in one of the two big concerts (directed by Mikis Theodorakis) that took place in Athens after dictatorship to honor democracy and freedom! I cannot describe my feelings to listen to a foreigner speaking about the historical events that occurred in my native country in the way he lived them. And I cannot describe my shock when he responded to “now you need to tell me who you are”, “Kalevi Kairemo” with his characteristic Finnish voice, as of course I recognized the name. I had the honor to meet Professor Kalevi Kairemo, whom I already knew and admired for his work, and professionalism and personality. Professor Kairemo thank you very much for giving me the opportunity to learn from you! Thank you for introducing me to PSMA-PET imaging and Lutetium-PSMA treatments, as also to the WARMTH community. Thank you for standing next to me, for all the guidance and assistance! I wish you the best in your life, and enjoy the “journeys” yet to come!

My dear friend Kalevi by Mike Sathekge, Pretoria, South Africa

About 17 years ago, I had the pleasure of attending an SNM meeting wherein I briefly met a tall, handsome and kind Gentleman, Prof Kalevi Kareimo. Ever since we have kept in touch with many deep, wide-ranging discussions on novel applications in nuclear medicine and the nature of creativity. I've learned many lessons over the years from working with Kalevi. His energy and commitment to excellence, engagement, and kindness are contagious. He is one of the few nuclear medicine physician that is a truly a physician scientist. He is an authority in engineering, chemistry, and clinical applications on nuclear medicine. He has made significant contributions to basic nuclear medicine, PET/CT, and recently theranostics. We have planned and collaborated on several topics, ranging from infection imaging, radionuclide therapy in skin cancer and PSMA targeted radionuclide therapy. He has also been a Ph.D. examiner of some of my students. We have enjoyed Notable meetings while advancing science at WARMTH and ISORBE meetings. Kalevi is a true professional and the embodiment of Good Work.

Professor Kalevi Kairemo together with professor Cipriani (right) and professor Mike Sathekge in Celano, Italy

Professors Kairemo, Cipriani and Sathekge ready to start dermobrachytherapy with Re-188 in Celano, Italy

Kalevi Kairemo and Mike Sathekge outside Levi Summit Conference Center in November 2012 in the Finnish Lapland.

The Globetrotter

Professor Kalevi Kairemo

Congress with Kalevi

Professor Irene Virgolini
President WARMTH 2018-2019
Department of Nuclear Medicine, Medical University Innsbruck, Austria

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WARMTH
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The Foundation of The WARMTH and the World Journal

My story with Ajit Padhy starts in 1999 when I was hired by the IAEA as an officer at the Division of Nuclear Medicine. G. Nair just had retired and Ajit Padhy had recently taken over the position of heading the Division. At the University of Vienna Rudolf Höfer had retired after a life-long dedication to Nuclear Medicine had taken over the Department of Nuclear Medicine. I had applied for the Director call of the Institute of Nuclear Medicine at the Lainz Hospital in the South of the City of Vienna, and was in a waiting position for the appointment. My former head Rudolf Höfer had always kept close contact to the IAEA, especially to G. Nair and, in this changing situation I was a proper and optimal young scientist for IAEA recruitment. In fact, in the half year when I part-time worked at the IAEA Ajit Padhy was starting to settle the Division of Nuclear Medicine at the IAEA onto a new level. Ajit Padhy was travelling a lot and mostly I remained alone with the other staff of the Division. My time at the office consisted basically in reviewing research applications from around the world within the established CRPs (Conserted Research Projects), sending experts from one country to the other. Ajit started to settle the „^{188}Re-Lipiodol liver project“ which, for many years, was one of his many major Nuclear Medicine projects, and which will be discussed later on in this booklet. Applications came from developing countries around the globe, but Ajit Padhy supported the colleagues from Asia the most. Ajit was working all day around, even at night, and sometimes his wife with the two small boys came to his office at the IAEA in the afternoon.

Once a day Ajit came into my room and enthusiastically said „Irene, we have to do the World Journal of Nuclear Medicine. You should be on the board, give me some ideas!“ We were talking about his world vision on Nuclear Medicine and, in his point of view, the lack of vision of the World Federation of Nuclear Medicine and Biology (WFNMB). We were discussing the different features of going to this or that country as IAEA representatives, and who should be on the Editorial Board of the World Journal from his many friends around the globe. A journal that would provide a unique publication platform for those colleagues who would not easily be able to publish their results in higher-ranked journals.Subsequently, he founded the World Journal of Nuclear Medicine (WJNM) which was lounged in 2002. Since then the WJNM was registered and produced in New Dehli, India, and indexed under his name.

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The problems of governmental and industrial supply in many developing countries of the world bothered him a lot. Ajit Padhy was a Nuclear Medicine therapy man despite of being an all-in-through Nuclear Medicine physician. Thyroid disease projects, especially thyroid cancer throughout the world were of his primary interest. Bringing people together from around the world was his goal and to implement the Nuclear Medicine therapy worldwide. The WFNMB was moving around the world with congresses but did not provide much support for the younger colleagues from developing countries. Ajit`s goal was to train the younger colleagues, encourage them and educate them for a better future. Make things possible where there is no way, give them a little hand, a bit of money from the own pocket. Engage them into research projects, encourage them to prepare an abstract. Give them a bit, they would be so happy and proud and make something out of nothing, have a step and start moving towards a better world. The WARMTH indeed has many testamonies that this concept works for the individual and certainly may subsequently affect families and friends.

Quickly Ajit Padhy had decided that he would dedicate his work at the IAEA to nuclear therapy, that there is a lack of training facilities and education in the field especially for people of the developing world. Subsequently, the 1st ICRT was soon assigned and took place in Limassol, Cyprus in 2005, which was then followed by many other meetings – more the less annually – until today. Clearly, the separation from The WFNMB was performed successfully and many members of the WFNMB also became members of The WARMTH later on, attending the annual ICRT´s and making friendships in The WARMTH network.

Ait Padhy in his congress invitation letter for the 2nd ICRT-2007 in Ulaanbaator, Mongolia mailed to me "*The meetings organized by the World Radiopharmaceutical Therapy Council (WRPTC) are clearly conceptually different from all other conferences. There is no registration fee. Everyone pays for himself or herself to attend the congress. We try to keep the expenses as low as reasonably possible so that professionals from all parts of the world and from all levels of nuclear medicine practice can attend. All participants stay in the same hotel. There are no parallel sessions. All participants participate in all scientific activities of the conference. All participants participate in all social activities as well. All in all these meetings are the "meetings of friends", belonging to the global nuclear medicine family*".

While the ICRT´s were the major meetings of the increasing number of participants the idea of founding a separate scientific society took a while. In fact, the WRPTC under the chair of Ajit Padhy (Co-Chairmen were Alan Perkins, UK and Richard Baum, Germany) met in Cartagena, Colombia, for the 4th ICRT-2009 during the ALASBIMN congress chaired by Patricia Bernal, Colombia. Some considerations were the existing larger societies and industrial support for a new society, and also that the time of Ajit Padhy at the IAEA was ending in 2006 after a duration of seven years as officers at the IAEA are not easily contracted for live-long. This meeting in Cartagena was only later renamed by me as "ICRT-2009".

Ajit Padhy noted in his invitation letter for Cartagena emailed to me: "*Upon the second Members' Assembly of WRPTC, which was held during the First International Symposium on Radiopharmaceutical Therapy (ISRT-2008) in Goa, India, on 30th October 2008; approval was given for the formation of a larger and more democratic International Organization to replace World Radiopharmaceutical Therapy Council (WRPTC). The new organization will be called **W**orld **A**ssociation of **R**adionuclide & **M**olecular **TH**erapy (WARMTH); it will be inaugurated at Cartagena during the ICRT-2009. I would invite you to participate in the next Members' Assembly of our organization and **witness the historic event of "birth of WARMTH"**.*

The constitution of The WARMTH was subsequently approved by the (1) General Assembly of the WRPTC, held on 4th November 2009 at Cartagena, Colombia, and was then (2) subsequently approved and adopted by the 1st General Assembly of WARMTH, which was held on 7th November 2009 at Cartagena, Colombia.

The WARMTH was then subsequently registered in New Dehli, India (Registration No:/S 84634, registered under the Societies` Registration Act of 1860). The immediate address of WARMTH in 2009 was the Department of Nuclear Medicine & PET, Max Devki Devi Heart & Vascular Institute, Saket, New Delhi, India.

A revised version of the Constitution of The WARMTH was presented to, and subsequently approved and adopted by, the General Assembly of WARMTH, which was held on the 6th May 2015 during the 10th ISRT at Innsbruck, Austria.

Following ongoing discussions on the Indian tax system, under the presidency of Suresh Srivastava, USA (2017 - 2018), the move of The WARMTH from India to the USA was finally adopted and approved by The WARMTH General Assembly during the ICRT-2017 held in Vienna, Austria. Following the agreement all members of The WARMTH society registered in India became members of the WARMTH society registered in the State of Delaware, USA, The **„WARMTH Inc"**!

The ICRTs of The WARMTH

ICRT	LOCATION	CONGRESS PRESIDENT
1st ICRT-2005	Limassol, Cyprus	Ajit Padhy, Savvas Frangos
2nd ICRT-2007	Ulaanbaatar, Mongolia	Ajit Padhy, Sereegotov Erdenechimeg
3rd ICRT-2008 = ISRT	Goa, India	Ajit Padhy
4th ICRT-2009 = ISRT	Cartagena, Colombia	Ajit Padhy, Patricia Bernal
5th ICRT-2010 =ISRT+WFNMB	Capetown, South Africa	Ajit Padhy, Annare Ellmann
6th ICRT-2011	Ho Chi Min City, Vietnam	Ajit Padhy, Nguyen Chau
7th ICRT-2012	Levi, Finland	Ajit Padhy, Kairemo Kalevi
8th ICRT-2013	Manila, Philippines	Emerita Barrenechia
9th ICRT-2014 +WFNMB	Cancun, Mexico	Richard Baum, Horacio Amaral
10th ICRT-2015	Innsbruck, Austria	Irene Virgolini
11th ICRT-2016	Kochi, India	Partha Choudhary
12th ICRT-2017 +IAEA	Vienna, Austria	Irene Virgolini, Diana Paez
13th ICRT-2018 +WFNMB	Melbourne, Australia	Irene Virgolini, Sze Ting Lee
14th ICRT-2019	Nanjing, China	Feng Wang
15th ICRT-2020	Coxbasar, Bangladesh (virtual)	Raihan Hussain
16th ICRT-2021 + ALASBIMN	South America (virtual)	Partha Choudhary, Mariela Agolti
17thICRT-2022 +WFNMB	Kyoto, Japan	Mike Sathekge, Seigo Kinuya

1st ICRT-2005, Limassol, Cyprus

Window on World Radiopharmaceutical Therapy

INTERNATIONAL CONFERENCE ON
RADIOPHARMACEUTICAL THERAPY (ICRT-2005)

Organized by:
World Radiopharmaceutical Therapy Council (A Subsidiary body of WFNM&B)
Limassol, Cyprus, 11-14 October 2005

You are most cordially invited

Important Information

Dates: 11-14 October 2005
Venue:
St. Raphael Resort
Limassol, Cyprus
Conference web address:
http://www.nucleardiagnostics.com.cy/
and follow the link: ICRT-2005

For Details Please Contact:

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World Journal of Nuclear Medicine, Volume 4, Number 2, April 2005

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2nd ICRT-2007, Ulaanbaatar, Mongolia

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4th ICRT-2009, Cartagena, Colombia

Congress President: Patrica Bernal Trujillo

WORLD RADIOPHARMACEUTICAL THERAPY COUNCIL (WRPTC)

A Subsidiary Body of World Federation of Nuclear Medicine & Biology (WFNMB)

3rd INTERNATIONAL CONFERENCE ON
RADIOPHARMACEUTICAL THERAPY (ICRT-2009)

Cartagena, Colombia, 3-7 November 2009

Invited Lectures

Targeted drug delivery systems for Imaging Purposes	Prof. Kalevi Kairemo (Finland)
PBPK modeling for dosimetry of nonclinical and clinical radioimmunotherapy	Prof. Kalevi Kairemo (Finland)

Poster Presentations

Scintigraphy and modelling time activity curves of salivary glands after IMRT for Head & Neck Cancer	Dr. Kalevi Kairemo (Finland)

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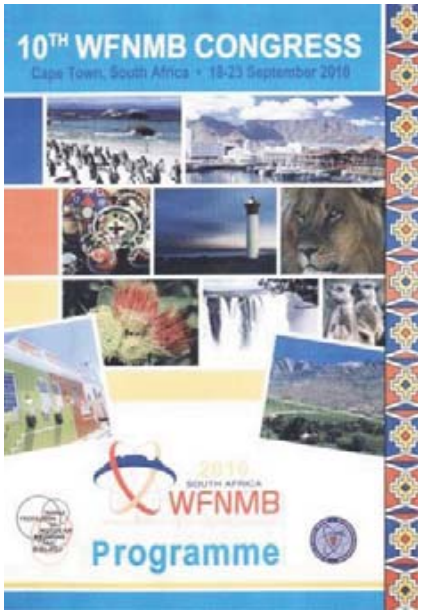
5th ICRT, Capetown September 18-23, 2010



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2ND INTERNATIONAL SYMPOSIUM ON RADIOPHARMACEUTICAL THERAPY
ISRT-2010

IN CONJUNCTION WITH THE 10th WORLD CONGRESS OF WFNMB
CAPE TOWN, SOUTH AFRICA

PART-1
21 September 2010 (08.00-13.00 hrs)

10.00 – 11.30 Scientific Session-2: Plenary Lectures
Chairpersons: Prof. G. Wisemann (USA), Prof. Kalevi Kairemo (Finland)

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6th ICRT-2011, Ho Chi Min City, Vietnam

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7th ICRT-2012, Levi, Finland

Congress-President: Kalevi Kairemo

"The idea of having WARMTH conference in the Cold was presented first time in Cartagena 2009. This idea got a great welcome. Anyhow, final decision was made in Capetown 2010. The original plan was to arrange it in November 2011, but it was postponed until 2012 because of a higher probability for Northern Lights. The time in November 2012, was chosen because of full moon, beginning of dark season and guaranteed snow. The practical limiting factor was the alpine skiing season, because World cup typically starts in Levi, also in 2012/2013. Additionally European Alpine cup has competitions in Levi, but we succeeded in finding the one week time slot.
In the Levi facility, winter is a guaranteed success. In November 2012, there was more than 150 cm snow, and the first snow brought light and new energy after the autumn darkness. The conference venue Levi Summit Conference and Exhibition Center, is located on the fell, in the leading winter holiday resort in Finland, which is located in the Northern part of the country, in the so called Fell-Lapland, about 170 km north from the Arctic Circle in the middle of pure and wild nature. All the multiple and high quality facilities, from luxury accommodation to high-class restaurants and souvenir shops, are within walking distance from each other and the unspoiled nature is just around the corner. The population density in Lapland is approximately 1 person per 2 km², meaning that all the equipment had to be brought from Helsinki or other cities.
In the Levi conference, the temperature varied from +1 – - 24 C, and there was 1-1.5 m snow everywhere. The best transportation from the conference center down to the village was by ski lift"

Candle Lighting Ceremony 26.11.2012 in Levi. *Watanabe (JPN), Elgazzar (EGY/KUW), Padhy (IND/SIN), Turner (AUS), Kairemo (FIN), Baum (GER), Bernal (COL), Srivastava (USA) and Dougal (IND)*

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ICRT 2012 — 7th International Conference on Radiopharmaceutical Therapy
Levi, Finland
25 – 29 November 2012

Venue: Levi Summit Conference Centre, Levi, Finland

DAY 1: SUNDAY, 25 NOVEMBER 2012

0900 – 1600	**REGISTRATION**	
1430 – 1605	**SCIENTIFIC SESSION 1: PRE-CONFERENCE SYMPOSIUM ON NUCLEAR CARDIOLOGY**	Auditorium, Ground Floor
	Session Chairpersons: 1. Dr Pankaj Dougall, Nuclear Medicine and PET-CT, Max Super Speciality Hospitals, New Delhi, India 2. Dr Kok Tian Yue, Nuclear Medicine and PET, Singapore General Hospital, Singapore	
1430 – 1455 PC-1	**Myocardial Viability – Implications for Clinicians** Dr Carlos D Libhaber, Nuclear Medicine, University of the Witwatersrand, Chris Hani Baragwanath Hospital, Johannesburg, South Africa	
1455 – 1520 PC-2	**Role of Radionuclide Imaging in Heart Failure** Prof Zuo-Xiang He, Nuclear Medicine, Fu Wai Hospital & Cardiovascular Institute, Beijing, China	
1520 – 1540 PC-3	**New Experimental Tracers for Myocardial Ischemia** Prof Henry Bom, Nuclear Medicine, Chonnam National University Hospital, Jeonnam, Korea	
1540 – 1605 PC-4	**Assessment of Cardiac Dyssynchrony: A Nuclear Approach** Prof Chetan Patel, Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India	
1605 – 1630	**COFFEE / TEA / TRADE EXHIBITION**	
1630 – 1830	**SCIENTIFIC SESSION 2: PRE-CONFERENCE SYMPOSIUM ON ARCTIC ENVIRONMENT**	Auditorium, Ground Floor
	Session Chairpersons: 1. Prof Mauri Yla-Kotola, University of Lapland, Finland 2. Prof Kalevi Kairemo, Molecular Radiotherapy & Nuclear Medicine, Internationational Comprehensive Cancer Center Docrates, Helsinki, Finland	
1630 – 1655 PC-5	**Hospitals, Hospitality and Hosting Health – An Arctic Avenue** Prof Johan Edelheim, Multidimensional Tourism Institute, University of Lapland, Rovaniemi, Finland	
1655 – 1705 PC-6	**Human Thermal Responses During Reindeer Safaris in Cold** Dr Susanna Paakkola, Arctic Centre, University of Lapland, Rovaniemi, Finland	
1705 – 1730 PC-7	**Northern Lights Through the Eyes of a Space Scientist** Prof Thomas Ulich, Director, Sodankyla Geophysical Observatory, University of Oulu, Oulu, Finland	
1730 – 1745 PC-8	**Glaciological Research in Svalbard** Dr Martina Schafer, Arctic Centre, University of Lapland, Rovaniemi, Finland	
1745 – 1805 PC-9	**Arctic Sculptures, Snow & Ice** Prof Timo Jokela, University of Lapland, Rovaniemi, Finland	
1805 – 1830 PC-10	**Many Faces of Love** Prof Kaarina Maatta, University of Lapland, Rovaniemi, Finland	
1930 – 2200	**WELCOME DINNER**	Restaurant Okta, Ground Floor Hotel Levi Panorama
2200	**END OF DAY 1**	

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DAY 2: MONDAY, 26 NOVEMBER 2012

P-7	**Bone Metastases from Differentiated Thyroid Carcinoma: Clinical Features and Long Term Follow Up** Dr Nurun Nahar, et al (Bangladesh)	
P-8	**Salivary Gland Tumor After Radioiodine Therapy for Well Differentiated Thyroid Carcinoma: A Case Report** Prof Lutfun Nisa, et al (Bangladesh)	
P-9	**Radioactive Iodine Ablation in Children and Adolescents with Differentiated Thyroid Carcinoma** Dr Yusta Tuti Jatari, et al (Indonesia)	
P-10	**The Advantages of Routine Radiothyroablation in Well Differentiated Thyroid Carcinoma Patients** Dr Hapsari Indrawati, et al (Indonesia)	
P-11	**Clinical Outcome of Differentiated Thyroid Carcinoma with Lymph Node Metastasis : A Retrospective Analysis of Patients Treated at a Single Institute** Dr Faria Nasreen, et al (Bangladesh)	
P-12	**Papillary Thyroid Carcinoma after Maximum Radioiodine Therapy with Persistent Disease (A Case Study)** Dr Ryna Z Marliana, et al (Indonesia)	
P-13	**Clinical Behavior of Follicular Variant of Papillary Thyroid Carcinoma at INMU** Dr Sadia Sultana, et al (Bangladesh)	
P-14	**Detection and Treatment of Lung Metastases in Differentiated Thyroid Carcinoma** Dr Zeenat Jabin, et al (Bangladesh)	
P-15	**Clinical Significance of Thyroglobulin Antibody Pattern in Patients with Differentiated Thyroid Carcinoma: Preliminary Study** Dr Ivana Dewi Mulyanto, et al (Indonesia)	
P-16	**Two Cases with Unusual Uptake in the Whole Body Scan with Radioiodine 131: Textiloma; Miliary Tuberculosis** Dr Ben Rais Aouad Nozha, et al (Morocco)	
P-17	**A Rare Pediatric Case of Metastatic Papillary Thyroid Carcinoma in the Brain** Dr Karina Michaela Dela Cruz, et al (Philippines)	
P-18	**Diagnostic Difficulty Due to Incidental Fibrous Dysplasia in a Patient with Metastatic Follicular Thyroid Cancer and the Possible Association of these Entities with McCune Albright Syndrome** Dr Sumbul Zaheer, et al (Singapore)	
P-19	**The Value of PET/CT in the Diagnosis and Therapy of Thyroid Cancer** Dr Emerita Barrenechea, et al (Philippines)	
P-20	**Radioiodine Treatment for Thyrotoxicosis in Childhood and Adolescence: Treatment and Outcome** Dr Sirianong Namwongprom, et al (Thailand)	
P-21	**Follow-up of High Risk Thyroid Cancer Patients with Bone and Lung Metastases** Dr Rosanna Morales, et al (Peru)	
P-22	**Low Dose Radioiodine Ablation for Differentiated Thyroid Carcinoma (DTC) - A Retrospective Analysis** Dr Damayanthi KK Nanayakkara, et al (Sri Lanka)	
P-23	**Clinical Outcome of Radioactive Iodine Therapy Among Patients with Hyperthyroidism in St. Luke's Medical Center-Philippines** Dr Irene Bandong, et al (Philippines)	
P-24	**Hürthle Cell Carcinoma – The Nuclear Medicine Specialist Point of View** Dr Ana Ugrinska, et al (Macedonia)	
P-25	**Role of Thyroglobulin (Tg) Level and Whole-Body Scan (WBS) After I-131 Therapy in Patients with Differentiated Thyroid Cancer** Dr Shankar Biswas, et al (Bangladesh)	
P-26	**Potential Response of Grave's Disease Associated with Thymic Hyperplasia After Radioactive Iodine 131 Therapy: A Case Report** Dr Bonan A. Mendoza, et al (Philippines)	
P-85	**Experience with 30 mCi Iodine-131 Ablation Therapy for DTC in Sarawak General Hospital** Dr Dahlia Saidin, et al (Malaysia)	

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DAY 2: MONDAY, 26 NOVEMBER 2012

0800 – 1600	**REGISTRATION**	
0830 – 0900	**SCIENTIFIC SESSION 3: OPENING**	Auditorium, Ground Floor
	Welcome Prof Kalevi Kairemo, Local Organising Chairman, ICRT 2012	
	Opening Remarks Prof Ajit Kumar Padhy, International Organising Chairman, ICRT 2012 & President-WARMTH	
	WARMTH Candle Lighting Ceremony Prof Harvey Turner, Prof Ajit Kumar Padhy, Prof Richard P Baum, Prof Alan Perkins, Prof Kalevi Kairemo & Other Members of WARMTH Governing Body	
0900 – 1100	**SCIENTIFIC SESSION 4: THYROID DISEASES I**	Auditorium, Ground Floor
	Session Chairpersons: 1. Prof Mike Sathekge, Nuclear Medicine, University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa 2. Prof Ralph McCready, Nuclear Medicine, Royal Sussex County Hospital, Brighton, United Kingdom	
0900 – 0920 S-1	**Subclinical Hyperthyroidism – To Treat or Not to Treat with Radioiodine** A/Prof Grzegorz Kaminski, Endocrinology & Radioisotope Therapy, Military Institute of Medicine, Warsaw, Poland	
0920 – 0940 S-2	**Graves' Ophthalmopathy & Radioiodine Therapy** Dr Emerita Barrenechea, Nuclear Medicine, Veterans Memorial Medical Centre, Quezon City, Philippines	
0940 – 1000 S-3	**Thyroid Cancer and Nuclear Accident** Prof Naoyuki Watanabe, Radiological Sciences, Gunma Prefectural College of Human Health, Maebashi, Japan	
1000 – 1020 S-4	**Use of Rh-TSH (Thyrogen) in Thyroid Cancer – A Review** Dr Sze Ting Lee, Nuclear Medicine & PET, Ludwig Institute for Cancer Research, Heidelberg, Australia	
1020 – 1040 S-5	**Modern Imaging in Detection of Iodine Negative-Tg Positive Differentiated Thyroid Cancer** Prof Jasna Mihailovic, Nuclear Medicine, Oncology Institute of Vojvodina, Novi Sad, Serbia	
	ORAL PRESENTATIONS	Auditorium, Ground Floor
1040 – 1050 O-1	**Efficacy of Different Protocols of Radioiodine Therapy for Treatment of Toxic Nodular Goiter: Systematic Review and Meta-Analysis of the Literature** Dr R Zakavi, et al (Iran)	
1050 – 1100 O-2	**Early Radioiodine Ablation Post Thyroidectomy with Recombinant TSH (r-TSH) Stimulation and its Impact on Performance Status, Versus Thyroxine Abstinence Protocol in Differentiated Thyroid Carcinoma : Initial Results of a Randomized Prospective Clinical Trial** Dr P Choudhary, et al (India)	
1100 – 1130	**COFFEE / TEA / TRADE EXHIBITION**	
1100 – 1130	**POSTER PRESENTATIONS**	
	Session Coordinators: 1. Dr Ruben Ogbac, Nuclear Medicine, St Luke's Medical Center, Quezon City, Philippines 2. Dr Erdenechimeg Sereegotov, Nuclear Medicine, First Central Hospital, Ulaanbaatar, Mongolia	
P-1	**What is the Alternative to Radioiodine Therapy in Diffuse Pulmonary Metastasis from Papillary Thyroid Carcinoma in Children** Dr Kaouthar Chatti, et al (Tunisia)	
P-2	**Thyroid Cancer Treated at the Clinical Center Banja Luka. A Review of 5 Years Experience** Dr Zvezdana Rajkovaca, et al (Serbia)	
P-3	**Optimization of 90Y-antiCD20 Preparation for Radioimmunotherapy** Dr Amir R Jalilian, et al (Iran)	
P-4	**Optimized Preparation of [64Cu]-DOTA-Trastuzumab for PET Applications** Dr Amir R Jalilian, et al (Iran)	
P-5	**Significance of Post-Therapy SPECT-CT Scan in Differentiated Thyroid Cancer** Dr Rajesh Kumar, et al (India)	
P-6	**Patient's Specific Dosimetry for Radioiodine Therapy of Thyroid Cancer and Comparison with Fixed Doses** Dr Noreen Marwat, et al (Pakistan)	

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DAY 2: MONDAY, 26 NOVEMBER 2012

1130 – 1305	**SCIENTIFIC SESSION 5: BONES & JOINTS / METASTATIC BONE PAIN PALLIATION**	Auditorium, Ground Floor
	Session Chairpersons: 1. Prof Izak Garty, Nuclear Medicine, Central Emek Hospital, Afula, Israel 2. Dr Sze Ting Lee, Nuclear Medicine & PET, Ludwig Institute for Cancer Research, Heidelberg, Australia	
1130 – 1150 S-10	**Intermittent Pneumatic Compression: Effect on MDP Uptake – A Potential Method to Facilitate Therapy** Prof Abdelhamid Elgazzar, Medical Faculty, University of Kuwait, Safat, Kuwait	
1150 – 1210 S-11	**Radionuclide Imaging of Bone Metastases: Science & Practice** Dr Gopinath Gnanasegaran, Nuclear Medicine, Guy's & St Thomas Hospital NHS Foundation Trust, London, United Kingdom	
1210 – 1225 S-60	**Radiosynovectomy-Procedure Review and Description of A Multicentre Study to Measure the Safety and Efficacy of Radiosynovectomy Performed with Y-90 Citrate Colloid and Re-186 Sulfide** Dr James Warrington, Nuclear Medicine, London Health Sciences Centre, London, Canada	
1225 – 1245 S-12	**Radiosynovectomy in the Treatment of Arthritis** Dr Knut Liepe, Nuclear Medicine, GH Kassel, Kassel, Germany	
1245 – 1305 S-19	**Assessing Tuberculosis Response to Therapy** Prof Mike Sathekge, Nuclear Medicine, University of Pretoria & Steve Biko Academic Hospital, Pretoria, South Africa	
1305 – 1400	**LUNCH / TRADE EXHIBITION**	Restaurant Okta, Ground Floor Hotel Levi Panorama
1400 – 1600	**WARMTH GOVERNING BODY MEETING (GOVERNING BODY MEMBERS ONLY)**	
1400 – 1613	**SCIENTIFIC SESSION 6: THYROID DISEASES II**	Auditorium, Ground Floor
	Session Chairpersons: 1. Dr Knut Liepe, Nuclear Medicine, GH Kassel, Kassel, Germany 2. Dr Achmad Hussein Sundawa Kartamihardja, Nuclear Medicine, Dr Hasan Sadikin General Hospital, Bandung, Indonesia	
1400 – 1425 S-7	**Clinical Role of F-18 FDG PET/CT for Differentiated Thyroid Cancer Before and After High Dose I-131 Therapy** Prof Henry Bom, Nuclear Medicine, Chonnam National University Hospital, Jeonnam, Korea	
1425 – 1445 S-8	**Role of SPECT-CT in Diagnosis, Staging and Follow Up of Patients with Thyroid Diseases** Dr Sonya Sergieva, Nuclear Medicine, Sofia Cancer Center, Sofia, Bulgaria	
1445 – 1500 S-9	**Management of Differentiated Thyroid Cancer: A Single Centre Experience & Lessons Learnt in the Last 20 Years** Dr Shazia Fatima, Nuclear Medicine, Nuclear Medicine, Oncology & Radiotherapy Institute, Islamabad, Pakistan	
1500 – 1525 S-6	**Therapeutic Approaches in Thyroid Cancer – What is Next to Standard Treatment?** Dr Daniel Putzer, Nuclear Medicine, Medical University Innsbruck, Innsbruck, Austria	
	ORAL PRESENTATIONS	Auditorium, Ground Floor
1525 – 1533 O-3	**Clinical Significance of Measurement of Serum Anti Thyroglobulin Antibodies (ATgAb) in the Follow Up of Differentiated Thyroid Carcinoma** Dr Javaid Irfan, et al (Pakistan)	
1533 – 1541 O-4	**Consequences of Misadministration in Handling of Radiopharmaceuticals** Prof Ajai Kumar Shukla (India)	
1541 – 1549 O-5	**Experience with 177Lu-EDTMP Regarding Improvement in Quality of life and Bone Pain Palliation** Dr Ghazal Jameel, et al (Pakistan)	
1549 – 1557 O-6	**Hydroxyapatite Particles Labelled with Beta-Emitting Lanthanoids for Radiosynovectomy** Dr Mohammad Sohaib, et al (Pakistan)	
1557 – 1605 O-7	**The Pilot Study To Evaluate the Effectiveness of Radiosynoviorthesis (RSO) of Sacro-iliac Joints with Re-186** Dr Marika Vereb, et al (Germany)	
1605 – 1613 O-8	**Radiation synovectomy with Yttrium (90Y) Citrate in rheumatoid arthritis patients- 5 years of follow up** Dr Ljiljana Jaukovic, et al (Serbia)	

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1413 – 1630 COFFEE / TEA / TRADE EXHIBITION / TRADE EXHIBITION

1413 – 1630 POSTER PRESENTATIONS

Session Coordinators:
1. Dr Ana Ugrinska, Institute of Pathophysiology and Nuclear Medicine, Skopje, Macedonia
2. Dr Arne Pokel, Nuclear Medicine Centre, East-Tallinn Central Hospital, Tallinn, Estonia

P-27 Effectiveness of Radiation Synoviorthesis with 153Sm (SIT) Citrate Related to Preexisting Radiological Damage in Rheumatoid Arthritis Patients
Dr Boris Aghinotis, et al (Serbia)

P-28 Treatment Efficacy of Sm-153 Lexidronate for Pain Management of Bone Metastases: The First Experience in Iran
Dr Nasser-Khalesi Ayati, et al (Iran)

P-29 Clinical Characteristics, Efficacy of I-131 Therapy and Outcome of Patients with Differentiated Thyroid Cancer having Bone Metastases – A Retrospective Study
Dr Sadaf Butt, et al (Pakistan)

P-30 Production, Quality Control and Biological Evaluation of 153Sm-lorPSTMP and 153Sm-TTHMP as a Possible Bone Palliation Agent
Dr Zahish Nasser, et al (Iran)

P-31 Effectiveness of Strontium-89 Therapy in Multiple Bony Metastases Patient with CA. Breast and CA.Prostate
Dr Om Prakash Sinha, et al (India)

P-32 A Study on Strontium-89 Irradiation for Treatment of Post-Operative Conjunctival Squamous Cell Carcinoma
Prof Rakhan Hussain, et al (Bangladesh)

P-33 The Synthesis, Radiolabeling and First Biological Evaluation of a New 188Re-Complex for Radiotherapy of Bone Metastases
Dr Samaneh Zolghadri, et al (Iran)

P-34 Post- Therapy Procedures and Imaging Properties of Samarium-153 vs Strontium-89
Mr Roy Martin A Dizon, et al (Philippines)

P-35 Semi-Quantitative Estimation of Samarium-153 Oxadrone Therapy Results of Metastatic Bone Disease in Mono - Regime and in Combination with Bisphosphonates
Dr Nigora Rasulova, et al (Uzbekistan)

P-36 Preparation and Biodistribution of 89mTc and 188Re Labeled Zoledronic Acid
Dr Olga Klimentyeva, et al (Russia)

P-37 Radiopharmaceutical Based on Monopotassium Salt of Hydroxyethilendiphosphonic Acid Labeled with 188Re for Therapy of Bone Metastases
Dr Vasiliy Petrov, et al (Russia)

P-38 Potential Role of Semi-Quantitative Analyses of Bone Metastases in Evaluation of Radionuclide Therapy Response
Dr Nigora Rasulova, et al (Uzbekistan)

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Levi, Finland
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DAY 2: MONDAY, 26 NOVEMBER 2012

1530 – 1650 SCIENTIFIC SESSION 7: MOLECULAR IMAGING & RADIONUCLIDE THERAPY Auditorium, Ground Floor

Session Chairpersons:
1. Dr Michael Tumbiger, Radiation Oncology, H. Lee Moffitt Cancer Center, Tampa, USA
2. Dr William Macdonald, Nuclear Medicine, Royal Perth Hospital, Perth, Australia

1630 – 1650 S-14 Potentially required number of PET apparatus in Asia and Latin America including Mexico
Prof Naoyuki Watanabe, Radiological Sciences, Gunma Prefectural College of Human Health, Maebashi, Japan

1650 – 1710 S-15 Treatment Response Evaluations using current imaging modalities
Prof Rakesh Kumar, Nuclear Medicine, All India Institute of Medical Sciences, New Delhi, India

1710 – 1730 S-16 Actinidine – A Novel Approach for Targeting Prostate and Ovarian Cancer
Prof Andrew Scott, Nuclear Medicine & PET, Ludwig Institute for Cancer Research, Heidelberg, Australia

1730 – 1750 S-17 Percutaneous Radionuclide Therapy (PERTH)
Prof Ralph McCready, Nuclear Medicine, Royal Sussex County Hospital, Brighton, United Kingdom

1750 – 1810 S-18 Current Status of PET Radiopharmaceuticals in PET/CT Guided Radiotherapy Treatment Planning
Dr Antonija Bosnjakovic, PET/CT Center, Poliklinika Medikol, Zagreb, Croatia

1810 – 1830 S-19 Development of New Radiopharmaceuticals for Diagnosis and Treatment of Arthritis
Prof Vijay Kumar, Nuclear Medicine & PET, Westmead Hospital, Sydney, Australia

1930 – 2300 FUTSAL INAUGURAL CEREMONY Restaurant Tamas

- WARMTH Awards
- Dinner

2300 END OF DAY 2

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DAY 3: TUESDAY, 27 NOVEMBER 2012

0810 – 0850 SCIENTIFIC SESSION 8: WARMTH: HISTORY, FUTURE PERSPECTIVES & INTERNATIONAL COLLABORATIONS Auditorium, Ground Floor

Session Chairpersons:
1. Prof Harvey Turner, Nuclear Medicine, Fremantle Hospital, Fremantle, Australia
2. Dr Suresh Srivastava, Collider-Accelerator Department, Brookhaven National Laboratory, New York, USA

0810 – 0830 S-20 History of WARMTH
Prof Ajit Kumar Pathy, Nuclear Medicine & PET, Singapore General Hospital, Singapore

0830 – 0850 S-21 IAEA Perspectives on Radionuclide Therapy
Prof Adriana Duatti, Nuclear Applications, IAEA, Vienna, Austria

0850 – 0910 S-22 WFNMB Perspectives on Radionuclide Therapy
Prof Andrew Scott, President Elect, WFNMB (2014-2018), Australia

0910 – 0930 S-23 Future Prospects of Radionuclide Therapy in Korea
Prof Dong Soo Lee, Nuclear Medicine, Seoul National University Hospital, Seoul, Korea

0930 – 1105 SCIENTIFIC SESSION 9: NEURO-ENDOCRINE TUMORS I Auditorium, Ground Floor

Session Chairpersons:
1. A/Prof Grzegorz Kaminski, Endocrinology & Radionuclide Therapy, Military Institute of Medicine, Warsaw, Poland
2. Dr Vikram Lele, Director, Nuclear Medicine, Jaslok Hospital & Research Centre, Mumbai, India

0930 – 0955 S-24 Personalized Radionuclide Therapy of Cancer – Will It Remain a Dream or Become Reality?
Prof Richard P Baum, THERANOSTICS Center for Molecular Radiotherapy/Imaging, Zentralklinik Bad Berka, Bad Berka, Germany

0955 – 1020 S-25 Innsbruck Medical University: Long-term Results in Patients Undergoing Peptide Receptor Radionuclide Therapy (PRRT)
Prof Irene Virgolini, Nuclear Medicine & PET, Medical University of Innsbruck, Innsbruck, Austria

1020 – 1045 S-26 MITA: Labeled Somatostatin Analogues in Therapy
Dr Chiara Grana, Nuclear Medicine, European Institute of Oncology, Milano, Italy

1045 – 1105 S-27 Clinical Trial Evaluation of Radiopeptide Therapy of Neuroendocrine Tumours
Prof Harvey Turner, Nuclear Medicine, Fremantle Hospital, Fremantle, Australia

1105 – 1130 COFFEE / TEA / TRADE EXHIBITION / TRADE EXHIBITION

1105 – 1130 POSTER PRESENTATIONS

Session Coordinators:
1. Dr Martha Yondo, Nuklearmedizin, Klinikum Kassel, Kassel, Germany
2. Dr Masita Mahana, Nuclear Medicine, Polokwane Provincial Hospital, University of Limpopo, Pietersburg, South Africa

P-39 Selective Internal Radiation Therapy using 131Iodine-MI Microspheres: A Practical Demonstration of Personalised Artery Specific Dosimetric Modelling
Ms Toh Ying, et al (Singapore)

P-40 Production and Quality Control of [188 Re]-EDTA-Bevacizumab for Therapeutic Applications
Dr Alireza Khanlarei, et al (Iran)

P-41 Assessment of Human Effective Absorbed Dose of 67Ga-EDC Based on Biodistribution Rat Data
Dr Hassan Yousefnia, et al (Iran)

P-42 Radiation Safety Consideration in MIT- Microsphere Therapy
Dr Ashish Jha, et al (India)

P-43 SPECT/CT & PET-CT in Imaging Neuroendocrine Tumours: Pearls and Pitfalls
Dr Sadia Salam, et al (Bangladesh)

P-44 Fast Preparation of 131I-MIBG for Therapy Purposes in Nuclear Medicine
Dr Ali Sahari, et al (Iran)

P-45 Ga-68 DOTATATE PET/CT in Tumour-Induced Osteomalacia
Dr Ahmad Al Tamimi, et al (Singapore)

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P-46 Safety and Efficacy of Peptide Receptor Radionuclide Therapy after Liver Transplantation in Progressive Neuroendocrine Neoplasms
Dr Harshad Kulkarni, et al (India)

P-47 Role of Ga-68 Somatostatin Receptor PET-CT in the Determination of Molecular Response to Radiofrequency Ablation of Hepatic Metastases from Neuroendocrine Neoplasms
Dr Harshad Kulkarni, et al (India)

P-48 Octreo it or Not! Renal Function can Actually Improve after Peptide Receptor Radionuclide Therapy
Dr Harshad Kulkarni, et al (India)

1130 – 1155 SCIENTIFIC SESSION 10: NEURO-ENDOCRINE TUMORS II / LYMPHOMA Auditorium, Ground Floor

Session Chairpersons:
1. Prof Richard P Baum, THERANOSTICS Center for Molecular Radiotherapy/Imaging, Zentralklinik Bad Berka, Bad Berka, Germany
2. Prof Bozena Birkenfeld, Nuclear Medicine, Uni Lubelskiej, Szczecin, Poland

1130 – 1150 S-28 An Update on PRRT in India
Dr Vikram Lele, Nuclear Medicine, Jaslok Hospital & Research Centre, Mumbai, India

1150 – 1210 S-29 Somatostatin Analogs as Possible Theragnostic Molecules for Advanced Prostate Cancer
Prof Omar Alonso, Nuclear Medicine, Clinical Hospital, University of Uruguay, Montevideo, Uruguay

1210 – 1230 S-30 Phase II Study of First-Line Ludine-131-Rituximab Radioimmunotherapy of Follicular Non-Hodgkin Lymphoma: The INITIAL Study
Dr William Macdonald, Nuclear Medicine, Royal Perth Hospital, Perth, Australia

1230 – 1250 S-31 Low-Dose, Involved Field Radiotherapy Just Prior to Radioimmunotherapy for Relapsed/Refractory B-Cell Lymphoma
Dr Michael Tondiger, Radiation Oncology, H. Lee Moffit Cancer Center, Tampa, USA

1250 – 1310 S-32 Radioimmunotherapy (RIT) of Follicular Non Hodgkin's Lymphoma (FNHL): The State of the Art
Prof Irak Gafty, Nuclear Medicine, Central Emek Hospital, Afula, Israel

1310 – 1400 LUNCH / TRADE EXHIBITION Restaurant Oleta, Ground Floor; Hotel Levi Panorama

1400 – 1540 SCIENTIFIC SESSION 11: DOSIMETRY / RADIOPHARMACY Auditorium, Ground Floor

Session Chairpersons:
1. Prof Frank Roesch, Institute of Nuclear Chemistry, University of Mainz, Mainz, Germany
2. Prof Vijay Kumar, Nuclear Medicine & PET, Westmead Hospital, Sydney, Australia

1400 – 1420 S-3 Paving the Way to Personalized Medicine for Treatment of Cancer and Inflammatory Disorder
Dr Suresh Srivastava, Collider-Accelerator Department, Brookhaven National Laboratory, New York, USA

1420 – 1430 S-61 Cu-117m-DOTA-Annexin for Imaging and Treating Vulnerable Plaque
Dr Gilbert Gonzales, Collider-Accelerator Department, Brookhaven National Laboratory, New York, USA

1430 – 1440 What it takes to Build a Radiopharmaceutical Product in the Age of Dwindling Financial support
Dr Immanuel Thangiya, Essex Woodlands Health Ventures, (EWHV), USA

1440 – 1500 S-34 Personalized Image-Based Dosimetry for Radionuclide Therapies
Prof Anna Celler, Radiology, UBC, VGH Research Pavilion, Vancouver, Canada

1500 – 1520 S-35 A New Approach of Individual Dosimetry
Dr Matthias Blaickner, Health & Environment Department, Biomedical Systems, AIT Austrian Institute of Technology, Vienna, Austria

1520 – 1540 S-36 New Options to Label Biomolecules with Trivalent Radiometals Adding Non-Aqueous Solvents
Prof Frank Roesch, Institute of Nuclear Chemistry, University of Mainz, Mainz, Germany

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1540 – 1600	**COFFEE / TEA / TRADE EXHIBITION / TRADE EXHIBITION**
1540 – 1600	**POSTER PRESENTATIONS**
P-49	**Evaluation and Calculation of Human Absorbed Dose of Tl(III)-201F -DTPA-HigG based on Biodistribution Data in Rats** Dr Alireza Khorrami, et al (Iran)
P-50	**Assessment of Human Effective Absorbed Dose of 111In–DTPA–Buserelin Based on Biodistribution Rat Data** Dr A Lahooti, et al (Iran)
P-51	**Biodistribution of an Ultra Small Super Paramagnetic Iron Oxide Nano Particles in Balb/c Mice** Dr Saeed Shanehsazzadeh, et al (Iran)
P-52	**Development of a Radiolabeled Glucagon for SPECT Imaging** Ms Mahdokht Jouiaei, et al (Iran)
P-53	**Biological and Dosimetry Studies of Four Radiolabeled of Rituximab for Human Based on Distribution Data in Rats** Dr Edalat Radfar, et al (Iran)
P-54	**Investigating the Effectiveness of Low Dose and High Dose Radioiodine Ablation for Post Surgical Thyroid Remnants in Patients with Differentiated Thyroid Carcinoma at Kuala Lumpur Hospital** Dr Nor Salita Ali, et al (Malaysia)
P-55	**Evaluation and Dosimetry Studies of Human Absorbed Dose of Various Age Groups of 90Y-DOTA-Cetuximab Based on Distribution Data in Rats** Dr Ariandokht Vakili, et al (Iran)
P-56	**Development of Ho-166 Chitosan for Hepatocellular Carcinoma** Dr Hassan Yousefnia, et al (Iran)
P-57	**Development and Characterization of Clinical-Grade 64Cu-DOTA-Trastuzumab for HER2/Neu Oncology Imaging Using Dual Head SPECT** Dr Behrooz Alirezapour, et al (Iran)
P-58	**In-Vitro and In-Vivo Evaluations of a Novel Potential Folate Receptor Imaging Agent** Dr Esmail Mollarazi, et al (Iran)
P-59	**Synthesis, Quality control, Biological Evaluation by a Kinetic Model of [90Y]-DOTA-Cetuximab for Radioimmunotherapy Purpose** Dr Ariandokht Vakili, et al (Iran)
P-60	**Development of a New In-111 Quinolate Complex as a Possible Imaging Agent** Dr Yousef Fazaeli, et al (Iran)
P-61	**Development of In-111 and Ga-67 Maltolate Complexes as Imaging Agents** Dr Yousef Fazaeli, et al (Iran)
P-62	**Synthesis, Radiolabeling and Biological Evaluation of a New 111Indium-Porphyrin Complex as an Imaging Agent** Dr Yousef Fazaeli, et al (Iran)
P-63	**Synthesis, Characterization and Biological Evaluation of a new 131Iodo porphyrin complex as an imaging agent** Dr Yousef Fazaeli, et al (Iran)
P-64	**Synthesis, labeling optimization and Biological Evaluation of 111Indium 5,10,15,20-Tetrakis (3,5-di Hydroxyphenyl) Porphyrin Complex as an Imaging Agent** Dr Yousef Fazaeli, et al (Iran)
P-65	**Our Experience in the Safe and efficient delivery of Radionuclide Therapy for Neuroendocrine Tumorswith Lu-177 DOAT-TATE** Mr S Somanesan, et al (Singapore)
P-66	**Preparation and Quality Control of Lutetium-177 Bleomycin as a Possible Therapeutic Agent** Dr Hassan Yousefnia, et al (Iran)
P-67	**Development of [177Lu]-Tetra Phenyl Porphyrin Complexes as Possible Imaging Agents** Dr Hassan Yousefnia, et al (Iran)

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DAY 3: TUESDAY, 27 NOVEMBER 2012

1600 – 1740	**SCIENTIFIC SESSION 12: DEVELOPMENTS IN THERAPEUTIC RADIOPHARMACEUTICALS**	Auditorium, Ground Floor
	Session Chairpersons: 1. **Prof Alan Perkins, Radiological & Imaging Sciences, Nottingham University Hospital, Nottingham, United Kingdom** 2. **Prof Irene Virgolini, Nuclear Medicine & PET, Medical University of Innsbruck, Innsbruck, Austria**	
1600 – 1620 S-38	**Nanostructures and Their Multiplex Labeling with Targeting Ligands and Radioisotopes** Prof Jae Min Jeong, Nuclear Medicine, Seoul National University College of Medicine, Seoul, Korea	
1620 – 1640 S-39	**Prospects of Lu-177/Y-90 Production and Future Radionuclide Therapy in Korea** Dr Sun-Ju Choi, Director, Radioisotope Research Division, Korea Atomic Energy Research Institute, Daejeon, Korea	
1640 – 1700 S-40	**Experience of Platform Construction and Clinical Trial of New Radionuclide Therapy in Korea** Dr Gi Jeong Cheon, Nuclear Medicine, Korea University, Seoul, Korea	
1700 – 1720 S-41	**Introducing the Animal Models for Evaluation of New or/and Already Existing Radiopharmaceuticals** Prof Emilija Janevik-Ivanovska, University "Goce delcev", Faculty of Medical Sciences, Stip, Republic of Macedonia	
1720 – 1740 S-37	**Review of Available and Future Radionuclides Useful for Radiotherapeutics: Industrial and Regulatory Limitations** Dr Richard Zimmermann, Chrysalium Consulting, France	
1740 – 1815	**SCIENTIFIC SESSION 13: RADIONUCLIDE THERAPY QUIZ**	Auditorium, Ground Floor
	Session Chair & Moderator: 1. **Dr Gopinath Gnanasegaran, Nuclear Medicine, Guy's & St Thomas Hospital NHS Foundation Trust, London, United Kingdom**	
1815 – 1930	**WARMTH MEMBERS' ASSEMBLY** **ALL MEMBERS OF WARMTH TO ATTEND THE MEETING**	Auditorium, Ground Floor
1930	**END OF DAY 3**	
1930	**FREE EVENING** **(Participants to plan their own activities)**	

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DAY 4: WEDNESDAY, 28 NOVEMBER 2012

0800 – 0910	**SCIENTIFIC SESSION 14: ALPHA THERAPY**	Auditorium, Ground Floor
	Session Chairpersons: 1. **Prof Richard P Baum, THERANOSTICS Center for Molecular Radiotherapy/Imaging, Zentralklinik Bad Berka, Bad Berka, Germany** 2. **Prof Naoyuki Watanabe, Radiological Sciencos, Gunma Prefectural College of Human Health, Maebashi, Japan**	
0800 – 0825 S-42	**Radium-223 (Alpharadin) in The Treatment Of Skeletal Metastases in Prostate Cancer Patients** Prof Øyvind S Bruland, Onclogy, University of Oslo, Norwegian Radium Hospital, Oslo, Norway	
0825 – 0850 S-43	**GlioblastomaTherapy with Substance P labelled with Bismuth-213 – Initial Experience** Prof Leszek Krolicki, Dr Jolanta Kunikowska, Dr Henryk Koziara, Dr Alfred Morgenstern, F Bruchertseifer, Maciej Jakuciński, Dr Dariusz Pawlak, Dr Renata Mikolajczak, Dr Bartosz Krolicki and Dr Sławomir Barszcz Nuclear Medicine Department, Medical University of Warsaw, POLAND; European Commission, Joint Research Centre, Institute for Transuranium Elements; Institute of Oncology, Maria Skłodowska-Curie Memorial Cancer Center, Warsaw Branch, Warsaw, Poland; Nuclear Medicine Department Brodrowski Hospital, Warsaw, Poland; National Centre for Nuclear Research, Radioisotope Centre POLATOM, Otwock-Swierk Poland **(To be presented by Dr Jolanta Kunikowska)**	
	ORAL PRESENTATIONS	Auditorium, Ground Floor
0850 – 0900 O-9	**Cis-Diamminedichloroplatinum (II) Enhancement of Antitumor Effect of In-111-Labeled N-Myc Antisense Oligonucleotides in Nude Mouse-Grown Human Neuroblastoma** Prof Naoyuki Watanabe, Radiological Sciences, Gunma Prefectural College of Human Health, Maebashi, Japan	
0900 – 0910 O-10	**KI67 or/and 18FDG PET/CT? Which Do We Need for Qualification Patients to Peptide Receptor Radionuclide Therapy (PRRT) ?** Dr Jolanta Kunikowska, Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland	
0910 – 1100	**SCIENTIFIC SESSION 15: BREAST CANCER & MISCELLANEOUS**	Auditorium, Ground Floor
	Session Chairpersons: 1. **Dr Gregory Wiseman, Mayo Clinic, Minnesota, USA** 2. **Dr Nei Wen Long, Radiation Oncology, National Cancer Centre Singapore, Singapore**	
0910 – 0935 S-44	**Contribution of Nuclear Medicine in Early Breast Cancer: From Sentinel Node to IART® (Intra-Operative Avidination For Radionuclide Therapy)** Dr Chiara Grana, Nuclear Medicine, European Institute of Oncology, Milano, Italy	
0935 – 0955 S-45	**Positron Emission Mammography (PEM): A Perspective** Dr Patricia Bernal, Nuclear Medicine, Fundacion Santa Fe de Bogota, Bogota, Colombia	
0955 – 1020 S-62	**Oncolytic Viral Therapy** Prof Akseli Hemminki, University of Helsinki / Docrates Cancer Center, Finland	
1020 – 1040 S-46	**Statistics – Interesting and Useful** Prof Janez Stare, Biostatistics, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia	
1040 – 1100 S-47	**Role of Nuclear Medicine in Oncological Surgery** Prof Bozena Birkenfeld, Nuclear Medicine, Uni Lubelskiej, Szczecin, Poland	
1100 – 1130	**COFFEE / TEA / TRADE EXHIBITION / TRADE EXHIBITION/ POSTER VIEWING**	

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	POSTER PRESENTATIONS
	Session Coordinators: 1. **Dr Butch Magsombol, Nuclear Medicine & PET, Singapore General Hospital, Singapore.** 2. **Dr Lucia Kaliska, Nuclear Medicine, Institute of Nuclear Medicine & Molecular Medicine, Banska Bystrica, Slovakia**
P-68	**Role of PET/CT in Initial Staging of Lung Cancer** Dr Xuan Canh Nguyen, et al (Vietnam)
P-69	**Pleuroperitoneal Communication Detected by Technetium 99m-tagged Macroaggregated Albumin (MAA) Radionuclide Peritoneal Scintigraphy in a Chronic Kidney Disease Patient on Peritoneal Dialysis: A Case Report** Ms Carla Mari Macaisa , et al (Philippines)
P-70	**Significant Impact of a Sngle End of Treatment F-18 FDG PET/CT Study as a Prognostic Indicator and Predictor of Final outcome in Non-Metastatic Squamous Cell Carcinoma of Head and Neck Region** Dr Partha Choudhury, et al (India)
P-71	**SPECT-CT for the Diagnosis of Primary Hyperparathyroidism** Dr Marina Garcheva, et al (Bulgaria)
P-72	**Variations of Gates' GFR Among Different Work Stations** Mr Rey Martin Jr Goco (Philippines)
P-73	**Measurement of Non-Uniformity in Gamma Cameras: Effect of Crystal Hydration** Dr Milena Dimcheva, et al (Bulgaria)
P-74	**Correlation of Wall Motion Score and Left Ventricular Ejection Fraction by Gated SPECT Myocardial Perfusion Imaging** Prof Raihan Hussain, et al (Bangladesh)
P-75	**PET/CT & SPECT/CT in Imaging Prostate Cancer: Tracers, Advantages & Limitations** Dr Sadia Salam, et al (Bangladesh)
P-76	**Clinical Interest of Hybrid Imaging in Lung Cancer** Prof Ben Rais Aouad Nezha, et al (Morocco)
P-77	**The Clinical Impact of 18-F Flurocholine PET/CT in the Management of Prostate Cancer** Dr Anbalagan Kannivelu, et al (Singapore)
P-78	**The Role of Sentinel Lymph Node Biopsy in the Prediction of Metastatic Spread of Malignant Melanoma** Dr Anca Zamfirescu, et al (Romania)
P-79	**Role of Contrast Enhanced 18F- FDG PET- CT in Restaging of Pancreatic Carcinoma** Dr Arun Gandhi, et al (India)
P-80	**Controversy over Dense Breast Imaging: Are We Using All the Armaments in Our Arsenal; A Review of Molecular Breast Imaging's Potential Role in the Battle Against Breast Cancer** Dr S Krishna Kumar, et al (Singapore)
P-81	**Site Specific Radioiodination of HER2-Targeting Affibody Molecules Using Iodophenetylmaleimide Decreases Renal Uptake of Radioactivity** Strand J, Nordeman P, Honarvar H, Altai M, Larhed M, Orlova A, Tolmachev V Uppsala University, Uppsala, Sweden
P-82	**Is PET and PET/CT useful in Pediatrics?** De Leon D, Dr Emerita Bamenecheа (Philippines)
P-83	**Developing a Nuclear Medicine Outreach Program. The Polokwane Experience** Dr Masha Maharaj (South Africa)
P-84	**Tc-99m MIBI Scan in Multiple Myeloma** Dr Raluca Militelu, et al (Romania)

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1130 – 1310	**SCIENTIFIC SESSION 15: LIVER AND GI CANCER**	Auditorium, Ground Floor
	Session Chairpersons: 1. Dr Patricia Bernal, Nuclear Medicine, Fundacion Santa Fe de Bogota, Bogota, Colombia 2. Prof Jae Min Jeong, Nuclear Medicine, Seoul National University College of Medicine, Seoul, Korea	
1130 – 1150 S-48	**Clinical use of Rhenium-188 from the Tungsten-188/Rhenium-188 Generator** Dr Knut Liepe, Nuclear Medicine, GH Kassel, Kassel, Germany	
1150 – 1210 S-49	**SIR-Spheres in HCC** Dr Jarosław Cwikła, Nuclear Medicine, Faculty of Medical Science, University of Varmia and Masuria Olsztyn Poland	
1210 – 1230 S-50	**Re-188 Lipiodol Therapy for HCC – A New Approach and Perspective from the Rhenium Users' Group** Prof Ajit Kumar Padhy, Nuclear Medicine & PET, Singapore General Hospital, Singapore	
1230 – 1250 S-51	**I-131-Lipiodol Therapy in Local Disease Control and Survival in Patients with Advanced Hepatocellular Carcinoma and Metastatic Liver Disease from other Primary Tumors: Our Initial Experience** Dr Kumarswamy Kallur , Nuclear Medicine, Healthcare Global Enterprises Pvt Ltd, Bangalore, India	
1250 – 1310 S-52	**Therapy of Colorectal Cancer Tumours with an Agonist DR5 Antibody** Prof Andrew Scott, Nuclear Medicine & PET, Ludwig Institute for Cancer Research, Heidelberg, Australia	
1310 – 1410	**LUNCH / TRADE EXHIBITION**	Restaurant Okta, Ground Floor Hotel Levi Panorama
1410 – 1550	**SCIENTIFIC SESSION 16:** **MISCELLANEOUS/NEW THERAPIES/ FUTURE TRENDS**	Auditorium, Ground Floor
	Session Chairpersons: 1. Dr Chiara Grana, Nuclear Medicine, European Institute of Oncology, Milano, Italy 2. Dr Emerita Barrenechea, Nuclear Medicine, Veterans Memorial Medical Centre, Quezon City, Philippines	
1410 – 1430 S-53	**Outside the Box: Challenging Cases for Radioimmunotherapy** Dr Michael Tomblyn, Radiation Oncology, H. Lee Moffitt Cancer Center, Tampa, USA	
1430 – 1450 S-54	**Ancient Features of Personalizing Cancer Treatment; Learning from Radionuclide Therapy in the Era of Targeted Therapies** Dr So Won Oh, Nuclear Medicine, Seoul National University Boramae Hospital, Seoul, Korea	
1450 – 1510 S-55	**Quantitative Imaging of Radiotracer Biodistributions** Prof Anna Celler, Radiology, UBC, VGH Research Pavilion, Vancouver, Canada	
1510 – 1530 S-56	**Quality of Life (QOL) Assessment in Neuroendocrine Tumor (NET) Patients** Prof Irene Virgolini, Nuclear Medicine & PET, Medical University of Innsbruck, Innsbruck, Austria	
1530 – 1550 S-57	**Quality of Life in Oncological patients and Radionuclide Therapy** Mr William Claxton, Carcinoid & Neuroendocrine Tumor Society , Singapore	
1550 – 1615	**COFFEE / TEA / TRADE EXHIBITION / TRADE EXHIBITION**	
1615 – 1645	**SCIENTIFIC SESSION 17: RADIONUCLIDE THERAPY QUIZ**	Auditorium, Ground Floor
	Session Chair & Moderator: 1. Dr Gopinath Gnanasegaran, Nuclear Medicine, Guy's & St Thomas Hospital NHS Foundation Trust, London, United Kingdom	
1645 – 1725	**SCIENTIFIC SESSION 18: FINAL SESSION**	Auditorium, Ground Floor
	Session Chairpersons: 1. Prof Andrew Scott, Nuclear Medicine & PET, Ludwig Institute for Cancer Research, Heidelberg, Australia 2. Prof Abdelhamid Elgazzar, Medical Faculty, University of Kuwait, Safat, Kuwait	
1645 – 1705 S-58	**Radionuclide Therapy: From Radium to Radium** Prof Alan Perkins, Radiological and Imaging Sciences, Nottingham University Hospital, Nottingham, United Kingdom	
1705 – 1725 S-59	**Outpatient Therapeutic Oncology** Prof Harvey Turner, Nuclear Medicine, Fremantle Hospital, Fremantle, Australia	

DAY 4: WEDNESDAY, 28 NOVEMBER 2012

Ski lift during the Levi conference, and a picture from the conference center outside (afternoon)

Oenophilous dinner in Kaukonen, ine/licqueur from 37 countries.

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1725 – 1815	**WARMTH MEMBERS' ASSEMBLY** **ALL MEMBERS OF WARMTH TO ATTEND THE MEETING**	Auditorium, Ground Floor
1815 – 1930	**CLOSING**	Auditorium, Ground Floor
	Awards: Best Oral presentations & Posters	
	Impressions from Participants	
	Welcome to ICRT 2013 (Cairo, Egypt) Prof Abdelhamid Elgazzar, Local Organising Chairman, ICRT 2013	
	Declaration of Results of WARMTH Elections for The Next Governing Body (2013 – 2014)	
	Impressions Prof Richard P Baum, THERANOSTICS Center for Molecular Radiotherapy/Imaging, Zentralklinik Bad Berka, Bad Berka, Germany	
	Impressions Prof Alan Perkins, Radiological and Imaging Sciences, Nottingham University Hospital, Nottingham, United Kingdom	
	Impressions Prof Kalevi Kairemo, Local Organising Chairman, ICRT 2012	
	Closing Remarks Prof Ajit Kumar Padhy	
1930	**END OF SCIENTIFIC PROGRAM**	
2000	**DINNER: Theme "Blue Dress"** **Participants are requested to wear something blue (Any shade of blue)**	Restaurant Okta, Ground Floor Hotel Levi Panorama
2300	**END OF DAY 3**	

DAY 5: THURSDAY, 29 NOVEMBER 2012

	SIGHT-SEEING TOUR & OENOPHILOUS DINNER
0830	**Departure from Hotel**
0830 – 1200	**Whole Day Excursion To Rovaniemi: Part I** • Arctic Circle • Santa Claus Village • Arctic Science Museum
1200 – 1400	**LUNCH**
1400 – 1800	**Whole Day Excursion To Rovaniemi: Part II** • Arctic Circle • Santa Claus Village • Arctic Science Museum
1800 – 2200	**Oenophilous Dinner & Closing**

DAY 6: FRIDAY, 30 NOVEMBER 2012

Departure to respective countries

Santa Claus Village




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8th ICRT-2013, Manila, Philippines

Congress-President: Emerita Barrenechea

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9th ICRT-2014, Cancun, Mexico



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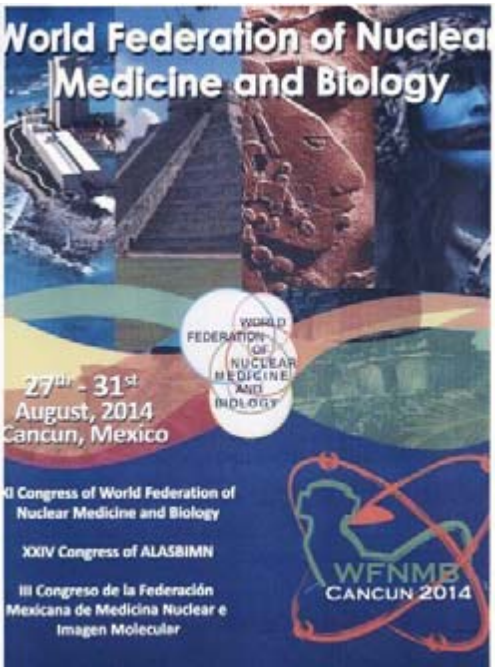

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10th ICRT-2015, Innsbruck, Austria

Congress-President: Irene Virgolini

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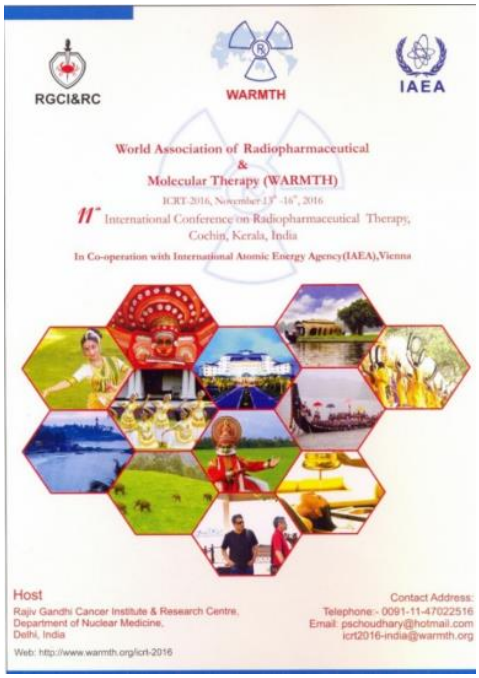
11th ICRT-2016, Kerala, India

Congress-President: Partha Choudhury



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12th ICRT-2017, Vienna, Austria

Congress-President: Irene Virgolini

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13th ICRT-2018, Melbourne, Australia

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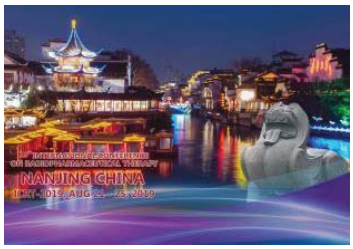
14th ICRT-2019 Nanjing, China
Congress-President: Feng Wang



Congress Venue ICRT-2019 Nanjing

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MARMTH Member Assembly Meeting

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15th ICRT-2020 Virtual Congress Coxbazar, Bangladesh
Congress-President: Raihan Hussain

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COVID-19 and the 15th ICRT Virtual Congress

The world is going through difficult times and we are all trying to find solutions in different unique ways to keep us and our families safe. "Break the chain" has been a common slogan for all the countries which we can achieve by physical distancing and therefore most of the countries are in complete lockdown. I believe at this point in time we are gradually moving towards the peak of the corona crisis and thinking about the post-pandemic life expected in the next few months.

I am sure all of us are carrying out our professional work in our own unique ways and probably this is the time for us to "work from home", educating our peers and finish writing out our completed research projects, for which there is always a paucity of time amidst our routine daily work schedule.

I want to reiterate the fact that education is a critical part of WARMTHs mission and to achieve this, virtual curriculum will be the key now at this point in time. There are few scientific papers already in print regarding our practice during the COVID times and I am sure all of you must have gone through it.

In continuation of the efforts for education the Nuclear Medicine and diagnostic Imaging Section of the IAEA, under the dynamic leadership of **Dr. Diana Paez**, has organized a series of webinars and information on the COVID-19 pandemic and it's impact to the practice of nuclear medicine.

The Society of Nuclear Medicine and Molecular Imaging resource section is another source of virtual information and can be accessed here. The European Association of Nuclear Medicine COVID-19 resource page can be accessed here.

My dear friends at this time of crisis we all should join hands to protect our patients, their caregivers, our staff, and families.

Stay safe, stay healthy. Practice physical distancing but social solidarity as we say in India. "*Jan Hai toh Jahan Hai*" meaning *IF YOU HAVE LIFE, YOU HAVE THE WORLD.*

With my warm regards,

Partha Choudhury
President (WARMTH)

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17th ICRT-2022 Kyoto, Japan

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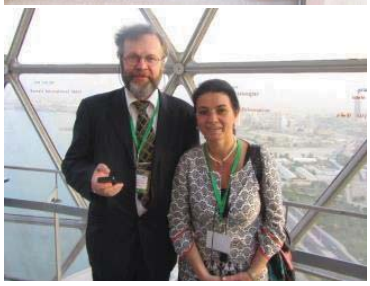
2011, Kuwait

WARMTH International Workshop on Radionuclide Therapy & Annual Conference of Kuwait Society of Nuclear Medicine March 28-30, 2011, Venue: Mövenpick Hotel & Resort Al Bida'a, Samiya



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ISRT's and supported Symposia and Congresses of The WARMTH

		LOCATION	CONGRESS PRESIDENT
2008	9th Asia Oceania Congress of Nuclear Medicine and Biology, October 2008	New Delhi, India	Ajit Padhy
2010	Singapore Radiological Society & College of Radiologists 19th Scientific Meeting, February 2010	Singapore	Ajit Padhy
2011	Singapore Nuclear Medicine Update, March 2011	Singapore	Ajit Padhy Antony Goh
2011	WARMTH International Workshop on Radionuclide Therapy & Kuwait Society of Nuclear Medicine, March 2011	Kuwait	Abdelhamid Elgazzar Ajit Padhy
2011	1st World Congress on Ga-68 and Peptide Receptor Radionuclide Therapy (PRRNT), June 2011	Bad Berka, Germany	Richard Baum
2013	National Symposium in Routine Clinical Practice, March 2013	Yangon, Myanmar	Kyin Myint, Ajit Padhy
2013	South Indian Society of Nuclear Medicine	Coimbatore, India	Ajit Padhy
2015	11th AOCNMB and 54th Autumn Meeting of the Korean Society of Nuclear Medicine	Jeju Island Korea	Henri Bom
2015	1st World Rhenium Congress	Coimbatore	Ajit Shinto
2016	Therapy Center of Excellence of the SNMMI	San Diego, USA	Suresh Srivastava
2017	2nd World Rhenium Congress	Coimbatore, India	Ajit Shinto
2017	Therapy Center of Excellence of the SNMMI	Denver, USA	Suresh Srivastava
2018	Therapy Center of Excellence of the SNMMI	Philadelphia, USA	Dan Pryma
2018	22nd Annual Scientific Meeting of the Indonesian Society of Nuclear Medicine	Bandung, Indonesia	Ayu Rosemeilia Dewi
2018	ISRT	Helsinki, Finland	Kairemo Kalevi
2019	ISRT + 3rd Serbian Meeting on Hybrid Imaging and Molecular Therapy	Novi Sad, Serbia	Jasna Mihailovic
2019	20 Years Anniversary of Cyprus SNM	Limassol, Cyprus	Savvas Frangos
2020	ISRT + IPET (IAEA)	Vienna, Austria	Diana Paez Partha Choudhury

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2011, Bad Berka, Germany

Congress-President: Richard Baum, Frank Rösch

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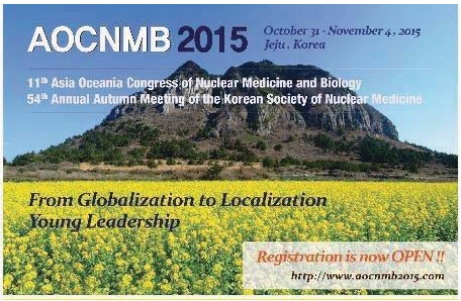
2015, Jeju, Korea



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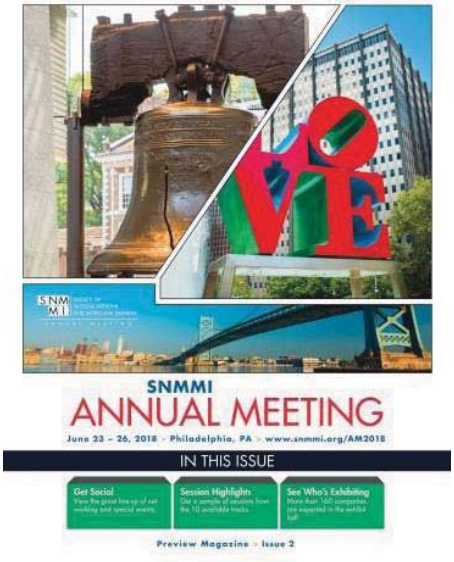
2018 SNMMI Annual Meeting Philadelphia USA



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EANM Düsseldorf, Germany (October 13-17, 2018)

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ISRT 2018, Helsinki, Finland

Congress-President: Kalevi Kairemo

- *"The Helsinki ISRT-2018 was arranged because the last full ICRT was arranged in 2016 in Cochin, Kerala, India in 2016. In 2017 and 2018, WARMTH Conferences were one day events both in Vienna (EANMC) and Melbourne (WFNMB). This ISRT-2018 Conference was held in downtown Helsinki in Paasitorni Congress Center in November 18-20, 2018. This three day event had 151 registered participants from 53 countries, and from the WARMTHs perspective it did not make any deficit nor any profit. IAEA supported travel of 20 participants from developing countries to this conference.*
- *Minister of Health Pirkko Mattila gave an opening speech the Conference, followed by a Candle light ceremony (picture).*
- *City of Helsinki and Mayor of Helsinki (Health Section Sanna Vesikansa) arranged a reception in the City Hall. I had arranged a private Tram transportation to the City hall and after that a city sightseeing tour by the same tram.*
- *There was an extensive program for a three day event, consisting of 20 posters and 41 oral presentations in 9 sessions (attachment). The abstracts were all published in World Journal of Nuclear Medicine.*
- *Multiple high quality presentations were given, but the most important presentation was the 45-min Ajit Padhy Oration entitled "New Insights in Theranostics" was given by Steven M. Larson from Memorial Sloan-Kettering Cancer Center, New York (h-index 118, more than 700 publications).*
- *There was a special Nuclear Cardiology Session, arranged by Juhani Knuuti. He also got the Lifetime Achievement Award from WARMTH (h-index 75, more than 500 publications). A specific nuclear oncology/ oncology session was organized by the University of Texas MD Anderson Cancer Center. A session dedicated Radiation Biology and Hazards was arranged by Seigo Kinuya (JPN) and Bennett S. Greenspan (USA), SIRT session by Aviral Singh (GER) and Patrick Flamen (BEL), NET session by Irene Virgolini (AUT), PSMA session by Richard P. Baum (GER), and Alpha emitter -session by Jean-Francois Chatal (FRA) and Oyvind Bruland (NOR). The Thyroid session was organized by Mark Tulchinsky (USA), Ilya Sleptsov (RUS) and Raihan Hussein (BGL).*
- *One of the achievements in the Helsinki ISRT-2018 was the "Theragnostics Day Proclamation" which also was published in World Journal of Nuclear Medicine (WJNM 2019; 18: 212). Additonally, the collaborations between SNMMI, WFNMB, IAEA and WARMTH were discussed intensively." (Kalevi Kairemo, November 2019)*

WARMTH
WORLD ASSOCIATION OF RADIOPHARMACEUTICAL AND MOLECULAR THERAPY

International Symposium on Radiopharmaceutical Therapy
Helsinki, 18-20 November 2018

DAY 1, SUNDAY, NOVEMBER 18, 2018

13.00 – 18.30	REGISTRATION for ISRT 2018
14.00 – 16.00	**SCIENTIFIC SESSION 1:** NUCLEAR CARDIOLOGY Moderators: Juhani Knuuti, Turku, Finland and Pietro Muto, Naples, Italy
14.00 – 14.30 O1	**Revolution in cardiac imaging: Quantitative perfusion, inflammation and hybrid imaging** Juhani Knuuti, Turku, Finland
14.30 – 15.00 O4	**Novel therapies of cardiac regeneration. How imaging can help in diagnosis, targeting and monitoring?** Seppo Ylä-Herttuala, Kuopio, Finland
15.00 – 15.30 O2	**Imaging innervation. Finally clinical applications?** Albert Flotats, Barcelona, Spain
15.30 – 16.00 O3	**Gauging cardiac repair, regeneration and inflammation with new molecular probes** James Thackeray, Hannover, Germany
16.00 – 16.30	**COFFEE & TEA BREAK**
16.30 – 18.45	**SCIENTIFIC SESSION 2:** NEW TRENDS IN ONCOLOGY AND PRECISION MEDICINE. Moderators: **Vivek Subbiah**, MDACC, Houston, TX, USA and **Homer Macapinlac**, MDACC, Houston, TX, USA
16.30 – 16.55 O5	**Personalized medicine and precision oncology,** Vivek Subbiah, Investigational Cancer Therapeutics, UT MD Anderson Cancer Center
16.55 – 17.20 O6	**Precision oncology in rare tumors: adopting the orphans,** Roman Groisberg, Division of Medical Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA
17.20 – 17.45 O7	**Optimizing patient selection for phase 1 clinical trials: lessons from targeted therapy and immunotherapy drug development,** Shiraj Sen, Drug Development, Sarah Cannon Research Institute at HealthOne; Denver, CO, USA

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17.45 – 18.20 O8	**Target discovery for precision oncology using large public databases,** Jason Roszik, Department of Genomic Medicine, UT MD Anderson Cancer Center
18.20 – 18.45 O12	**Re-188 Lipiodol Liver Cancer Project – an update on current status,** Ajit Shinto, Coimbatore, India
WARMTH CONGRESS DINNER 1	
19.30 – 22.30	Restaurant Meripaviljonki

DAY 2, MONDAY, NOVEMBER 19, 2018

08.00 – 18.00	REGISTRATION for ISRT 2018
09.00 – 11.00	**OPENING CEREMONY**
Welcome Address	Partha Choudhury, President-Elect, WARMTH
Opening Remarks	Kalevi Kairemo, Congress President, ISRT-2018, WARMTH
Welcome Address	Pirkko Mattila, Minister of Health, Finland
WARMTH Candle Lighting Ceremony	WARMTH Board Members
AJIT PADHY ORATION	Steven M. Larson, MSKCC, NY, USA
O10	**"New Insights in Theragnostics"**
presenter	Andrew M. Scott, Melbourne, Australia
11.00 – 11.30	**COFFEE & TEA BREAK**
11.30 – 13.00	**SCIENTIFIC SESSION 3:** RADIOEMBOLISATION AND LIVER THERAPIES Moderators: Patrick Flamen, Brussels, Belgium and Aviral Singh, Bad Berka, Germany

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11.30 – 11.55 O11 **Personalized SIRT based on predictive dosimetry, regio functional reserve measurement and molecular imaging**, Pat Flamen, Jules Bordet Institute, Brussels, Belgium

11.55 – 12.20 O9 **Oncolytic viruses,** Akseli Hemminki, University of Helsinki

12.20 – 12.40 O13 **Biologic dosimetry in SIRT**, Katherine Vallis, University of Oxford,

12.40 – 13.00 O14 **Intra-arterial PRRT of SSTR-expressing liver tumors**, Av Singh, Bad Berka, Germany

Posters: P1 ***The quantitative analysis of post-selective internal radiat therapy (SIRT) ^{90}Y microspheres PET/CT in hepatocell carcinoma in comparison with ^{99m}Tc-labelled macroaggrega albumin (MAA) planar and SPECT/CT,*** Ngoc Ha Le, Tran Hung I Hospital, Ho Chi Minh City, Vietnam

13.00 – 14.00 **LUNCH AT THE CONGRESS CENTER PAASITORNI**

14.00 – 16.00 **SCIENTIFIC SESSION 4:** NEW RADIONUCLIDE THERAPIES / RADIATION HAZARDS/ SAFETY ISSUES
Moderators: Seigo Kinuya, Kanazawa, Japan and Kazuko Ohno, Fukushima, Japan

14.00 – 14.30 O15 **Boron neutron capture therapy and world's first accelerat based BNCT facility at Southern Tohoku General Hospi** Yoshihiro Takai, Southern Tohoku BNCT Research Center, Japan

14.30 – 15.00 O16 **What did we learn from the Fukushima accident?** Ohtsura Ni Radiation Effects Research Foundation, Hiroshima/ Nagasaki, Japan

15.00 – 15.30 O17 **Regulatory nuclear safety aspects, Linear No-Thresh Hypothesis of risk from low-level radiation exposure,** Bennet Greenspan, Society of Nuclear Medicine and Molecular Imaging, USA

PANEL-discussion: Regulatory/ nuclear safety aspects

Moderators: Seigo Kinuya, Kazuko Ohno and Bennet S Greenspan

Posters: P2 ***Establishment of incident reporting programme and lesson learnt in unsealed radionuclide therapy,*** Noreen Marwat, Nuclea Medicine Oncology and Radiotherapy Institute, Pakistan

P3 ***Practices across Pakistan how medical emergency is handled i case of patients who has undergone unsealed radionuclide therapy,*** Noreen Marwat, Nuclear Medicine Oncology and Radiotherapy Institute, Pakistan

16.00 – 16.30 **COFFEE & TEA BREAK**

16.30 – 18.15 **SCIENTIFIC SESSION 5:** *PROSTATE CANCER: PSMA RADIOLIGAND THERAPY (PRLT) – WHAT DO WE KNOW AND WHAT IS NEW?*
Moderator: Richard P. Baum, Bad Berka, Germany

16.30 – 16.45 O18 **Introduction to PRLT,** Richard P. Baum

16.45 – 17.00 O19 **Dosimetry following Lu-177 PSMA radioligand therapy and an insight into novel nadionuclides for theranostics of prostate cancer,** Aviral Singh, Bad Berka, Germany

17.00 – 17.15 O20 **Dosimetry in PSMA radioligand therapy of metastasized prostate cancer using Lu-177 PSMA I&T and Lu-177 PSMA-617** Christiane Schuchardt, Bad Berka, Germany

17.15 – 17.45 O21 **PSMA targeting and therapy trials in Australia,** Andrew M. Scott, Melbourne, Australia

17.45 – 18.00 O22 **Ac-225- and Bi-213- PSMA-617 radioligand therapy in patients with castration resistant prostate cancer**, Mike Sathekge, Pretoria, South Africa

18.00 – 18.15 O23 **[^{18}F]AIF-PSMA-HBED-CC and ^{177}Lu-PSMA-617 as a potential theragnostic tandem and comparison with 68Ga-PSMA-HBED-CC in high-risk prostate cancer patients at initial staging**, Omar Alonso, CUDIM, Montevideo, Uruguay

Posters: P4 ***^{177}Lutetium-prostate-specific membrane antigen radionuclide treatment of lymph node metastatic prostate cancer with PSA recurrence: A cohort study***, Finn Edler von Eyben, Odense, Denmark

P5 ***Dosimetry in Molecular Radiotherapy - Bad Berka Experience***, Christiane Schuchardt, Bad Berka, Germany

P6 ***Web-Monitoring Tool for ^{177}Lutetium-PSMA Treatments in Prostate Cancer Patients***, Kalevi Kairemo, Helsinki, Finland

18.25 *Tram transportation to the City Hall in front of the Scandic Paasi hotel (Hakaniemi Square stop 0252)*

WARMTH CONGRESS DINNER 2

19.00 – 20.30 **CITY HALL of Helsinki, Mayor Reception**

20.45 -21.45 *Tram transportation from the City Hall (Market Square stop) to the Scandic Paasi hotel (Hakaniemi Square) including sightseeing in Helsinki*

DAY 3, TUESDAY, NOVEMBER 20, 2018

08.00 – 08.45 REGISTRATION for ISRT 2018

8.45 – 11.00 **SCIENTIFIC SESSION 6:** THYROID CANCER – QUO VADIS?
Moderators: Mark Tulchinsky, PA; USA & Raihan Hussain, Dhaka, Bangladesh

Debating Controversies in Radioiodine Imaging and Therapy of Thyroid Cancer

8.45 – 9.00 O24 **Introduction-thyroid cancer management,** Mark Tulchinsky, Hershey, PA, USA

9.00 – 9.15 O25 **Total vs. subtotal thyroidectomy. East, West , what´s the best?** Ilya V. Sleptsov, St. Petersburg, Russia

9.15 – 9.30 O26 **Dosimetric approach of thyroid cancer**, Henry Bom, Chonnam, South Korea

9.30 – 9.45 O27 **Management of I-131 refractory thyroid cancer: a multimodality approach**, Partha Choudhury, New Delhi, India

9.45 – 9.55 O28 **Prevalence of genetic duet and its influence on the prognosis of differentiated papillary thyroid carcinoma patients**, Sanjana Ballal, New Delhi, India

9.55 – 10.00 O29 **Comments -thyroid cancer management**, Raihan Hussain, Dhaka, Bangladesh

Panel discussion: Moderator Mark Tulchinsky

Panelists: Raihan Hussain, Henry Bom, Partha Choudhury and Ilya Sleptsov, St. Petersburg, Russia

10.05 – 10.30 **"Radioiodine Imaging Before, After, Both or Neither ... and How?"**

10.30 – 10.55 **"Controversies in Radioiodine Side-Effects: Confusion About Salivary Damage and Secondary Malignancy"**

Posters: P7 ***Antithyroglobulin antibody as a marker of successful ablation therapy in differentiated thyroid cancer,*** Ayu Rosemeilia Dewi, Universitas Padjadjaran, Indonesia

P8 ***Importance of isolated raised thyroglobulin antibody in follow up and management of differentiated thyroid cancer***, Ray Soumendranath, Tata Medical Center, Kolkata, India

P9 ***Contribution of manual fusion in thyroid cancer whole body study with I-131. Case Report***, Mariela Agolti, Parana, Argentina

P10 ***Contribution of manual fusion in thyroid cancer whole body study with I-131,*** Mariela Agolti, Parana, Argentina

11.00 – 11.10 Lifetime Achievement Awards & Group Photo

Irene Virgolini, President, WARMTH & Kalevi Kairemo

11.10 – 11.30 COFFEE & TEA BREAK

11.30 – 13.00 **SCIENTIFIC SESSION 7:** PEPTIDE RECEPTOR/ NEW THERAPIES
Moderator: **Irene Virgolini, Innsbruck, Austria**

11.30 – 11.45 O30 **Value of FDG in NET: importance of dual tracer imaging,** Margarida Rodrigues Radischat, Innsbruck, Austria

11.45– 12.00 O31 **Value of Re-PRRT in NET,** Anna Yordanova, Bonn, Germany

12.00– 12.15 O32 **PRRT in G3-NEN,** Aviral Singh, Bad Berka, Germany

12.15– 12.35 O33 **New peptides for PRRT in Non-NETs,** Irene Virgolini, Innsbruck, Austria

12.35– 12.50 O34 **Long-term side effects and quality of life, patients view** Josh Mailman, San Francisco, USA

12.50– 12.58 O35 **A correlation between c-Fos expression and radioiodine in breast cancer cell lines**, Aisyah Elliyanti, Andalas University/ Dr.M.Djamil Hospital, Indonesia

Posters: P11 ***First ex-vivo experience with I- radiation and radioguided surgery technique in meningioma and neuroendocrine patients***, Chiara Maria Grana, European Institute of Oncology, Milan, Italy

P12 ***Lutetium-labelled DOTA-TOC and radionuclide therapy (PRRT) in China: First Experience***, Feng Wang, Nanjing, China

P13 ***Developing neuropeptide Y (NPY) nanoconstructs as potential theranostic agents***, Irfan Ullah Khan, Institute of Nuclear Medicine & Oncology, Lahore, Pakistan

13.00 – 14.00 **LUNCH AT THE CONGRESS CENTER PAASITORNI**

14.00 – 16.00 **SCIENTIFIC SESSION 8:** NEW ALPHA- THERAPIES
Moderators: Oyvind Bruland, Oslo, Norway and Roy Larsen, Oslo, Norway

14.00– 14.30 O36 **Predicting the future of Alpha: clinical indications and radioisotopes of choice?** Jean-Francois Chatal, Arronax, Nantes, France

14.30– 14.50 O37 **Radiometabolic therapy with ^{223}Ra-dichloride: the European Institute of Oncology experience**, Chiara Maria Grana, European Institute of Oncology,Milan, Italy

14.50– 15.10 O38 **Ra-223 in osteosarcoma –Ph I-trial**, Vivek Subbiah, MD Anderson Cancer Center, USA

15.10– 15.30 O39 **Ra-224 labelled biodegradable carbonate microparticles (Radspherin®) to combat microscopical residual peritoneal carcinomatosis**, Tina Bønsdorf, Oncoinvent AS, Oslo, Norway

15.30– 15.50 O40 **"Dual-alpha" - an expanding technology for development of targeted alpha therapies**, Asta Juzeniene, Norwegian Radium Hospital, Oslo, Norway

Posters: P14 ***Clinical case of benefit due to deviation in Ra-223 treatment schedule***, Tatiana Kochetova, MRRC, Obninsk, Russia

P15 ***Personalized molecular imaging with bone scintigraphy, NaF-PET, and FDG-PET for evaluation of osteosarcoma response to Radium-223***, Kalevi Kairemo, Houston, TX, USA

P16 ***Treatment response evaluation in soft-tissue osteosarcoma metastases using fluoride-18 (^{18}F)-PET/CT radiomics analysis for ^{223}Ra-therapy***, Kalevi Kairemo, Houston, TX, USA

P17 ***Substantiation of an individual therapeutic dose of ^{153}Sm-oxabiphor for the treatment of bone metastases***, Ganna Grushka, Grigorev Institute for Medical Radiology, Ukraine

P18 ***Radionuclide therapy for bone pain palliation in anemic patients: role of erythropoietin***, Sukanta Barai, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

P19 ***^{18}F-fluoroethyltyrosine PET/CT: the European Institute of Oncology experience in brain tumors***, Chiara Maria Grana, European Institute of Oncology, Milan, Italy

P20 ***Pharmaceutical development of the therapeutic radiopharmaceutical based on –emitting Sm-153 in heat-sensitive carrier for brachytherapy of tumors of various locations***, NM Tolbit, Karpov Institute, Obninsk, Russia

15.50 – 16.20 COFFEE & TEA BREAK

16.20 – 17.00 **SCIENTIFIC SESSION 9:** FUTURE ASPECTS OF COLLABORATION OF WARMTH, IAEA AND WFNMB – ROUND TABLE DISCUSSION
Moderator: Irene Virgolini, Innsbruck, Austria

WARMTH perspective, Partha Choudhury, President-Elect

IAEA Perspective, NN, Vienna

WFNMB perspective, Andrew M. Scott, Melbourne, Australia

SNMMI perspective, Bennett Greenspan, USA

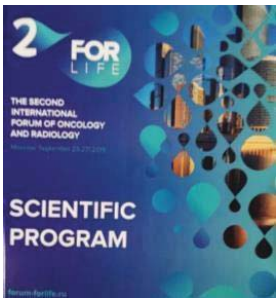
O41 Presentation of ICRT 2019, Feng Wang, Nanjing, China

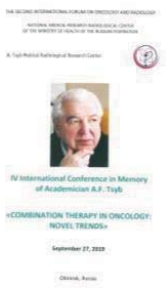
O42 Closing remarks, Kalevi Kairemo

Candle Lighting Ceremony 19.11.2018 in Helsinki. Minister Pirkko Mattila(FIN), Kairemo (FIN), Baum (GER), Mailman (USA), Singh (IND/GER) and Hussein (BGL).

City of Helsinki Reception 19.11.2018 (City Hall). Deputy Mayor Sanna Vesikansa speaking (left), tram transportation and sightseeing (Kairemo as tour guide, right).

Group photo 20.11.2018





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EANM 2019 Barcelona, Spain

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2019-ISRT Limassol, Cyprus

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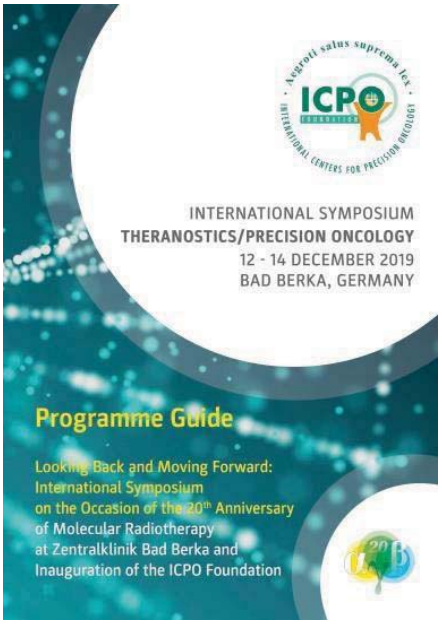
BAD BERKA 2019



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2021 - TALLINN

HYBRID SYMPOSIUM ON RADIONUCLIDE THERAPY OF ADVANCED PROSTATE CANCER

September 23, 2021

The Great Hall, Estonian Academy of Sciences, Kohtu str 6, Tallinn, Estonia

12:30 Registration, coffee

13:15 **Welcome and Introduction**, Eve Kalk, East Tallinn Central Hospital, Estonia

Greetings

Scientific program

Moderator: Kalevi Kairemo, Helsinki, Finland

13:30 **Therapy options for castration resistant prostate cancer in Estonia**. Helis Pokker, Head of Oncology and Haematology Clinic, The North Estonia Medical Centre (in Estonian, slides in English)

14:00 **Options for radionuclide therapies of metastatic prostate cancer in Estonia**. Aime Pokot, Head of Nuclear Medicine Centre, East Tallinn Central Hospital, Estonia (in Estonian, slides in English)

14:30 **177Lu-PSMA in radioligand therapy of metastatic castration resistant prostate cancer**. Irene Virgolini, Director of the University Clinic for Nuclear Medicine, Innsbruck, Austria

Coffee break

15:30 **225Ac-PSMA in radioligand therapy of metastatic castration resistant prostate cancer**. Mike M. Sathekge, Head of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, South Africa

16:30 **223Ra therapy in the multidisciplinary care of metastatic prostate cancer**. Homer Macapinlac, Chair of the Department of Nuclear Medicine at the University of Texas M.D. Anderson Cancer Center in Houston, Texas, USA

17:00 **Questions and answers**

17:30 – 18:30 *Buffet dinner*

SYMPOSIUM ON THERAGNOSTICS

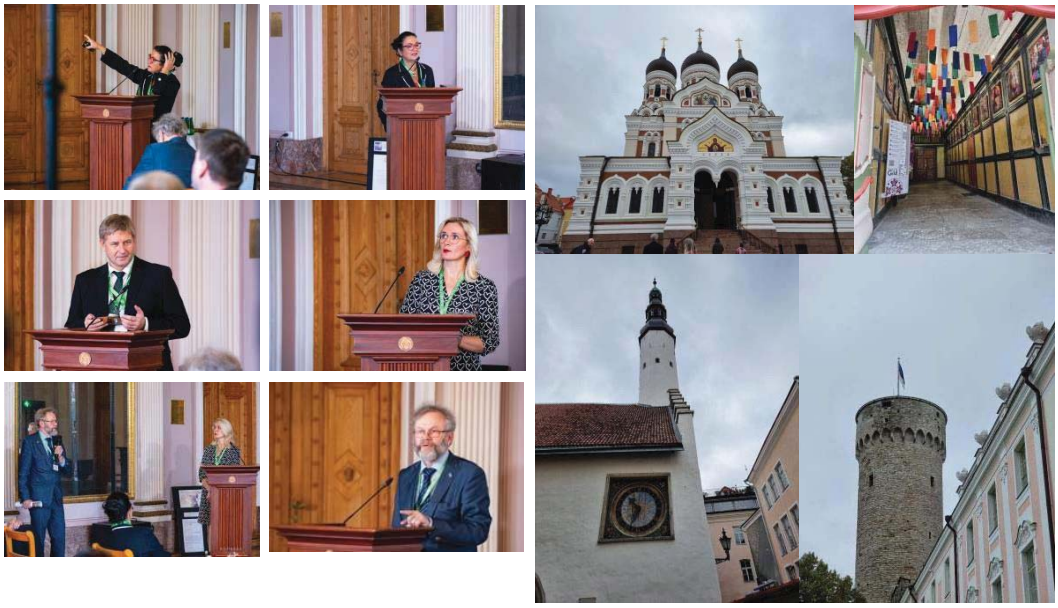
The Evolution of Radionanotargeting towards Clinical Precision Oncology
Launching A Festschrift in Honor of Kalevi Kairemo

September 24, 2021
The Great Hall, Estonian Academy of Sciences
Kohtu tn 6, Tallinn, Estonia

12:30	**Registration**, *lunch and coffee*
13:00	**Introduction**, Antti Jekunen
	Scientific program **Moderator**: Antti Jekunen, Turku/Vaasa, Finland
13:10	**Future aspects of theragnostics**, Steven M. Larson, Chair, Molecular Imaging and Therapy Service, Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, USA
13:40	**Management of Thyroid Cancer: radioiodine and beyond**, Partha S. Choudhury, Director, Nuclear Medicine, Rajiv Gandhi Cancer Center & Research Institute, Delhi, India
14:10	**The discovery of radioiodine: Saul Hertz's story**, Barbara Hertz, Dr. Saul Hertz Archives, Greenwich, CT, USA
14:30	*Coffee break. Introduction of the residence of Estonian Academy of Sciences*
15:10	**Future aspects of PSMA-theragnostics in prostate cancer**, Mike M. Ketheger, Head of Nuclear Medicine, University of Pretoria and Steve Biko Academic Hospital, South Africa
15:40	**Theragnostics in Neuroendocrine Neoplasms**, Irene Virgolini, Director of the University Clinic for Nuclear Medicine, Innsbruck, Austria
16:10	**Ra-223 therapy in the Multidisciplinary Care of Cancer Patients** (prostate cancer, breast cancer and osteosarcoma), Homer Macapinlac, Chair of the Department of Nuclear Medicine at the University of Texas M.D. Anderson Cancer Center in Houston, USA
16:40	**Molecular Imaging for Antibody-Drug Conjugate Therapy**, Andrew M. Scott, Director, Tumour Targeting Laboratory, Olivia Newton-John Cancer Research Institute, Melbourne, Australia
17:10	**Questions and answers**
17:30	**Closing of the symposium**

To participate in the symposium in the hall of the Academy of Sciences on site, it is necessary to bring a Covid-19 vaccination passport or a certificate of Covid-19 passage during the last 6 months or a negative result of PCR test from last 24 hours, and the participant has no Covid-19 symptoms.

If you have any questions regarding logistics, please contact konverents@tlk.ee




BAYER
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Kalevi Kairemo

Prof. Kairemo graduated with an MSc(Eng) degree from Helsinki University of Technology in 1980 before undertaking medical training (MD (86), Ph.D. (93)) at the University of Helsinki, Finland. He undertook specialist training in Clinical Chemistry (94), Nuclear Medicine (96), Health Care Administration (02) and Clinical Pharmacology (06) at Helsinki University Central Hospital. He attained a post-doctoral research fellowship at Memorial Sloan-Kettering Cancer Center in 1989-93 in New York.

Prof. Kairemo has held posts as Professor of Clinical Chemistry at the Norwegian University of Science and Technology (1998-9), Professor of Nuclear Medicine at Uppsala University Hospital in Sweden (2001-5), and as Head of the Nuclear Medicine Division, Department of Oncology at Helsinki University Central Hospital (2004-9). From 2009-2018, he has held the position of the Chief of Nuclear Medicine and Molecular Radiotherapy (Theragnostics) at the Docrates Cancer Center in Helsinki. From 2015, he acted as the Visiting Professor in the Nuclear Medicine Department, The University of Texas, MD Anderson Cancer Center, Houston, TX; his last visit was in 2019.

Prof. Kairemo has also held posts in the industry as Medical Director of CTT Cancer Targeting Techolologies (2001-6), Medical Director of Imanext Ltd (2006-8), and Clinical Director at Advanced Accelerator Applications SA in 2009 (now Novartis Co.).

Prof. Kairemo has vast experience in the development of tumour-seeking compounds, including monoclonal antibodies, specific phage-display peptides and cytotoxic drugs, and he has coordinated several EU Research Programme proposals, including the National Coordinator and Management Committee Member for the European Union COST Action Project (BM 0607, Targeted Radionuclide Therapy) from 2007-11. He also served as Governing Body Member in 2009-2012, again in 2018-2021, and now as the President-Elect in the World Association of Radiopharmaceutical and Molecular Therapy (WARMTH). He has also been active in hosting short-term scientific visits for students from developing countries.

Besides a few patents, Prof. Kairemo has published more than 250 original publications in peer-reviewed journals (H-index 34). He received the Lifetime Achievement Award from WARMTH in 2012, and was appointed the President of the 7th International Conference on Radiopharmaceutical Therapy held in November 2012 in Levi in Finnish Lapland. In 2014, Dr. Kairemo hosted ISORBE Symposium and Workshop "Cell Labelling and Cell Therapies" in Helsinki. He also organized the International Symposium on Radiopharmaceutical Therapy (WARMTH) in November 2018 in Helsinki.