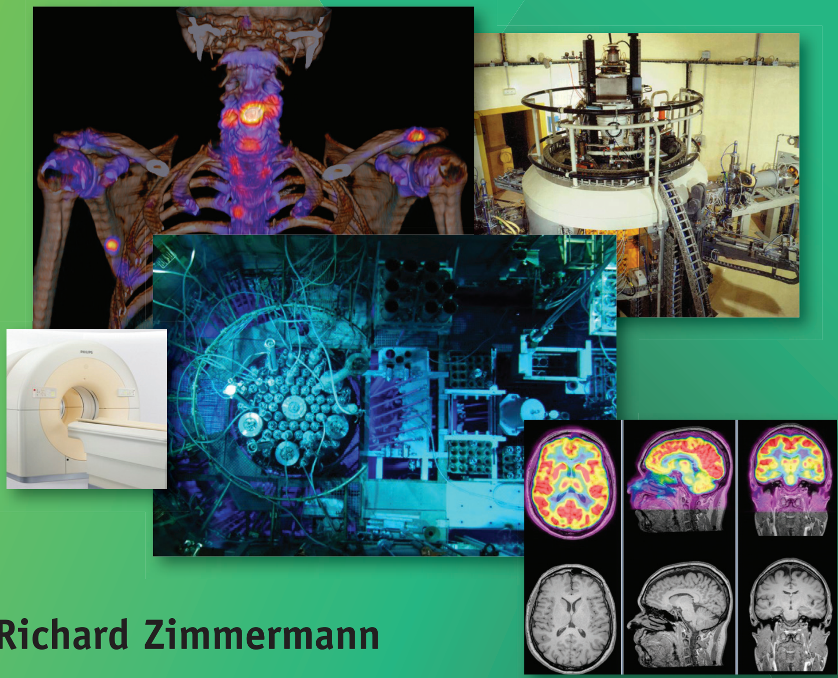
Nuclear Medicine

Radioactivity for Diagnosis and Therapy

2nd edition



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edp sciences

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To Christiane

This work is dedicated to all the anonymous persons who are directly or indirectly involved in the discovery, development, preparation, handling and application of radiodiagnostics and radiotherapeutics. They are technicians, cyclotronists, engineers, radiochemists, radiopharmacists, biologists, clinicians, nurses, scientists, salesmen, specialists of radioprotection and safety, experts in quality and logistics, environment professionals, regulatory affairs authorities, maintenance specialists, archivists, etc., Without their precious contribution, nuclear physicians and radiotherapists would not be able to bring to their patients – who are often affected by extremely invalidating diseases, sometimes considered as incurable – the benefit of these extremely complex and particularly efficient products.

Hence, this work is also dedicated to all patients that have benefited, could benefit, or will benefit from the progress of this technology.

CONTENTS

PREFACE

Richard Zimmermann offers a very complete and didactic work to better understand nuclear medicine, an unknown medical discipline that touches on all fields of human pathology.

This book has the merit of addressing all aspects related to the diagnostic and therapeutic use of radioisotopes, by exhaustively describing the current clinical applications with an opening on the products under development. But it also explains in a pedagogic way what are the physical principles, technological developments, and regulatory constraints that apply to this field of medicine. This book is intended for the general public and will allow readers, be they neophytes, healthcare professionals, or health policy representatives, to better understand the huge clinical impact of this technique.

At a time when a certain radiophobia was developing in the world as a result of catastrophic nuclear accidents, it was important to explain the interest and the major contribution of nuclear power in medical practice. With this excellent work, Richard Zimmermann shares his knowledge and greatly contributes to the debate.

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Past President of the European Association of Nuclear Medicine

INTRODUCTION AND DEFINITIONS

Nuclear medicine covers the area of a medical practice based on the resources of physics, its tools and products – nuclear meaning related to the nucleus of the atom – in order to be applied both for diagnosis and therapy. In both cases, a substance containing a radioactive isotope or **radionuclide** (one speaks about a radiolabelled substance) is directly administered to a patient. The radiolabelled product travels through the body to reach and accumulate specifically in a biological tissue or an organ. The concentration of this radionuclide in the targeted tissue or organ is favoured by the design of the organic or biological substrate, or **vector,** on which this radionuclide is grafted. Depending upon the type of emitted radioactivity, this product will be useful either to locate the targeted tissue or organ (diagnosis), or to initiate the destruction of these cells (therapy).

The term **radiotracer** refers to the notion of minute (trace) amounts of the substances in use, and also to the advantageous ability to "trace" the dissemination of the molecule in the body as a consequence of the linked radioactivity (light). The selection of the radionuclide is based on the nature of the emitted radiation, its physical properties, i.e. energy and half-life, and its chemical properties. They will define the final purpose of these molecules, called **radiopharmaceuticals**, among which molecules dedicated to diagnosis are called **radiodiagnostics**. The diagnosis imaging technology – also called scintigraphy – is obtained by means of substances labelled with γ-emitter isotopes. The development of imaging acquisition technology associated with powerful information technology software has resulted in the development of the tomography technology, generating cross sections images and tri-dimensional pictures. Some radioactive elements can be used for therapeutic purposes thanks to their different physico-chemical properties; indeed, their short distance ionising effect leads to cell destruction. The use of these vectors in association with therapy radionuclides, essentially β-or α emitters, is called **vectorised** or **metabolic radiotherapy**. Such radiolabelled drugs used in therapy are also called **radiotherapeutics.**

The use of radioactivity generated by external sources (radiotherapy), including particle beam generators such as neutron therapy and proton therapy, remains under the control of radiotherapists. Hence, nuclear physicians have limited interactions with these technologies. The same applies to **brachytherapy,** also called **curietherapy**, a technology devoted to the use of permanent or temporary radioactive implants for the treatment of tumours. Still, these technologies will be described in this work. Finally, analogue sources (mainly X-rays) are used in **radiology** to obtain organ image data from different angles around the body; they are not part of nuclear medicine either.

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Nuclear Medicine, What For?

After about seven decades of development and practice, nuclear medicine has recently reached a turning point. Indeed, over the past ten years, nuclear medicine has undergone three major technological breakthroughs directly impacting the way patients are handled. These three technical revolutions resulted from the implementation of very high capacity computer systems capable of handling the huge amount of data associated to the powerful imaging acquisition systems; the development of the system called hybrid imaging, and in particular the PET/CT equipment associated to the extension of the PET manufacturing network; and the demonstration of the efficacy and specificity of radiotherapeutics.

The new imaging modalities that appeared on the market at the dawn of the new millennium, as well as the new molecules and therapeutic technologies associated to radioactivity, open new and promising perspectives that fascinate experts from other medical disciplines – oncologists, haematologists and neurologists in particular. At the same time, the conventional pharmaceutical industry took an interest in these modalities – particularly in therapy; additional funding is now available for larger development programs.

This work does not intend to put forward new therapies and original answers to pathologies that seem hopeless. Physicians do have all the competencies required to prescribe the most appropriate treatments for specific patients and diseases. This book simply aims to provide detailed information with easily understandable words to a public most often unaware that such a discipline exists, and that it brings a new breath of life to diagnosis and therapy, especially in oncology.

For a long time, therapy by means of nuclear medicine was restricted to very difficult cases and last-chance treatments. Up to now, physicians recommended that metabolic radiotherapy should only be used after surgery, chemotherapy, and external radiotherapy protocols repeatedly failed. One forgets much too quickly that Iodine-131 has been used in thyroid cancer treatment since 1945. For the past sixty years, more than 90% of all thyroid cancers have been successfully treated – and most of them definitely cured – thanks to this nuclear medicine method. However, one ought to admit that, until recently, this therapeutic success was the only one reported in this field.

In most cases, nuclear medicine was essentially limited to being a support for diagnosis, mainly based on two different scintigraphy methods.

In this introductory chapter, we will see how patients can benefit from the knowledge acquired over the past half-century in the field of nuclear medicine, and learn about revolutionary new techniques and medicinal products. We will also take a look at all the opportunities offered by this technology in association to other innovative medical modalities.

WHAT DO WE CALL CANCER?

All living beings originate from a single cell which divides, grows, and continues to multiply while undergoing differentiation, in order to form the specific cells units of specific tissues and various organs that make up an individual. The production of these cells follows a complex predefined process, at a rhythm that is also predetermined. However, mature bodies stop expanding, and the production of new cells concentrates on specific growth mechanisms such as for hair or blood, and also as part of repair mechanisms such as skin regeneration or wound self-repair. The lifespan of a cell is limited; hence, its renewal is necessary.

Taking into account the impressive number of cells required to build a complete body, the process regularly deviates, giving birth to cells with unexpected structures. In addition, cells are continually subject to external stress and chemical aggressions – called the toxic effect – and this factor also interferes with the process of cell reproduction. Although the body is well-adapted to automatically correct or destroy these aberrant cells, sometimes such new entities find a more hospitable – or in any case less hostile – environment in which they can reproduce identically. When these new types of cells are not rejected by the organism, they create a new tissue called a tumour.

Tumours may either be benign or malignant. Benign tumours are not cancers, because they do not propagate themselves at the expense of neighbouring healthy and normal cells. If necessary, they can be easily removed without any consequence and without recurrence, and above all they do not represent a vital risk to the patient.

Malignant tumours, on the other hand, are composed of abnormal cells which divide and grow in a wild fashion, invading the tissue to the point of destroying it or preventing its proper functioning. Malignant tumours grow at the expense of neighbouring healthy cells, taking their nutriments. They divide, and grow to the detriment of healthy tissue, and at a later stage they spread and travel along the blood or lymphatic system, re-implanting themselves at remote places. This new distant cell colony, called

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a metastasis, has the same properties as the original tumour cells, and will also continue to grow. In turn, these metastases invade and colonise other tissues, causing the disease to spread further again.

Each tumour cell is a malformation of a healthy cell of a very specific type. Therefore, it can be identified by the organ from which it originated. As the formation of a metastasis is only a remote colony, that is to say a relocated reproduction of these same cells, metastases of an identified type will display the same properties as the cells belonging to the original tumour. Thus, the primary tumour and the metastases of a tumour originating in the prostate will both be treated in an identical way, even if the latter are located in another organ far from the prostate. It is therefore important to determine the origin of a cancer – i.e. the primary tumour – in order to be able to treat the metastases, even long after the original primary tumour has been removed.

A patient being treated for lung cancer and showing metastases of the liver is not suffering from liver cancer, but from a lung cancer that has spread. This person will be treated for lung cancer via a therapeutic protocol that greatly differs from liver cancer treatment.

Lymphomas and leukaemia are particular cancers that form in the blood precursor cells (hematopoietic system). These abnormal cells circulate in the blood and lymphatic systems, and reproduce to the detriment of blood cell production. They are sometimes called liquid cancers in order to be distinguished from solid tumour cancers.

I. THE ORIGINAL CASE OF THYROID CANCER

Iodine-131 has historically played a key role in nuclear medicine; we shall therefore start with this drug. The earliest imaging trials, followed by the first therapeutic treatments of hyperthyroid disease with injected radioactivity, began in 1942 under the control of American physician Saul Hertz. In 1946, he demonstrated that not only did thyroid tumours disappear following Iodine-131 treatment, but also all metastases, thus proving the therapeutic efficacy of this technique. This incontestable advantage is linked to the fact that thyroid tissue is the only tissue capable of absorbing iodine. This fixation also includes the metastases, as these tissues are originating from the thyroid cells and are of the same biological structure as the originating primary thyroid cancer cells. Today, the injection of radioactive iodine remains essential for the diagnosis of thyroid diseases as well as for their treatment *(see Chapter 6, Section I below)*. Unfortunately, it remains the unique example of human tissue fixing a radionuclide in such a specific manner.

Nevertheless, iodine having demonstrated some additional physico-chemical advantages, isotopes from this family could be used for other applications in nuclear medicine when linked to active vectors.

II. THE DIAGNOSIS ASPECT

Nuclear medicine imaging is first of all a functional imaging tool used to check if a tissue or an organ functions, i.e. if it is alive. Contrarily to all other imaging modalities, only nuclear medicine can prove brain death for example. Magnetic Resonance Imaging (MRI), X-rays (X), or Ultrasounds (US) are unable to make the difference between dead and living tissues, and will only provide a nice three-dimensional image of the brain. Radioactive tracers will provide an image only from functional brain cells. Obviously, this imaging technology is not used in such an extreme case, and a cheaper electroencephalogram (EEG) will provide the same information in a simpler way. However, this example shows that this technology is extremely powerful as it can be used to monitor the functioning of the brain, the heart (necrosis, infarction), or the growth rate of a tumour invading a tissue *(Chapter 4)*. Therefore, almost every organ can be visualised in terms of biological function, and tracers are now available for nearly all tissues (bone, liver, kidney, heart, lung, gastro-oesophageal tract, etc.) and fluids (blood, cerebro-spinal fluid, urinary excretion tract, etc.). The nuclear medicine technology is a true functional imaging tool, whereas all other imaging technologies must be considered as morphological imaging tools.

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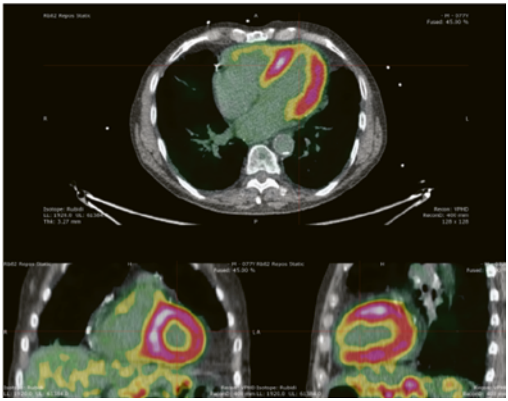

PET cardiac imaging using Rubidium-82 as a tracer. The three images clearly show the shape of the cardiac muscle from three different angles (top, front, and side). Defects identified in the overall shape of the muscle heart are indicative of ischemia or necrosis.

Courtesy Keosys Nantes, France

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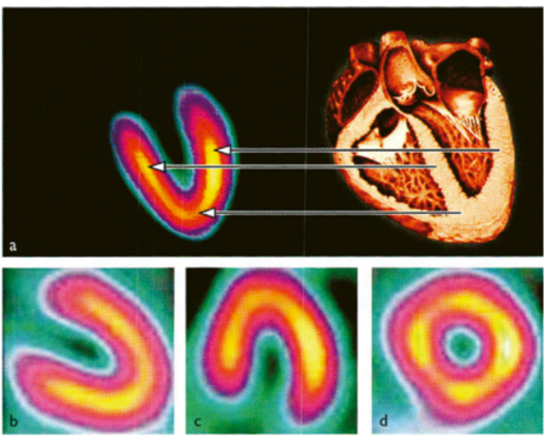
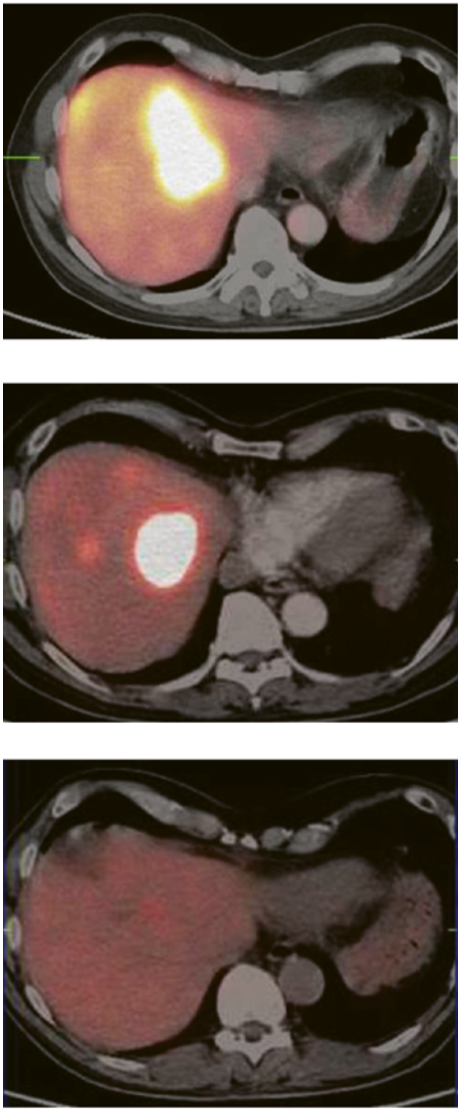


(a) Cardiac image obtained after injection of Technetium-99m tetrofosmin. The radioactive substance is integrated into the active healthy cells. The cells' incorporation level is directly linked to the rate of radioactivity, which is represented by a colour scale depending on the intensity level. One can therefore clearly superimpose the muscular part of the heart that will show a U-shape in a section scanned from the front (b) or from the side (c), and a doughnut shape (d) if seen from the top. Any reduction in size of this area, any missing colours indicate an ischaemic area. If the image of this area does not resume to a normal colour set following a stress test (bicycle or treadmill), one can consider that this area corresponds to a necrosis. Medical treatment will be adapted accordingly.

Courtesy GE Healthcare



16.

Efficacy of radiotherapeutics. From top to bottom: (a) large liver metastasis in a patient with Neuroendocrine tumor (pancreas cancer) before treatment – at this stage, life expectancy was about 6 months; (b) same patient one year after treatment with Yttrium-90 labeled somatostatin analogue; (c) liver image taken 3 years after treatment with the Lutetium-177 labeled somatostatin analogue. Images were obtained with the Gallium-68 somatostatin analogue.

Courtesy Zentralklinik Bad Berka, Germany (Prof R. Baum)