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Radionuclide Metabolic Therapy

Clinical Aspects, Dosimetry and Imaging

A Technologist's Guide

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Editors

Peștean, Claudiu (Cluj – Napoca)
Veloso Jéronimo, Vanessa (Loures)
Hogg, Peter (Manchester)

Contributors

Berhane Menghis, Ruth (Liverpool)
Bodet-Milin, Caroline (Nantes)
Chiti, Arturo (Milan)
Cutler, Cathy S. (Missouri)
do Rosário Vieira, Maria (Lisbon)
Faivre-Chauvet, Alain (Nantes)
Flux, Glenn (Sutton, Surrey)
Gorgan, Ana (Cluj – Napoca)
Kraeber-Bodéré, Françoise (Nantes)
Larg, Maria Iulia (Cluj – Napoca)
Lowry, Brian A. (Liverpool)
Lupu, Nicoleta (Cluj – Napoca)
Mantel, Eleanor S. (Philadelphia)
Mayes, Christopher (Liverpool)
Pallardy, Amandine (Nantes)
Peștean, Claudiu (Cluj – Napoca)
Piciu, Doina (Cluj – Napoca)
Rauscher, Aurore (Nantes)
Silva, Nadine (Lisbon)
Sjögreen Gleisner, Katarina (Lund)
Strigari, Lidia (Rome)
Szczepura, Katy (Manchester)
Testanera, Giorgio (Milan)
Vinjamuri, Sobhan (Liverpool)
Williams, Jessica (Philadelphia)

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Foreword

Nuclear Medicine is a composite discipline in which radionuclide therapy has a role of growing importance, with an increasing impact on clinical practice. Advances in radiopharmaceutical production and the implementation of a multidisciplinary approach in clinical medicine have propelled radionuclide therapy methods and application towards personalised treatment, therapeutic efficacy, patient comfort and radiation safety. Technologists are key figures in this process, since their competencies allow them to play an important role in every step necessary for successful treatment, from radiopharmaceutical preparation to administration. They are also the main actors in pre- and post-therapeutic imaging. The current book is specifically aimed at radiographers and technologists working in, or intending to work in, a Nuclear Medicine department with radionuclide therapy facilities, though it is also likely to be valuable for other healthcare professionals working in, or willing to work in, this challenging environment.

A successful radionuclide therapy unit is not only fundamental for patient care in Oncology, Endocrinology and Orthopaedics, but can also serve as a gold standard in an interprofessional and multidisciplinary approach to clinical medicine.

Following the successful PET-CT Tech Guide series, this book is the joint work of many professionals from different nations and fields of interest within Nuclear Medicine. I want to really thank all those people who have contributed to this work as authors and reviewers, without whom the book would not have been possible. I am proud to be able to welcome and thank our colleagues from the SNM (Society of Nuclear Medicine, United States) for their high-quality contributions. I also wish to extend particular gratitude to the EANM Dosimetry and Therapy Committee for their availability and expertise in the required fields. Special thanks are due to Claudiu Peştean, Vanessa Veloso Jerónimo and Professor Peter Hogg, for their incredible enthusiasm and competence in dealing with the editorial duties and organisational work. Finally, I remain extremely grateful to the EANM Executive Committee, the EANM Executive Secretariat, the Technologist Committee and all the EANM committees involved in the project.

With my warmest regards

Giorgio Testanera
Chair, EANM Technologist Committee

Introduction

Claudiu Peştean, Vanessa Veloso Jerónimo and Peter Hogg

This year we have focussed on radionuclide therapy for our book. For decades, radionuclide therapy has been used to help manage a range of malignant and benign diseases, and for many pathologies its utility is well known and well documented. In the early years the radionuclide range and the pathologies which could be managed (treatment and/or palliation) were limited. However, significant progress continues to be made, and there has been considerable expansion in the available therapeutic radionuclides and the pathologies which can be managed by them. On this basis we feel it is timely for this book to be published. The book brings together experts in the field of radionuclide therapy from Europe and America in order that they can share their theoretical knowledge and clinical/practical experience. These experts emanate from a range of professional backgrounds and include medical physicists, nuclear medicine physicians, radiographers, nuclear medicine technologists and others.

The book commences with background information about radionuclide therapy (Section I). If you are new to radionuclide therapy, then we suggest that special attention is paid to the first four chapters as the information covered will give you a good theoretical grounding; with this in mind you can progress to read about the clinical and technical aspects of radionuclide therapy in Section II. Here, attention is paid to how to conduct radiotherapy procedures and also the pathologies which it can treat and/or where it can be used for palliation. This section contains significant input from those who practice radionuclide therapy, especially nuclear medicine physicians and others who have a range of relevant clinical skills. In Section III we consider the future, and particular emphasis is placed on molecular therapy. The final chapter considers new radionuclides which may become valuable in the future.

We should like to thank the authors who have taken the time to write the chapters and also the reviewers who have provided constructive feedback to the authors. We acknowledge that writing and reviewing involves a considerable effort and we hope that the readers will find this book useful for training and practical purposes.

Acronyms

AFP	Alpha-fetoprotein
AJCC	American Joint Committee on Cancer
ALARA	as low as reasonably achievable
ALYSMPCA	Alpharadin® in Symptomatic Prostate Cancer clinical trial
Anti-TPO	anti-thyroid peroxidase antibodies
ATA	American Thyroid Association
AuNPs	gold nanoparticles
BED	biologically effective dose
BRAF gene	human gene precursor of B-Raf protein
BRMs	biological response modifiers
BSA	body surface area
BT	brachytherapy
CCK	cholecystokinin
CD20	B-lymphocyte antigen
COX	cyclo-oxygenase
CPPD	calcium pyrophosphate dihydrate
CR	complete response
CT	Computed Tomography
DIC	disseminated intravascular coagulation
DIMs	differentiating intermitotic cells
DLBCL	diffuse large B-cell lymphoma
DMARDS	disease-modifying anti-rheumatic drugs
DNA	deoxyribonucleic acid
DSB	double-strand break
DTC	differentiated thyroid carcinoma
EANM	European Association of Nuclear Medicine
EBRT	external beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
ETA	European Thyroid Association
FBC	full blood count
FIT	first-line indolent trial
FL	folicular lymphoma
FNAB	fine-needle aspiration biopsy
FPMs	fine postmitotic cells
FT_3	free T_3
FT_4	free T_4
FTC	follicular thyroid cancers
GFR	glomerular filtration rate
HAMA	human anti-murine antibody
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HEGP	high-energy general-purpose
HR	homologous recombination
IAEA	International Atomic Energy Agency
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiation Units and Measurements
ITLC	instant thin-layer chromatography
LET	linear energy transfer
LQM	linear quadratic model
LSF	lung shunt fraction
LT_4	levothyroxine
MAbs	monoclonal antibodies

MCTs	multipotential connective tissue cells
MIBG	metaiodobenzylguanidine
MIRD	Medical Internal Radiation Dose Committee
MRI	Magnetic Resonance Imaging
MRT	Molecular radiotherapy
MTC	medullary thyroid carcinoma
NCI	National Cancer Institute
NETs	neuroendocrine tumours
NHEJ	and non-homologous end joining
NHL	non-Hodgkin's lymphoma
NPs	nanoparticles
NTCP	normal tissue complication probability
OR	overall response
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography integrated with Computed Tomography
PR	partial response
PRRT	peptide receptor radionuclide therapy
PRRT	Peptide receptor radionuclide therapy
PTC	papillary thyroid cancers
PVNS	pigmented villonodular synovitis
RA	rheumatoid arthritis
RAIU	radioactive iodine uptake test
RBE	relative biological effectiveness
RECIST	Response Evaluation Criteria in Solid Tumours
RIT	Radioimmunotherapy
ROIs	regions of interest
RPMs	reverting postmitotic cells
SCID	Severe Combined Immunodeficiency
SPECT	Single Photon Emission Computed Tomograpy
SPECT/CT	Single Photon Emission Computed Tomograpy with Integrated Computed Tomography
SRS	somatostatin receptor scintigraphy
SSTRs	somatostatin receptors
SWNT	single-walled carbon nanotubes
T_3	triiodothyronine
T_4	thyroxine
TACE	transarterial chemo-embolisation
TAE	transcatheter embolisation
TCP	tumour control probability
Tg	thyroglobulin
THPAL	trimeric phosphino alanine
TNF	tumour necrosis factor
TRab	anti-thyrotropin receptor antibodies
TSH	thyroid stimulating hormone
TTP	time to progression
US	ultrasound
VIMs	vegetative intermitotic cells
VOIs	volumes of interest
WBS	whole-body scanning
WFH	World Federation of Hemophilia
WHO	World Health Organization

Section I

1. Principles in Radionuclide Therapy

Eleanor S. Mantel and Jessica Williams

Introduction

Not long after the discovery of radium by Marie and Pierre Curie in 1898, Alexander Graham Bell predicted its use to treat tumours in 1903. Within 10 years, radium had indeed been used to treat a multitude of diseases [1]. The discovery of radium thus directly led to the progress in radionuclide therapy. While radionuclide therapy has evolved over the years, the basic theory has stayed the same. Radionuclide therapy uses ionising radiation to kill or shrink abnormal cells and tumours by damaging the cells' DNA, which causes them to stop growing. Although these treatments are delivered systemically, they are cell specific, targeting distant metastases throughout the body as well as the primary tumour. The cessation of cell growth allows not only for palliative therapy, but the complete ablation of certain cancerous disease processes while eliciting a low or no physiological response from the patient. This is attributed to the patient-specific dosing, which potentially keeps the levels of toxicity to a minimum. This, in turn, helps to improve the patient's tolerance to treatment and may improve prognosis and outcome.

All of the therapies discussed in this chapter are accomplished by utilising beta-emitting isotopes to deliver a high localised radiation dose. Beta particle emission occurs when the ratio of neutrons to protons in the nucleus is too high. An excess neutron is transformed into a proton and an electron. The proton stays in the nucleus and the electron is expelled. Often, gamma-ray emission accompanies the emission of a beta particle. Typically, if there are gamma emissions, they follow the decay of the beta. It is this gamma ray emission that allows some of the isotopes, at lower doses, to be used for diagnostic and dosimetric purposes prior to treatment. Every isotope has a unique energy that is produced. The energy of the particle itself determines how much speed a beta particle has, how far it can penetrate and how much energy it emits to the tissue. As with all radioactive emitters, beta emitters must be shielded. Beta shielding is, generally, achieved using Lucite or plexiglass. Lucite and plexiglass are the materials of choice for shielding in an attempt to reduce the number of bremsstrahlung interactions and production of X-rays. However, in some high-dose or high-energy therapies that have a component of gamma decay, lead shielding may be used as well.

Generally, medical therapies have a benefit versus risk ratio that must be considered. When considering a radionuclide therapy regimen, one needs to review the patient's medical history to determine whether he or she is an ideal candidate for the treatment. Each specific radionuclide therapy has its own set of relative and absolute contraindications. Some common contraindications in female patients include pregnancy and breastfeeding [2-6]. Adherence to radiation safety precautions and instructions is essential for all radiotherapy administrations. For patients unable to adhere to certain

restraints following the treatment (for example, patients with urinary incontinence [2]), an in-patient admission might be necessary. Admission to the shielded isolation ward may be required for patients receiving treatments with certain high-energy isotopes or at high doses, depending on the regulatory requirements [2].

Radioisotopes and their uses in radionuclide therapy

In this chapter, we will explore a number of isotopes that can be used for radionuclide therapy. Since each of the isotopes can be used either independently or bound to another chemical compound, they are employed to treat different disease processes.

Iodine-131

A commonly used isotope for radiotherapy is iodine-131 (^{131}I). ^{131}I is a beta emitter with a principal gamma ray of 364 keV (81% abundance) and beta particles with an energy of 0.61 MeV. Its half-life is 8.1 days and it has an average range in tissue of 0.4 mm. ^{131}I is produced by the irradiation of tellurium-130 in a nuclear reactor. While some patients may be treated on an out-patient basis, regulatory requirements may necessitate those receiving high doses of ^{131}I to have an extended stay in a lead-lined room as an in-patient. Patients receiving these higher doses require special handling in an effort to minimise radiation exposure to those around them.

Given in its natural form, ^{131}I-sodium iodide is used to treat residual thyroid cancer and metastatic disease by ablating any residual tissue after partial or complete thyroidectomy. ^{131}I-sodium iodide is also used to treat non-cancerous diseases such as hyperthyroidism and non-toxic multinodular goitre. The dose is administered orally and can be in capsule or liquid form since this radionuclide is readily absorbed from the gastrointestinal tract into the salivary glands, gastric mucosa and thyroid tissue. Because both malignant and benign disease processes are treated utilising ^{131}I, the dose will differ from one patient to another. Doses generally range from 1.11 to 11.1 GBq.

Prognosis following ^{131}I therapy varies among cancer patients. While patient age, gender, pathology of the cancer, grading and size all have an effect on how thyroid cancers behave, they still have a favourable prognosis. The well-differentiated types of thyroid cancer, follicular and papillary, generally have better outcomes than the other types (medullary and anaplastic), with 10-year survival rates of between 92% and 98%. However, 5-20% of patients with well-differentiated thyroid cancer will experience loco-regional relapse that requires additional treatments and/or surgery [7].

Patients with hyperthyroidism that is treated with ^{131}I-sodium iodide have a high response rate. Those given a higher dose of ^{131}I-sodium iodide (600 MBq) have a higher cure rate but also an increased incidence of hypothyroidism [8].

^{131}I-labelled metaiodobenzylguanidine (MIBG) is an analogue of noradrenaline [2] and therefore is taken up by the adrenergic nervous system. It is this uptake that makes ^{131}I-MIBG the tracer of choice when treating a number of different cancers and diseases. When ^{131}I is tagged to MIBG, it can be used to treat stage III or IV neuroblastoma, inoperable phaeochromocytoma, inoperable carcinoid tumour, inoperable paraganglioma and metastatic or recurrent medullary thyroid cancer [2]. The dose is administered via slow intravenous infusion and ranges between 3.7 and 11.2 GBq. Approximately 60% of patients treated for phaeochromocytoma respond to this therapy. Thirty percent see a regression in tumour size while 30% experience symptom relief; unfortunately, however, about a third of the patients have no response at all [7].

^{131}I-Lipiodol is another form of ^{131}I radiotherapy and is used to treat inoperable primary hepatic carcinoma. Lipiodol is a naturally iodinated fatty acid ethyl ester of poppy seed oil. This iodine-labelled product consists of fat droplets of approximately 20–200 µm in diameter. Lipiodol is administered directly into the hepatic artery in a volume of 2–3 ml. The standard dose administered is 0.9–2.4 GBq. ^{131}I-Lipiodol targets cancer cells, causing cytotoxicity in the tumour cells while sparing the normal cells and tissues surrounding the tumour. While a majority of the dose is retained in the liver, lung fibrosis is a common complication when high lung uptake is identified. ^{131}I-Lipiodol was found by Raoul et al. to have reduced tumour size in approximately 55% of those treated [9].

^{131}I-tositumomab is a murine monoclonal antibody that is used to treat CD20-positive, follicular, non-Hodgkin's lymphoma refractory to rituximab and in relapse. The therapy is administered intravenously. On the basis of the initial dosimetric calculations, most patients receive a therapeutic dose of 2,590–3,330 MBq, but there is a wide variation in dose range. Patients who have previously received murine antibodies must have a negative serum human anti-murine antibody (HAMA) result before proceeding with additional treatment regimens. Use of ^{131}I-tositumomab is also contraindicated in patients with hypersensitivity to murine (mouse) proteins. It has been found that patients undergoing this therapy have a 63% response rate with a median duration of 25.3 months [7].

Yttrium-90

Yttrium-90 (^{90}Y) is a beta emitter with a half-life of 2.7 days and an energy of 2.27 MeV. It has an average soft tissue range of 3.6 mm. ^{90}Y is produced by high-purity separation from strontium-90 (^{90}Sr), a fission product of uranium in a nuclear reactor.

^{90}Y-ibritumomab tiuxetan is a CD20-directed radiotherapeutic antibody used to treat patients with relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma (NHL) and previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy [6]. ^{90}Y-ibritumomab

tiuxetan is contraindicated in patients with hypersensitivity to murine (mouse) proteins. Four hours prior to administration of the ^{90}Y-ibritumomab tiuxetan, the patient receives rituximab therapy with the goal of clearing the majority of normal B cells so that the therapeutic dose is more focussed on the tumour cells. ^{90}Y-ibritumomab tiuxetan is administered intravenously through a 0.22-µm low-protein-binding in-line filter between the syringe and the infusion port. The dose itself is based on the patient's platelet count and actual body weight. Post-treatment evaluation is an important component of this treatment as thrombocytopenia and neutropenia are common adverse events, occurring in approximately 90% of patients. Seventy percent of rituxan-refractory patients treated with ^{90}Y-labelled rituxan showed an overall response that lasted 7.7 months [7].

^{90}Y-microspheres are utilised as a treatment in patients with non-resectable hepatomas and liver metastases [10,11]. Microspheres are a single-use, permanently implanted radiotherapy source. The radioactive microspheres are delivered directly to the liver via an intra-arterial catheter in the hepatic artery that supplies blood to the tumour. The microspheres are not metabolised nor are they excreted; therefore they remain within the tumour and continue to have a radiotherapeutic effect. Generally, the doses for these therapies are 1.5–2.5 GBq but choice of dose is patient dependent. It is important to determine the percent of lung shunting present prior to the administration of the treatment in order to ensure that the microspheres will localise in the intended tumour site and not end up in the stomach, lungs or small intestines. Cumulative dose is also taken into account in patients receiving consecutive treatments. Doses for patients with increased shunting or previous therapy administrations will be decreased appropriately.

There are two types of microsphere: resin and glass. Resin microspheres are 20–60 µm in diameter. The activity for a single resin microsphere is 40–70 Bq, with a total number of particles implanted of 30–60 x 10^6. Resin microspheres are routinely administered to patients with liver metastases from colorectal carcinoma. Response rates have been shown to be higher in patients receiving this therapy in conjunction with a chemotherapy regimen as compared to those receiving just the chemotherapy regimen, and it has also been shown that the former group has an improvement in time to progression [11]. The glass microspheres are 20-30 µm in diameter, with each milligram containing approximately 22,000–73,000 microspheres. The activity for a single glass microsphere is 2,500 Bq. Glass microspheres are used for compromised portal venous flow or portal vein thrombosis and in patients diagnosed with hepatocellular carcinoma (HCC), typically secondary to viral hepatitis or cirrhosis. According to clinical studies, the median survival rate depends on the dose administered. A 3.6-month median survival rate was documented for patients receiving a dose of

less than 80 Gy, while those receiving a dose greater than or equal to 80 Gy had a median survival rate of 11.1 months [10].

^{90}Y-silicate/citrate as a colloid is suitable for the treatment of inflammation of the synovium in the knee only [12]. This treatment is more commonly known as radiation synovectomy/radiosynoviorthesis. There are multiple indications for use of ^{90}Y-silicate/citrate for the treatment of joint pain arising from arthropathies, including: rheumatoid arthritis, spondylarthropathy (e.g. reactive or psoriatic arthritis), inflammatory joint diseases (e.g. Lyme disease) , Behçet´s disease, persistent synovial effusion, haemophilic arthritis, calcium pyrophosphate dihydrate (CPPD) arthritis, pigmented villonodular synovitis (PVNS), persistent effusion after joint prosthesis, undifferentiated arthritis where the arthritis is characterised by synovitis, synovial thickening or effusion.

The route of administration is intra-articular injection. In order to avoid leakage of the radiocolloid from the joint space and to ensure that it is absorbed by the phagocytes within the joint, the particle size must be between 10 and 20 µm. The size of the particles is also important in ensuring that the radiocolloid remains uniformly within the joint space without causing an inflammatory response. The dose commonly used is 185–222 MBq. It was found by Gencoglu et al. that 58% of patients had a good clinical response to this therapy, with the remainder having a fair or poor response [13].

Phosphorus-32

Phosphorus-32 (^{32}P) is a reactor-produced, pure beta-emitting radionuclide with a half-life of 14.3 days. The maximum beta particle energy is 1.71 MeV. The particle range in tissue is 8 mm.

^{32}P-sodium phosphate can be used for two different therapies: palliation of pain from bone metastasis and myeloproliferative diseases (polycythaemia vera and essential thrombocythaemia) [3,14].

Since ^{32}P-sodium phosphate accumulates in the hydroxyapatite crystal of the bones in a similar manner to phosphate, it is an ideal tracer for palliation of pain from bone metastasis. This therapy can be administered either intravenously or orally. The intravenous therapeutic dose is 117–370 MBq, while the oral dose range is commonly 370–740 MBq.

Another use for ^{32}P is in the treatment of polycythaemia vera and essential thrombocythaemia [3]. ^{32}P has been used successfully to treat polycythaemia vera since 1939. Doses are based on the patient's weight and blood counts. Intravenously administered doses range from 37 to 740 MBq, with an average dose range of 37–296 MBq. Some patients require repeat treatments and doses are adjusted as necessary depending on the patient.

^{32}P-chromic phosphate as a colloid is used in several contexts: for treatment of malignant effusions/malignant diseases of the serosal cavities and of cystic neoplasms and for radiosynoviorthesis.

While the treatment of choice for malignant effusions, in both the chest and the abdomen, is typically chemotherapy, ^{32}P-chromic phosphate does provide a possible alternative for some patients. This radiocolloidal suspension is administered via intracavitary injection directly into the serosal cavity (pleural, pericardial or peritoneal). Pre-treatment imaging with ^{99m}Tc-sulphur colloid is required to determine the overall distribution of the tracer as well as to quantify the loculation, if present. Common dose ranges are dependent on the area/cavity being treated. The suggested dose range for intraperitoneal administrations is 370–740 MBq, while for intrapleural administration it is slightly lower, at 222–555 MBq, and pericardial doses range from 185 to 370 MBq.

When ^{32}P-chromic phosphate is used for radiosynovectomy/radiosynoviorthesis the size of the colloid is extremely important. A particle size of 2–10 µm is needed to ensure that the particles can be engulfed by the phagocytes and do not leak from the joint space, potentially causing an inflammatory response. The dose, which is injected directly into the synovial joint, is determined by the size of the joint and ranges from 10–20 MBq for proximal interphalangeal joints to 185–222 MBq for knee joints.

Rhenium-186

Rhenium-186 (^{186}Re) is produced in a high flux reactor and emits a beta particle with an energy of 1.07 MeV, with a soft tissue range of 1.1 mm and a 9% abundant gamma emission with a photopeak of 0.137 MeV. The half-life is 3.7 days.

^{186}Re-etidronate is used for the palliation of pain from bone metastases, osteoblastic metastases or mixed osteoblastic lesions seen as areas of intense uptake on a bone scan, with the primary malignancy being either prostate or breast carcinoma. Low blood cell counts may be a relative contraindication when deciding to utilise this therapy option and should be evaluated carefully. The recommended dose is 1,295 MBq and it is administered intravenously [4]. Patients should be informed that their bone pain may actually increase in the first week after administration of therapy owing to a phenomenon called "pain flare". This should subside within 2–4 weeks post administration.

^{186}Re-sulphide as a colloid is used for radiosynovectomy/radiosynoviorthesis therapy. ^{186}Re-sulphur colloid is best used for hip, shoulder, elbow, wrist, ankle and subtalar joints [12]. The activity administered and the total volume administered are dependent on the joint to be injected. As with the other radiosynoviorthesis therapies, the route of administration is intra-articular. Dose ranges vary depending on the joint of interest: A typical hip and shoulder dose range is 74–185 MBq with a recommended volume of 3 ml. The wrist and subtalar dose range is 37–74 MBq with a smaller dose volume of 1–1.5 ml. The elbow dose range is 74–111 MBq with

a volume similar to that of the wrist volume of 1–2 ml. The ankle dose is 74 MBq with a recommended volume of 1–1.5 ml. The total activity of one session should not exceed 370 MBq [12].

Erbium-169

Erbium-169 (^{169}Er) is a beta emitter with an energy of 0.34 MeV that is produced in a high flux reactor. The soft tissue range is 0.3 mm. The half-life is 9.4 days.

^{169}Er-citrate colloid is used primarily for radiosynovectomy/radiosynoviorthesis and is most appropriately used for metacarpophalangeal, metatarsophalangeal and digital interphalangeal joints. The dose is administered intra-articularly and the site determines how much volume can be injected: the metacarpophalangeal dose is 20–40 MBq with a recommended volume of 1 ml, the metatarsophalangeal dose is 30–40 MBq with a recommended volume of 1 ml, and the proximal interphalangeal dose is 10–20 MBq with a recommended volume of 0.5 ml. The total dose injected should not exceed 750 MBq at any one time [12]. In a double-blind study it was found that treatment with ^{169}Er-citrate colloid had positive results in 58% of cases through destruction of the rheumatoid pannus [15].

Strontium-89

Strontium-89 (^{89}Sr) is a beta emitter with an energy of 1.46 MeV and a half-life of 50.5 days. The soft tissue range is 2.4 mm. This radionuclide interacts within the body in a similar way to calcium analogues. It rapidly clears from the blood and is absorbed in metastatic bony lesions.

^{89}Sr-chloride is another tracer utilised for palliation of pain from metastasis to the bones or mixed osteoblastic lesions from primary breast carcinoma or hormonally resistant prostate cancer or any other tumour presenting osteoblastic lesions seen as areas of increased uptake on bone scans [4,14]. The recommended dose is 150 MBq and administration is via slow intravenous infusion. Patients will generally begin to feel some pain relief 7–20 days after administration of the therapeutic dose. Low blood counts are a relative contraindication for this treatment. All patients should be monitored for changes in blood counts following this therapy.

Samarium-153

Samarium-153 (^{153}Sm) is a beta-emitting radionuclide produced from neutron irradiation of samarium-152 oxide. ^{153}Sm has an energy of 0.81 MeV and a soft tissue range of 0.6 mm. Its half-life is 1.9 days.

^{153}Sm-lexidronam is another therapeutic radiotracer used for palliation of pain from metastases to the bones or mixed osteoblastic lesions from primary prostate or breast cancer or any other tumour presenting osteoblastic lesions seen as areas of increased uptake on bone scans. The recommended dose is calculated as 37 MBq/kg and it is administered

intravenously. Since the administration of this radiotherapeutic agent can cause bone marrow suppression, it is important that the patient's blood count is monitored following the injection. Each patient's dose will be different as it is weight based. Patients may begin to experience pain relief as soon as one week after administration, and significant pain relief may last an average of 16 weeks, decreasing or eliminating the need for opiate medications [16]. This therapy appears to be a safe and efficacious method for treating patients with bone pain [17]. The shorter half-life permits a high dose to be delivered over a short period; this allows for multiple therapies if the pain is recurrent, which patients seem to tolerate well [18].

References Section I, Chapter 1

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Section I

2. Biological Effects of Ionising Radiation

Katy Szczepura

Introduction

The biological effects of ionising radiation are complicated and are influenced by many factors, including the amount and rate of energy imparted to the tissue, the type of radiation, the cell and tissue type involved, age and gender, and variation in individual sensitivity to radiation [1, 2].

This chapter discusses the biological effects of radiation, the definitions of patient dose and the calculation of risk, the way in which radiation causes damage, the effects that may occur and the different effects on tissues according to tissue type.

Definitions of dose in biological tissues

When ionising radiation interacts with a material, the ionisation and excitation that occur cause energy to be deposited within that material, known as dose. There are different definitions of radiation dose, depending on the situation under consideration.

Absorbed dose

The energy that is deposited per unit mass of a material during interactions of ionising radiation is known as *absorbed dose*. This is a measurable quantity and is defined as:

$$D = \frac{E}{m}$$

where D = absorbed dose, E = energy (joules) and m = mass (kg). Therefore the SI units of absorbed dose are J kg^{-1}; this is known as a Gray (Gy).

When the energy is absorbed in an organ it is known as *organ dose* and is defined as absorbed dose averaged over the whole organ.

Kerma

Another quantity used is kerma, which is also measured in Grays. Kerma is an acronym for *k*inetic *e*nergy *r*eleased per unit *ma*ss (or in matter or material). It describes the energy transferred per unit mass of irradiated material.

For low-energy ionising radiation, D and kerma are approximately the same, but at higher energies (>1 MeV) they start to differ. This is due to the fact that at higher incident energies, the secondary electrons that are produced may themselves have high energy and so deposit their energy outside the mass of interest, or may themselves produce bremsstrahlung radiation. This energy is included in the kerma measurement, but not in absorbed dose. Therefore the energy *released* and the energy *absorbed* are not the same in the mass of interest. Absorbed dose is the most useful measurement when considering biological effects of radiation.

Equivalent dose

It is important to consider the type of radiation that is depositing the energy to the tissue. Even for the same amount of energy, different radiation types cause differing amounts of damage.

Non-charged ionising radiation, such as photons, are known as indirectly ionising radiation; this is because an interaction of a photon and an atom will only cause a single ionisation, and most of the ionisation that then occurs is due to the secondary electron that is released.

Charged particles interact by means of the coulombic forces between the moving charged particle and the electrons in the atoms. With electrons only a small amount of energy is deposited per event and many thousands of events can occur along the path of the charged particle, which is relatively large compared to cellular dimensions; the ionisation density is therefore considered to be low. Heavy charged particles, such as alpha particles, travel much shorter distances and therefore the ionising events are more closely spaced and within distances comparable to a single strand of DNA.

For these reasons, different types of radiation cause different amounts of damage even for the same amount of energy deposited, with photons causing the least and heavy charged particles, the most. This is known as *linear energy transfer* (LET) and is defined as the sum of the energy deposited per unit path length of the radiation (Fig. 1) [3].

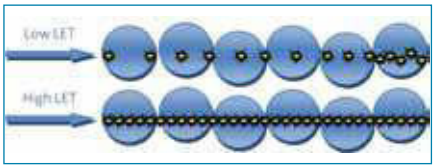

Figure 1: High and low LET [3]

The difference in biological effects due to the radiation type is reflected in the *radiation weighting factor* (W_R), which is defined as the ratio of the biological effectiveness of one type of radiation relative to that of X-rays, for the same amount of absorbed dose. The higher the W_R, the more damaging the radiation [4]. For regulatory purposes, W_R has been measured through experimentation and agreed internationally by governments and regulatory bodies. Table 1 [5] shows the W_R for common ionising radiations.

Radiation type and energy	Radiation weighting factor (W_R)
Photons, all energies	1
Electrons, muons, all energies	1
Protons >2 MeV	2
Alpha particles, fission fragments, heavy nuclei	20

Table 1: Radiation weighting factors [5]

The SI unit of equivalent dose is J kg^{-1}, but it is given the unit Sievert (Sv) to distinguish it from absorbed dose. Equivalent dose is mainly used for radiation protection purposes.

Relative biological effectiveness – weighted dose

More useful in the context of radionuclide therapy is *relative biological effectiveness* (RBE), defined as the ratio of a dose of a low-LET reference radiation to the dose of radiation that elicits the same biological response, quantitatively and qualitatively. The RBE depends on the radiation type, the dose rate, the distribution of dose in time, the cells (or tissues) exposed and the type of injury investigated.

When considering radionuclide therapy, the ICRP recommends that the organ dose is weighted by the RBE of the specific biological response. It is important to recognise the difference between W_R and RBE when considering dose to an individual: RBE is a quantity for deterministic endpoints measured under a specific set of experimental conditions and is tissue and source location dependent, whereas W_R is a single set of values chosen by committee review and so has less value when considering dose to an individual.

Guidance on appropriate values for the RBE for deterministic effects can be found in ICRP publications 58 [6] and 92 [5] and International Commission on Radiation Units and Measurements (ICRU) report 67 [7].

Effective dose

Absorbed and equivalent dose take into account the amount of energy, the mass of the tissue and the radiation used, but they do not take into account the type of tissue being irradiated.

Organs have different sensitivities to radiation, known as radiosensitivity, based on their tissue type, which will be discussed in more depth later in this chapter. *Effective dose* (E) is a calculation that takes into account this variation in radiosensitivity. It is a calculation of risk of the patient developing fatal cancer due to the irradiation.

Each organ is given a *tissue weighting factor* (W_T), based on that organ's risk of developing cancer. A W_T for each organ has been calculated by the International Commission for Radiological Protection (ICRP) and attempts to provide a single number that is proportional to the overall detriment from a particular, often inhomogeneous, type of radiation exposure. The overall detriment represents a balance between cancer incidence, cancer mortality, life shortening and hereditary effects. Table 2 shows the most recent W_T as published by the ICRP [8].

Organ	Tissue weighting factor (W_T)	Sum of W_T values
Bone marrow (red), colon, lung, stomach, breast, remainder tissues[a]	0.12	0.72
Gonads	0.08	0.08
Bladder, oesophagus, liver, thyroid	0.04	0.16
Bone surface, brain, salivary glands, skin	0.01	0.04
Total	1.00	1.00

[a] Remainder tissues: adrenals, extrathoracic (ET) region, gall bladder, heart, kidneys, lymphatic nodes, muscle, oral mucosa, pancreas, prostate (♂), small intestine, spleen, thymus, uterus/cervix (♀)

Table 2: Recommended tissue weighting factors [8]

It is important to recognise that effective dose is a measurement of risk to an average person and is based on general populations; it should never be used to calculate the risk to an individual as it does not take into account the individual's age, gender or radiosensitivity.

Risk estimates are taken from groups of people with known exposures, such as the atomic bomb survivors of Hiroshima and Nagasaki in 1945. Differences in genetics, natural levels of cancer, diet, smoking, stress and unknown bias affect these results. The doses, and dose rates, during these events were much higher than the regulated dose levels used medically. There is growing evidence that there are variations in radiosensitivity that can affect the risk of radiation-induced cancer or, at higher doses, tissue damage. A proportion of this range is likely to be due to genetic differences, but recent studies demonstrate that lifestyle factors, particularly tobacco use, affect an individual's risk [2].

Effective dose calculation for radionuclides

A schema for calculation of absorbed doses has been developed by the Medical Internal Radiation Dose Committee (MIRD) and this methodology has been widely adopted. In addition, the ICRP has introduced biokinetic models and data. This has resulted in estimation of the effective dose for a large number of radiopharmaceuticals. The figures are given in mSv/MBq, meaning that an estimation of the effective dose to a single patient can be made simply by multiplying with the administered activity. It must be noted that variations from patient to patient can be very large; nevertheless, a rough estimation of the effective dose to the patient can be made. In order to calculate absorbed dose and organ doses for an individual patient, one requires knowledge of the emissions of the radionuclide, the activity administered, the activity in the specific organ and in all other organs, the size and shape of the organ, the kinetic properties of the radiopharmaceutical and its quality. These factors are not readily available for the individual patient.

DNA damage

The energy that is transferred during ionising radiation interactions can be used to break

chemical bonds. In living tissue this breaking of bonds can be detrimental to cells, and can kill the cell or cause it to reproduce abnormally.

The biological effects of ionising radiation are mainly due to damage to the nuclear DNA chain. Ionising radiation can directly interact with DNA to cause ionisation, thus initiating the chain of events that lead to biological changes [9] (10]. This is called *direct action*, which is the main process for radiation with high LET, such as alpha particles or neutrons. Ionising radiation can also interact with molecules within the cell, in particular water, to produce free radicals, which are able to go on to interact with the DNA chain and cause damage. This is called *indirect action* (11].

Deoxyribonucleic acid (DNA)

DNA is a complex macromolecule that contains the genetic instructions used in the development and function of all living tissues. It consists of *bases* attached to a "backbone" of alternating sugar and monophosphate molecules. The bases are: adenine (A), guanine (G), cytosine (C) and thymine (T). A and G are purines and are the two larger bases. C and T are pyrimidines and are the two smaller bases. Due to their size, a large base and a small base combine opposite to each other to create the well-known double helix (C and T together would be too small, A and G together would be too big). Because of the chemical structure of the bases, C and G are always paired, and T and A are always paired (Fig. 2) [12].

One of the most important features of DNA is that it can replicate and repair. During a process called *mitosis*, the cell divides and replicates its genetic material, becoming two distinct cells, hence allowing growth and reproduction of the cell.

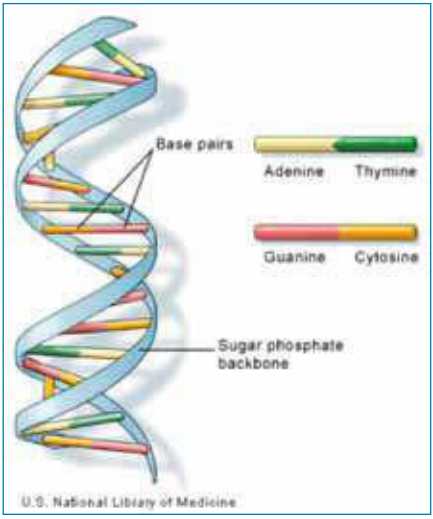

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Figure 2: DNA double-helix structure [12]

It is well recognised that the most important lesion caused by ionising radiation is the *double-strand break* (DSB), in which both strands in the DNA helix are severed. Once damaged, the DNA will attempt to repair itself. There are two main mechanisms of repair: homologous recombination (HR) and non-homologous end joining (NHEJ). In HR an undamaged DNA chain, with the same information, is used as a template to replicate the damaged part. The damage is removed and replaced by this replicated piece. NHEJ is

a rough form of repair in which the two damaged ends of the breaks are rejoined [11].

Once the repair mechanisms have been attempted, there are three main outcomes: the DNA has been repaired correctly and the cell becomes a *viable cell*; the DNA has been repaired incorrectly and the cell becomes a *mutated cell*; and the DNA was not able to be repaired and the cell becomes an *unviable cell*. If the DNA is repaired correctly, there is no lasting effect of the ionising incident, and so it needs no further consideration.

There are two categories of effects: *somatic effects*, where the damage affects the individual who has been exposed, and *genetic* or *hereditary effects*, where the damage occurs in the cells used for reproduction, known as *germ cells*, and so will affect subsequent generations.

Mutation

If the DNA has been repaired incorrectly, then the "code" within the cell is no longer correct. This is known as a mutation, and if this cell then replicates and multiplies, cancer can result. On occasion the mutation leads to the cell multiplying with no control and exceeds the natural rate of cell death; this can lead to the development of a tumour.

Apoptosis

Apoptosis is the regulated death that a cell undergoes naturally once it has completed its life cycle. If a cell has become unviable, then the cell may recognise this and go through apoptosis (Fig. 3) [12].

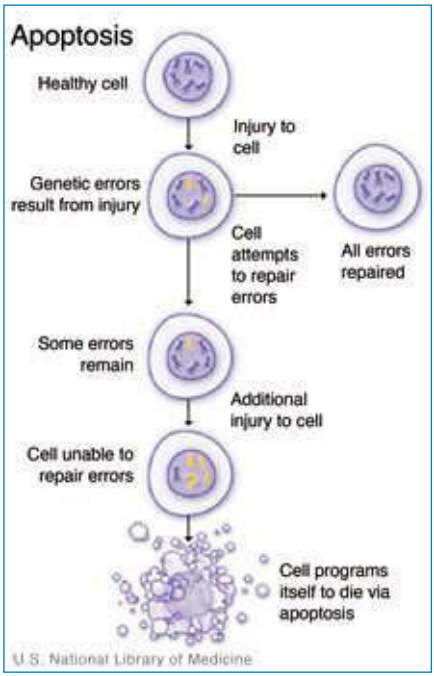

Figure 3: A damaged cell may undergo apoptosis if it is unable to repair genetic errors [12]

The effects that occur due to mutation and apoptosis are generally divided into two categories, deterministic and stochastic effects.

Deterministic effects

Deterministic effects describe how the radiation causes a large amount of cells to die, resulting in damage to the organ. The body is naturally capable of replacing killed cells, but there is a critical value at which the body can no longer compensate for the number of cells that are non-functioning or

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have died. Therefore there is a threshold radiation dose below which deterministic effects are not seen, and as the dose increases past this threshold value, the number of cells that die, and so the severity of the effect, increases.

Deterministic effects can be divided into two categories, acute and late effects. Acute effects occur in tissues that are rapidly proliferating, such as in the epithelial surfaces of the skin or alimentary tract. These cells are replaced by cells that are more tolerant to radiation, and these effects therefore subside after 3-4 weeks. Late effects are typically not seen for 6 months after irradiation and develop through complex interacting processes that are not yet well understood [13].

Effects are dependent on the area irradiated and the dose received. Acute effects include skin erythema, epilation, fatigue, nausea and vomiting, while late effects include tissue necrosis, sterility, cataracts and secondary cancers [13].

Thresholds and timelines for deterministic effects

Skin erythema/necrosis/epilation. Erythema occurs within 1-24 hours of exposure to doses greater than 2 Sv. Breakdown of the skin surface occurs approximately 4 weeks after 15 Sv has been received. Epilation is reversible after 3 Sv but irreversible after 7 Sv and occurs 3 weeks following exposure [14].

Cataracts. Cataract occurs due to accumulation of damaged or dead cells within the lens, the removal of which cannot take place naturally. Cataracts may occur after 0.5 Gy has been received, but may take years to develop [15].

Sterility. Radiation can impair the female germ cell function, leading to impaired fertility or infertility. The dose required to have this effect decreases with age as the number of cells decreases. Similarly, radiation exposure to the testes can result in temporary or permanent limitations in sperm production. Permanent sterility occurs after 2.5-3.5 Gy has been received by the gonads.

Acute radiation syndrome (radiation sickness). Radiation sickness involves nausea, vomiting and diarrhoea developing within hours or minutes of a radiation exposure owing to deterministic effects on the bone marrow, gastrointestinal tract and central nervous system [15].

Deterministic effects on the foetus. Deterministic effects during pregnancy depend not only on the radiation dose received but also on the gestational age at which it occurred. The embryo is relatively radioresistant during its pre-implantation phase but highly radiosensitive whilst organs are forming (at 2-8 weeks) and in the neuronal stem cell proliferation phase (at 8-15 weeks). Foetal radiosensitivity falls after this period. High

levels of radiation exposure in pregnancy can lead to growth retardation, in particular microcephaly. The threshold dose for this effect is high (>20 Gy), with other deterministic effects (hypospadias, microphthalmia, retinal degeneration and optic atrophy) having a lower threshold level of >1 Gy [15].

Stochastic effects

Stochastic means statistical in nature, and these effects arise through chance. Stochastic effects occur due to mutations in the DNA chain and have no threshold value. As absorbed dose increases, the risk of observing these effects increases, and the risk is considered proportional to the dose. The severity of the effect is not related to the absorbed dose; the person affected will either develop cancer or they will not.

Stochastic effects are cancer if the effect occurs in the person's own cells (somatic cells) and genetic mutations in subsequent generations if the effect occurs in the germ cells.

The tissue weighting factors discussed previously in this chapter are based on the risk of stochastic effects occurring. The risk is based on the tissue type that the organ consists off.

Radiosensitivity of cells

In 1906, experiments carried out by two French scientists on rodents defined the radiosensitivity of cells based on their fundamental characteristics. The Law of Bergonie and Tribondeau [16] states that radiosensitivity is based on three factors:

- The *mitotic rate*: The rate at which the cells divide and multiply: the higher the mitotic rate, the greater the radiosensitivity of the cell.
- The *mitotic future*: How long the cell is able to divide for: the longer the mitotic future, the greater the radiosensitivity of the cell.
- State of *differentiation*: An undifferentiated cell is an immature, embryonic or primitive cell. It has a non-specific appearance with multiple non-specific functions. A differentiated cell is highly distinct or specialised. Differentiation predicts how vulnerable a cell will be to radiation. The more differentiated a cell is, the more radioresistant it will be.

In 1968, Rubin and Casarett [17] defined five cell types with differing radiosensitivity according to the characteristics shown in Table 3 [16].

Cell type	Mitotic rate	Example	Radiosensitivity
Vegetative intermitotic cells (VIMs)	*Mitotic rate:* rapidly dividing *Mitotic future:* short *Differentiation:* undifferentiated	Erythroblasts Intestinal crypt cells Basal cells of the skin	Most radiosensitive
Differentiating intermitotic cells (DIMs)	*Mitotic rate:* actively dividing *Mitotic future:* eventually mature into a differentiated cell line *Differentiation:* first level of differentiation	Spermatogonia	Relatively radiosensitive
Multipotential connective tissue cells (MCTs)	*Mitotic rate:* irregularly divide if the body needs to replace them *Mitotic future:* relatively long *Differentiation:* more differentiated than VIMs or DIMs	Fibroblasts Endothelial cells	Intermediate radiosensitivity
Reverting postmitotic cells (RPMs)	*Mitotic rate:* do not normally divide, but can do so if the body needs to replace them *Mitotic future:* relatively long *Differentiation:* differentiated	Parenchymal cells of the liver Lymphocytes	Relatively radioresistant
Fixed postmitotic cells (FPMs)	*Mitotic rate:* do not and cannot divide *Mitotic future:* can be long or short lived *Differentiation:* highly differentiated	Some nerve cells Muscle cells Red blood cells	Most radioresistant

Table 3: Cell types with differing radiosensitivity according to the criteria of Rubin and Casarett [16]

A more modern way of considering the biological effects on a cellular level is the Michalowski classification of cells. Under this classification, cells fall into three categories:

- Stem cells – continuously divide and reproduce to give rise to both new stem cells and cells that eventually give rise to mature functional cells.
- Maturing cells arising from stem cells that through progressive division eventually differentiate into end-stage mature functional cells.
- Mature adult functional cells that do not divide.

Summary

Ionising radiation causes damage to tissues through ionisation, either directly with the cell or indirectly with water, leading to free radicals. The main target for damage is the DNA chain, where the ionisation causes breaks within the chain. Once damaged, the DNA will repair correctly, repair incorrectly or be so damaged that it will become non-functioning or die. Incorrect repair causes mutations, known as stochastic effects, whereas cell death leads to deterministic effects such as necrosis, which is required for effective radiotherapy.

Dose calculation is complex and highly dependent on the individual circumstances. Different terms exist, and are used depending on whether radiation protection or radiotherapy is under consideration. When considering populations, effective dose is useful in generalising risk, but when considering an individual one needs to look at the individual organ dose and consider the RBE for the ionising radiation being used.

Recent studies have shown that radiosensitivity is dependent on many factors when considering an individual, and that as well as age and gender, lifestyle factors and genetics testing may influence dose planning in the future [2].

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3. Dosimetry in Molecular Radiotherapy

Katarina Sjögreen Gleisner, Lidia Strigari, Glenn Flux

Introduction

[1]It is unthinkable that a patient would be treated with external beam radiotherapy (EBRT) or brachytherapy (BT) without prior treatment planning, and prescriptions are always made in terms of the absorbed dose delivered to target tissues and organs at risk. Molecular radiotherapy (MRT) is very similar to BT in that the radiation source is located inside the patient's body. However, in MRT the source is diffuse and therapy is normally given systemically as a radiopharmaceutical, whereas in BT solid radiation sources are used. Unlike in EBRT and BT, where the irradiation geometry and hence the absorbed dose distribution can be planned in advance, in MRT this distribution depends on the amount of radiopharmaceutical that accumulates over time in different tissues, something which varies between patients and therefore needs to be measured. Thus for MRT, the determination of the absorbed dose is more cumbersome. However, it is reasonable to assume that the effects of therapy, in terms of response and toxicity, are primarily dependent on the absorbed doses delivered, as for EBRT and BT, rather than on the level of activity administered. MRT dosimetry constitutes the bridge between the administered activity and the prediction of treatment effects, and has to be taken into consideration along with radiobiological characteristics of tissues. As in other radiation treatment modalities, it is essential that dosimetry in MRT is regarded as teamwork between biomedical technologists, radiographers, nuclear medicine technologists, medical physicists, and physicians specialised in oncology or nuclear medicine.

Internal dosimetry

Following administration, the radiopharmaceutical distributes in the patient's body according to pharmacokinetics specific to the radiopharmaceutical and the individual patient. A particle emitted at radioactive decay may impart its energy in close vicinity to the point of decay, i.e. in the same tissue in which it was emitted, or it may travel some distance before losing its energy, perhaps in another tissue (Fig. 1, K. Sjögreen Gleisner).

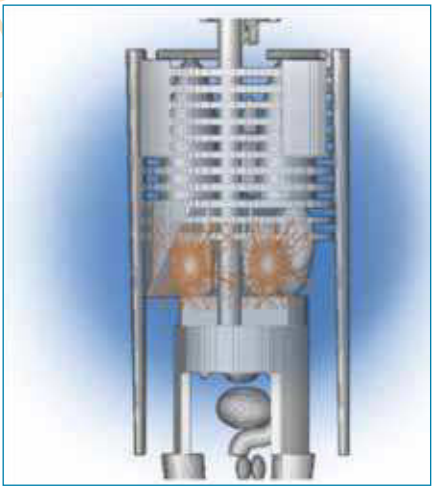
1. Quantities

The *activity* of a radioactive sample is the mean number of decays per second. The unit is Becquerel (Bq) which equals 1/s.

The *cumulated activity* is the number of decays that occur in a given region over a period of time. The unit is Bq s, or Bq h.

When ionising radiation travels through matter, it interacts and deposits energy. The energy imparted is the sum of all energy deposits in a given volume. The *absorbed dose* is the quotient of the mean energy imparted and the mass of the volume. The unit of absorbed dose is Gray (Gy), which equals 1 J/kg.

The term *'dose'* alone can be confusing and is best avoided, as this can refer to either the level of activity administered or the absorbed dose subsequently delivered.



K. Sjögreen Gleisner

Figure 1: The standardised reference geometry used to calculate the factors $S(r_T \leftarrow r_S)$ in the MIRD dosimetry schema. The figure mimics a situation where radiopharmaceutical is located in the kidneys, which thus constitute r_S. Particle radiation, illustrated in orange, mainly deposits energy locally, whereas emitted gamma radiation, illustrated in blue, reaches outside the patient's body.

The total amount of decays that occur within a tissue thus determines the totally emitted radiation energy from that tissue. In order to determine the distribution of absorbed dose, *D*, in a target region, r_T, knowledge is required concerning: (*i*) the total number of decays occurring in different tissues, (*ii*) the pattern with which the emitted particles impart their energy and (*iii*) the mass of the tissues where the energy absorption takes place.

The basic equation is given by:

$$D(r_T \leftarrow r_S) = \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S) \qquad \text{(Eq 1)}$$

The quantity $\tilde{A}(r_S)$ is called the *cumulated activity*. It represents (*i*) above and equals the activity in a source region r_S, integrated over time. The transport of radiation energy (*ii*) is difficult to calculate for every individual and therefore has been tabulated for standardised reference geometries, specific for radionuclide, age and gender. These so-called *S*-factors, $S(r_T \leftarrow r_S)$, describe the absorbed dose in a target region r_T, from activity residing in a source region r_S, and are given in units of mGy/(MBq s). The mass of the target tissue (*iii*) is implicitly included in the *S*-factors since these are calculated for tissue weights according to standard geometries. In order to be applicable for an individual patient, the *S*-factors need to be rescaled to the tissue weight of the individual patient.

Frameworks for calculation of the absorbed dose to individuals given a radiopharmaceutical are given by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and the International Commission on Radiological Protection (ICRP) [1], and guidance in reporting by the Dosimetry Committee of the European Association of Nuclear Medicine (EANM) [2].

Absorbed dose planning in MRT

Is it then possible to prescribe an MRT treatment based on absorbed dose? One possibility is to perform a pre-therapy study

using a tracer amount of radiopharmaceutical, and to determine the tumour and organ absorbed doses that are obtained as a result. Usually, this information is expressed as a factor describing the organ absorbed dose per administered activity, in units of mGy/MBq (Fig. 2, K. Sjögreen Gleisner).

K. Sjögreen Gleisner

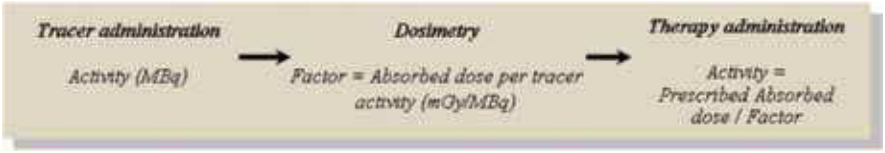


Figure 2: Outline diagram for planning the absorbed dose in an MRT treatment.

If the therapeutic administration is then given under similar conditions, this factor can be used to determine the activity that needs to be administered in order to deliver a prescribed absorbed dose to a given organ or tissue. A second possibility arises when patients are given a series of administrations at intervals of a few weeks to a few months, as is often the case for a radiopeptide or for iodine-131 metaiodiobenzylguanidine (^{131}I-mIBG) treatments of neuroendocrine cancers. In that case it is possible to plan a treatment according to the biokinetics obtained from a previous therapy procedure. These predictions in particular can be very accurate.

Measurement and quantification of the activity distribution

Radionuclides used for therapeutic purposes are those that emit particle radiation, such as electrons from beta-minus decay, or alpha particles. Such particles have a comparatively short range in tissue and rarely penetrate outside the patient's body. Often, radionuclides that emit both particles and gamma photons are preferable. Gamma photons behave differently from particles in that some interact whilst others penetrate the patient's body and thus allow measurement using an external counter or a scintillation camera. Activity quantification is based on determination of the level of emitted gamma radiation inside the body, from measurement of the penetrating gamma radiation. Given the level of emitted gamma radiation, the activity and consequently the level of emitted particle radiation can be calculated.

On a photon's passage from the site of decay to the detector or camera it travels through tissue. The probability that a photon will interact is mainly governed by two parameters: the atomic composition and the total thickness of the tissue along the photon trajectory. Having interacted, the photon may continue its passage, although in a different direction and with a lower energy. The photons that

provide correct information on the location of decay are those that penetrate without interaction, the so-called primaries. *Photon attenuation* is the reduction of the amount of such primaries. *Scattered photons* are those that are detected but have interacted along their passage and thus carry false information about the point of decay. Attenuation thus causes a loss of detected counts, so that a factor used for attenuation correction must have a value greater than one. Scatter causes a falsely increased count rate, and it is desirable to remove such counts.

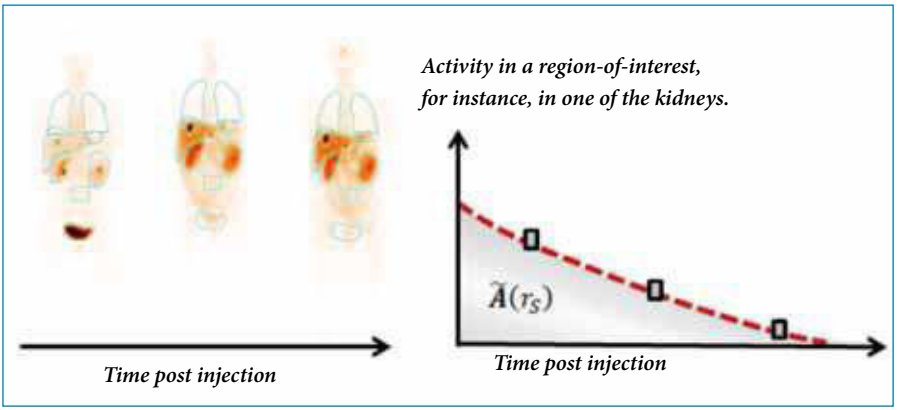
Practically, there are several methods for determining the amount of activity in a patient, and the choice of method depends on the level of accuracy required. All methods involve repeated patient measurements, since the aim is to follow the activity retention over time. The timing of the measurements needs to be distributed with regard to typical biokinetic behaviour of the radiopharmaceutical. It is an advantage if exactly the same equipment can be used for all measurements. It is also essential that clinical protocols are carefully set up, and that patient positioning follows agreed routines.

Probe-based measurements

The activity retention in the body can be assessed by serial measurements using a standard probe dose-rate meter. The first measurement will represent 100% of the administered activity if it is made shortly after infusion, but prior to voiding. By curve fitting of the retention curve and knowledge of the amount of administered activity, the total-body cumulated activity can be determined. It is important that the patient counter geometry is kept constant for all measurements that presence of metal near the patient or detector is avoided to keep the room scatter low and that care is taken to remove any possibly contaminated material in the room. For a gamma emitter such as ^{131}I, the total-body retention curve can be used for estimation of the red marrow absorbed dose [3, 4].

Image-based activity quantification

In image-based activity quantification the underlying idea is that each image element can be viewed as a detector, so that the pixel or voxel count rate reflects the number of detected photons in a particular position. By delineating a region or volume in an image, the total number of photons from a given anatomical region can be determined. The delineation of organs and tissues is central in the determination of the activity (Fig. 3, K. Sjögreen Gleisner).



K. Sjögreen Gleisner

Figure 3: Quantification of the activity in organs from planar gamma camera images. The left panel shows an example of images acquired during ^{177}Lu-DOTATATE therapy for neuroendocrine tumours at different times after administration. ROIs used for organ activity quantification are delineated in the images. For each ROI, a curve is fitted to the activity versus time data (right panel), and the cumulated activity is determined by calculation of the area under the curve.

This task may seem trivial but there are several aspects that need to be considered. Firstly, it is essential that the operator has good knowledge of the intrinsic properties of nuclear medicine images, where limited spatial resolution produces an image intensity which is distributed over a volume or area that is larger than the actual organ. Moreover, in order to achieve a good interpretation of the images it is important that the personnel who perform delineation are trained in anatomy and physiology and have easy access to the patient history and the results of other image-based examinations.

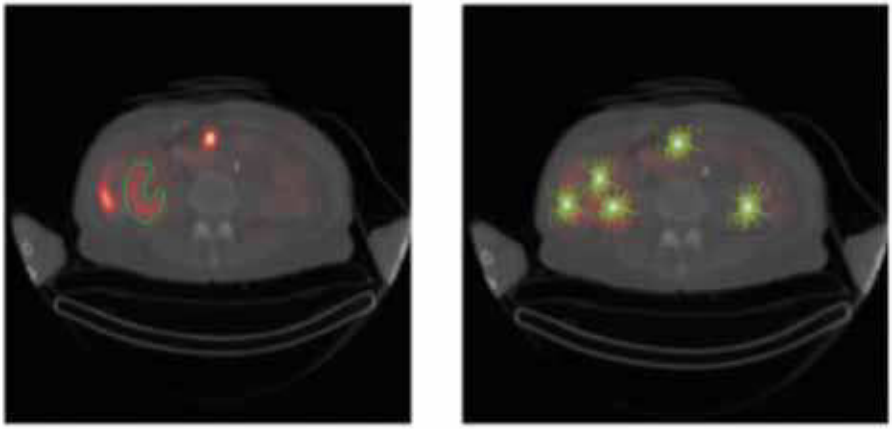
The most commonly employed method is still to acquire anterior-posterior planar scans and then apply the conjugate view method for activity quantification [5-7]. The advantages of this method are that the whole body is covered and that the acquisition time is comparatively short. A considerable drawback is that a planar image is a two-dimensional representation of a three-dimensional activity distribution, and it is difficult to compensate for activity residing in tissues lying over or under the organ of interest. It is thus considered to be best suited for estimation of the cumulated activity in the total body and larger organs for radiopharmaceuticals that exhibit a well-defined uptake with a low level of background activity. Attenuation correction can be performed based on transmission studies, obtained using an external radionuclide flood source or using an X-ray CT scout. It is then necessary for the patient

to maintain a similar position in the transmission and radionuclide imaging sessions. Tomographic imaging with SPECT and PET enables the activity distribution to be resolved in three dimensions. From such 3D images, measurements of the activity concentration can be determined for the body region covered by the scan. The preferred method for activity quantification is to include it as part of the image reconstruction, provided that corrections for attenuation and scatter can be included [8]. For such corrections, an attenuation map is required, and can be obtained from a CT study which is registered to the SPECT or PET study. In this regard, hybrid SPECT/CT and PET/CT systems offer significant advantages for the purposes of dosimetry. Although in principle SPECT and PET images allow determination of the activity concentration in a volume represented by each voxel, tissues that are small in comparison to the spatial resolution will be affected by resolution-induced "spill-out" of activity, with an underestimated activity concentration as a result. For SPECT the spatial resolution can be in the order of 1 cm or more, and the activity concentration in smaller organs such as the kidneys and tumours may be underestimated. This is the so-called partial volume effect and it should also be corrected for. Methods involving a combination of planar and tomographic imaging techniques have been explored, whereby the activity retention curve is measured by planar imaging and its amplitude is adjusted to absolute values of the activity concentration or absorbed dose rate as determined from SPECT/CT [9].

Radiopharmaceuticals used in radionuclide therapies generally have a relatively long biological half-life, which has to some extent limited more widespread use of fluorine-18 PET imaging for dosimetry. However, an increasing number of research studies are using longer-lived PET radionuclides for dosimetry purposes, including iodine-124 (4.2 days), zirconium-89 (3.3 days), copper-64 (12.7 h) and yttrium-86 (14.7 h) [10-12]. Also it has recently been determined that yttrium-90 can be imaged using PET [13], and this is now the subject of many research studies.

Calculation of the absorbed dose

From the values of the activity in a tissue at different times, the cumulated activity is determined by integration, and the mean absorbed dose can be determined using Eq. 1. Generally, this method is used when activity measurements are made using a probe for the total body, or when using planar imaging for whole-organ dosimetry. Quantitative SPECT/CT or PET/CT allows for dosimetry in smaller volumes using voxel-based methods (Fig. 4, K. Sjögreen Gleisner).



K. Sjögreen Gleisner

Figure 4: The left panel shows a transverse slice of a SPECT/CT study acquired during ^{177}Lu-DOTATATE therapy for neuroendocrine tumours. If quantitative tomographic reconstruction is available, then quantification of the activity, or activity concentration, in organs and tumours can be performed by delineating volumes of interest (VOIs) in SPECT/CT images. Such activity values can be used to calculate the absorbed dose according to the MIRD schema (Eq. 1). Another possibility (right panel) is to calculate the absorbed dose rate distribution on a voxel-by-voxel basis by using the SPECT/CT images as input to a Monte Carlo code that mimics the particle emission and subsequent interactions in the patient's body. The VOIs are then applied in the resulting absorbed dose rate image.

From the 3D distribution of activity concentration values, the absorbed dose rate distribution can be calculated using so-called point dose kernels or voxel *S* values, describing the energy deposition pattern around a point source located in water (or bone). This method assumes that the anatomical region is homogeneous in terms of density, such as soft tissues within the trunk. For body regions where the density is heterogeneous, as in the lungs, a direct Monte Carlo calculation is preferable. Here, the activity distribution from SPECT or PET is used as input to a Monte Carlo dose calculation code. If co-registration is available, the dose rate maps from SPECT/CT or PET/CT images acquired on different occasions can be used to calculate a 3D map of the absorbed dose [14] where organ delineation can be made. Otherwise, organ delineation needs to be performed in each separate image. Whichever dosimetry method is used, a determination of the mass of the target region is required. The mass can be determined using the CT image either on a voxel basis by applying a calibration relationship, such as is normally done in EBRT [14], or by delineating

the target region and assuming a reference value for the mass density.

Radiobiology

The aim of radiobiology is to establish relationships between the absorbed doses delivered and the radiobiological effects in tissues and tumours. Currently in MRT few such relationships have been established, but this is an area of intensive research. Radiobiological models in MRT can be adopted from EBRT and BT through calculation of the biologically effective dose (BED). The BED takes into consideration the absorbed dose, the absorbed dose rate and the capacity of tumours and tissues to repair induced radiation damage. Ideally the correlation between pre- and post-treatment dosimetry should be assessed to increase the predictive capability of absorbed dose-response relationships.

The 'four Rs' of radiobiology

The 'four Rs' of radiobiology summarise the main features of cell survival of tumours and normal tissues [15]:

- Repair: Powerful repair mechanisms counteract DNA damage induced by ionising radiation with a repair half-time, T_{rep}, from minutes to hours;
- Reoxygenation: Oxygen stabilises the effect of radiation. Hypoxic cells are the main obstacle to tumour curability, but, as the radiation dose is usually delivered over several days, there is sufficient time for its reoxygenation.
- Repopulation: During MRT, the cells in some tumours and some normal tissues grow, partially counteracting the cell killing. Repopulation in normal tissues is also an important mechanism to counteract acute side-effects.
- Redistribution: Cells have different radiosensitivity at different parts of the cell cycle. The highest radiation sensitivity is in the early S and late G2/M phase.

All of these mechanisms can be included in the linear quadratic model (LQM).

The linear quadratic model

The LQM applies to different treatment regimens, including MRT, and allows the use of BED, a quantity with the dimensions of Gy. This is useful to compare different irradiation schemes and to evaluate the impact of treatment in both tumours and normal tissues. The radiosensitivity of tumours and tissues can be considered using the parameters α, which represents the radiosensitivity and is lower for radioresistant cells, and the α/β ratio, which indicates the response to fractionation and to different dose rates. This ratio is approximately 10 Gy for tumours and 3 Gy for late-responding tissues.

Radiobiological models

The most commonly used radiobiological models are the tumour control probability (TCP) and the normal tissue complication probability (NTCP). The TCP depends on N^*, the initial number of clonogenic cells, which

is the fraction of cells that have the potential to proliferate and give rise to a tumour. Usually *N** is considered proportional to the tumour volume. Palpable tumours are usually characterised by 10^9 cells/cm^3 (large masses may contain 10^{12} cells/cm^3, while microscopic tumours/micrometastases contain about 10^6 cells/cm^3). As expected, a TCP value calculated at the same absorbed dose and with the same radiobiological parameters (α and β) decreases when *N** increases, as more cells require a higher absorbed dose for eradication. Obviously, tumour response also depends on concurrently given agents, such as chemotherapy.

Sparing of normal tissues is essential for a good therapeutic outcome. This is largely dependent on the tissue architecture, which is basically classified as serial or parallel. In serial organs (for example the spinal cord and intestines) even a small volume irradiated beyond a threshold absorbed dose can lead to whole organ failure. In parallel organs such as the liver, kidneys and lungs the effect depends on the irradiated volume.

NTCP models can predict the incidence of acute/late complications for serial/parallel organs. In EBRT early/acute reactions such as tiredness, nausea, vomiting, skin reddening, haematological toxicity and erythema occur typically during radiotherapy or within 3 months, while late reactions, such as fibrosis and liver/kidney failure, could occur even 6 months thereafter. The majority of MRT clinical data on toxicity are available for only a few organs [16]. The maximum tolerated dose depends on tissue and patient characteristics and can be lowered by the use of chemotherapy agents.

Normal tissues are more spared than tumours by a continuous low dose rate, and the LQM predicts a greater benefit due to multifractionated treatments, using an α/β of 3 Gy. However, full understanding of a dose-effect relationship is limited by a lack of reported clinical data. An improvement to the dose-response models should include the effects of non-uniform dose distributions [17, 18] as well as clinical risk factors.

Clinical evidence for dosimetry

A BED response curve for kidney damage has been reported after peptide receptor radionuclide therapy used for neuroendocrine tumours at high cumulative activities [19]. The LQM supports the evidence that multiple-cycle schemes decrease the incidence of nephrotoxicity.

Red marrow toxicity data have mostly been obtained from treatments with ^{131}I for thyroid carcinoma and from ^{131}I-mIBG therapy of neuroblastoma. In many studies, red marrow dosimetry is approached with great caution, and a maximum absorbed dose of 2 Gy to the blood (as a red marrow surrogate) is generally accepted [20] for radioiodine treatment of differentiated thyroid cancer. Recently a higher limit of 3 Gy has been proposed [21].

Lung toxicity data have also been mainly derived from the treatment of metastatic thyroid carcinoma with ^{131}I or from loco-regional liver treatments using ^{131}I-Lipiodol or ^{90}Y-labelled microspheres. In the literature, lung-related constraints are based on different criteria [21-23]. Radiation pneumonitis has also been seen in patients receiving ^{90}Y-TheraSphere as single treatment at doses ≥30 Gy. An empiric lung shunt [24] cannot be considered a dosimetric constraint. Severe radiation-induced lung toxicity, expected at doses of 25–27 Gy, were not observed in some studies, probably due to the overestimated normal lung absorbed dose [22]. In non-resectable primary or metastatic liver tumours, radioembolisation is an increasingly used loco-regional treatment. The partition model permits a distinction between tumour and normal liver doses [25], allowing the use of constraints for normal tissues. Moreover, TCP/NTCP models have been proposed [26]. Pre-treatment imaging seems feasible and attractive for radiobiological treatment optimisation [26-28]. Multi-cycle treatments would allow administration of higher activities and could improve the risk-benefit balance [29]. Other organs that affect the quality of life should also be included in the evaluation of treatment. Cells that are actively dividing and not as well differentiated, such as gonads, haematopoietic cells and the gastrointestinal tract, are most susceptible to radiation damage. In young and long-surviving patients, the gonads should be considered for assessment of temporary and permanent sterility risks.

Conclusion

After almost 70 years of the use of radionuclides to treat cancer, there is now a rapidly increasing awareness of the need to administer activities according to a predicted pattern of absorbed dose delivery, and to assess after a therapeutic procedure whether that predicted absorbed dose has in fact been delivered. This fundamental change in practice is being spurred on by the need for evidence-based medicine and the emerging interest in molecular imaging and personalised treatment. Whilst there is evidently an opportunity for much research, it remains the case that only with this cancer therapy can the agent responsible for treatment be imaged *in vivo* – this offers a potential for individualised treatment planning that is unprecedented. The greatest challenges at present are the need to quantify activity imaged by a gamma camera that is not well suited to the task (standardized uptake values have long been established for quantification with PET) and the development of radiobiology to understand the clinical implications of an absorbed dose. This field has been the slowest to develop of all cancer treatments, in part due to the relatively small numbers of patients treated at individual centres, but also due to the need for a multidisciplinary approach to what, in many centres, will be a new service. As dosimetry is at the heart of molecular radiotherapy, so imaging is at the heart of dosimetry. It is likely that changes in clinical practice will raise challenges and opportunities previously not encountered, but that the outcome will be significantly greater benefit to patients.

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4. Special Considerations in Radiation Protection: Minimising Exposure of Patients, Staff and Members of the Public

Claudiu Peştean and Maria Iulia Larg

Introduction

Nuclear medicine involves the use of radioactive tracers for medical purposes in diagnostic and therapeutic procedures. Besides its benefit, the radiation may affect the human body in different ways depending on the type of emitted rays, the activity of the radioactive sources, the physiological distribution and elimination of the radiotracer within the human body after administration, etc. Because the effects of the radiation on the human body may be destructive, it is necessary to implement special precautions when using radioactive substances.

Radiation protection's main target is to achieve a dose as low as reasonably achievable (the ALARA principle) for all the categories of individuals involved in procedures where ionising radiation is used (occupational staff, patients and public). To minimise the radiation exposure from a radioactive source, it is necessary to appropriately influence specific parameters, including:

- *Time*: as short a time as possible should be spent near a radioactive source.
- *Distance*: the maximum possible distance should be maintained from the radioactive source; this might involve using remote handling devices or keeping a safe distance from radioactive patients,
- *Shielding*: in some instances it is mandatory to use specific shielding devices when radioactive sources are manipulated.
- *Potential for contamination*: because unsealed radioactive sources are used, it is necessary to minimise the possibility of contamination (internal and/or external) [1].

Radiation protection concerns must be reflected in all aspects of activity in a nuclear medicine facility [1]:

- The facility should be appropriately designed and suitably located within the hospital, with appropriate circuits for patients and staff, radiopharmaceuticals, and radioactive wastes or supplies. The facility should have enough space and a sufficient number of rooms. It is mandatory to have specially designed spaces for all operations (including the storage and disposal of radioactive waste). A nuclear medicine facility needs to be authorised by competent authorities.
- All the equipment should be authorised and meet stipulated specifications. Equipment for safe handling should be available in the department for all procedures; radiation monitoring instruments should be available as required by national regulations.
- All staff must be competent and have received special training to ensure that they can work with radioactive material with minimal risk.
- Patients must be adequately informed about all relevant aspects of the administration of radioactive tracers.

Regulations and principles in radiation protection

All activities that involve the use of ionising radiations are performed under rules and guidance set out by regulatory bodies. In Europe, the European Commission issues specific directives for activities using ionising radiations. All member states have specific regulations which comply with the recommendations of the European Commission. These recommendations are designed to ensure the safety of all categories of individuals affected by activities using ionising radiations. Protection against ionising radiations is the goal of activity of many representative organisations at an international level, beyond Europe. The International Commission on Radiological Protection (ICRP) is the commission that developed and elaborated the international system of radiological protection. This system is used all over the world as a reference for all standards, legislation, programmes and practice of radiation protection. Documents like the Euratom Basic Safety Standards Directive [2], ICRP Publication 103 [3], and Council Directive 97/43/Euratom [4] are designed to ensure that activities (in general) and medical practices (in particular) using ionising radiation are performed in a way that respects the safety standards related to radiation protection.

All procedures in a nuclear medicine department involve the use of radioactive tracers for the purpose of diagnosis or therapy. In diagnostic procedures, gamma photon or positron emitters are used to obtain the images, while in therapeutic procedures, beta emitters are administered. In both situations, radiation protection has an important place in daily practice and staff must be well trained to respect the principles of radiation protection. Special precautions are needed when therapeutic procedures are performed in a nuclear medicine department because high activities are administered and because of the high energy of emitted particles. It is necessary to have specific procedures that allow therapy to be performed in safe conditions for patients and their families and also for professional staff and the environment generally.

Three categories of exposure may occur when a medical procedure is performed using ionising radiation:

- Occupational exposure: exposure of workers incurred during the course of their work [2].

- Medical exposure: this includes the exposure of patients as part of their own medical diagnosis or treatment, the exposure of individuals as part of occupational health surveillance, the exposure of individuals as part of health screening programmes, the exposure of healthy individuals or patients voluntarily participating in medical or biomedical, diagnostic or therapeutic, research programmes, and the exposure of individuals as part of medicolegal procedures [4].

- Public exposure: the radiation exposure to individuals, excluding any medical or occupational exposure [2].

The first key principle of radiation protection is *justification*. Every exposure must be justified; this means that the benefit must exceed the detriment caused by irradiation. From a nuclear medicine point of view, those procedures which are appropriate need to be continued, but when an equal outcome (in terms of diagnostic information or therapeutic effect) can be obtained without using irradiation, the exposure cannot be justified. The second principle is *optimisation*. This means that even when the exposure is justified, it must be kept at a level "as low as reasonably achievable taking social and economic factors into account" [5]. Optimisation in radionuclide therapy should include aspects such as: safe handling of radioactive sources, safe administration, adequate patient information, application of dose constraints to family members and the general public, suitable care of the hospitalised patient and adequate emergency procedures. Another principle of radiation protection is *limitation*. Limitation basically refers to the limitation of exposure for those categories of individuals to whom the principle applies: professionals (occupational exposure) and public (public exposure).

According to Article 80, Justification, of the Euratom Basic Safety Standards Directive, a medical exposure shall demonstrate a sufficient benefit against the detriment that it produces. A detailed description of this principle is as follows: the benefit should include all the potential diagnostic and therapeutic benefits, including the benefits to health or well-being of an individual and the benefits to society; the detriments shall be smaller than the benefits taking into account the efficacy, benefits and all the risks of the alternatives that have the same objective (diagnostic or therapeutic), without or with less exposure to ionising radiation. When we talk about detriment, we should also consider the detriment produced by exposure to staff and other individuals. The Basic Safety Standard Directive states that before it is generally adopted, any new technique that involves the use of ionising radiation must be justified; it also states that existing techniques shall be reviewed when new and important evidence about their efficacy or consequences is acquired. It is very important is to understand that when an exposure cannot be justified, it shall be prohibited [2].

Even when justified, all procedures involving ionising radiation must be optimised as the exposure should be as low as is reasonably achievable. Article 5 of the Euratom Basic Safety Standard Directive states that in all situations, radiation protection shall be optimised with the intent that the magnitude and likelihood of exposures and the number of individuals exposed are kept as low as reasonably achievable, economic and societal factors being taken into account. Article 81 of the same document explains how the optimisation in medical exposure is to be achieved:

- Doses applied for the purposes of radiodiagnostic and interventional radiology should be kept as low as is reasonably achievable consistent with acquiring the required imaging information, while in radiotherapeutic procedures the doses should achieve the intended result for the target volumes, while ensuring that exposure of non-target tissues is kept as low as possible.

- The national regulatory body and the government should promote the establishment, regular review and use of reference levels having regard to the available European reference levels.

- When research projects are performed and ionising radiation is used, individuals shall participate voluntarily and shall be appropriately informed about the risk of exposure; dose constraints shall be established for individuals for whom no direct medical benefit is expected.

- The optimisation process also covers the selection of equipment, consistent production of adequate diagnostic information or therapeutic outcome, and other "practical aspects" (e.g. quality control and the evaluation of patient and staff doses or administered activities).

- For carers and comforters, appropriate guidance and dose constraints shall be established.

- In the case of treatment or diagnostic procedures with radionuclides, the practitioner shall provide the patient with written information about the restriction of doses to persons in contact with the patient and about the risk of ionising radiation; this information shall be provided before the patient leaves the hospital or the department.

We have already mentioned the term "dose constraints". According to the Euratom Basic Safety Standard Directive, a dose constraint is "a constraint set as a prospective upper bound of individual dose used to define the range of options considered in the process of optimisation related to a given radiation source". Constraints are a part of optimisation; they may be applied to a department, to a procedure or to an individual patient. The sum of doses from constraints must always be below the dose limit established for the category of individuals to whom the constraint is applied. In general, dose constraints are expressed as an individual effective dose over a year or any other appropriate shorter period of time [5].

"Limitation" refers only to the public and occupational exposure, not the medical exposure [4]. According to the ICRP Publication 103 (The 2007 Recommendations of the International Commission on Radiological Protection), and also according to the Euratom Basic Safety Standards Directive, in planned occupational or public exposure, dose limits apply to the sum of all planned individual

exposures. For occupational exposure, the dose limit is expressed as an effective dose and the limit shall be 20 millisievert (mSv) in a year. This limit is mediated in a period of time of 5 years, i.e. 100 mSv in 5 years. In some special situations a maximum effective dose of 50 mSv in any single year is deemed acceptable, but the average dose over any 5 consecutive years shall not exceed 20 mSv per year. In the case of pregnant workers, additional limits are taken into account: exposure during the duration of the pregnancy shall not exceed 1 mSv. The limit for the lens of the eye is an equivalent dose of 150 mSv per year (this limit is currently being reviewed by the ICRP, according to ICRP Publication 103), the limit for the skin is 500 mSv per year (averaged on any cm^2 of the skin) and the limit for extremities (arms, forearms, feet and ankles) is 500 mSv per year. For the public, the limits are more restrictive, as would be expected. The limit for public exposure is 1 mSv in a year. According to the same documents and recommendations, for public exposure, the limit of the effective dose shall be 1 mSv in a year; in special circumstances the effective dose for public exposure is allowed to exceed this limit, but only on condition that over any 5 consecutive years, the averaged dose does not exceed 1 mSv per year. A limit for the equivalent dose to the eye has also been established, i.e. 15 mSv per year (this limit is currently being reviewed by ICRP, according to the ICRP Publication 103).

These are only the main aspects of and recommendations regarding radiation protection. In the documents that have already been mentioned, many other important aspects are mentioned that must be considered with reference to nuclear medicine practice in general and radionuclide therapeutic procedures in particular.

In relation to the justification, there are other important aspects regarding responsibilities, while in relation to optimisation, the above-mentioned documents contain important recommendations about dose constraints which must be well known to practitioners. Dose limits are explained in great detail, with provision of important information on the dose limits in pregnancy and during lactation and the dose limits for apprentices and students. These documents represent the starting point for any radiation protection perspective regarding practice in nuclear medicine.

Radiation protection in departments performing radionuclide therapy procedures

In order to keep the exposure as low as possible, respecting the recommendations and regulations previously discussed, adoption of a suitable approach to radiation protection is necessary. In a nuclear medicine department where metabolic radionuclide therapy is performed in addition to diagnostic procedures, account needs to be taken of various specific aspects relating to the department and its internal management, to the staff and procedures, and to the patient and his/her family (or members of the public who will come into contact with the patient).

The department and internal management

Departments where therapeutic procedures are performed need to have a special design in order to satisfy the special needs of therapy. The minimum requirements for such a department, from a radiation protection perspective, are:

- Special and separate designed circuits for radioactive and non-radioactive patients
- Specially designed storage room for isotopes
- Specially designed room and facilities for administration of radioisotopes
- Specially designed rooms for in-patients with separate facilities where the patient will remain after the therapeutic activity has been administered
- Specially designed storage rooms for radioactive waste
- Special decontamination room: for wet and dry decontamination
- A separate system for collection and storage of residual water and other household waste until decontamination prior to its release into the general waste system.

According to the Euratom Basic Safety Standards Directive, where necessary, the work area in a nuclear medicine department shall be designed as a controlled area (an area with controlled access where special rules are necessary to offer protection against ionising radiation or to prevent the spread of radioactive contamination) and a supervised area (an area where appropriate supervision is needed to ensure protection against ionising radiation).

Workers should be classified in two categories: *category A workers*, liable to receive an effective dose greater than 6 mSv per year or an equivalent dose greater than three-tenths of the dose limits for the lens of the eye, skin and extremities, and *category B workers*, who are liable to receive an effective dose exceeding 1 mSv per year but do not reach the value of 6 mSv [2].

The internal rules, protocols and guidelines followed and used in the department should ensure that the procedures respect all radiation protection principles and that all activity complies with international recommendations and national legislation relating to radiation protection.

The staff and procedures

Due to the complexity and the potential risk of radionuclide therapy procedures, it is important that the staff of the nuclear medicine department are well-trained specialists and that procedures are performed safely and in accordance with good practice. The hazard for staff is influenced by the chemical form of the radiopharmaceutical, by its physical properties (half-life, radiation energy and type) and by its biological properties (after administration, the

radiopharmaceutical may affect personnel depending on its biodistribution and biological half-life). The hazard is also influenced by the time spent close to unsealed sources (e.g. capsules, vials or even irradiated patients) and is proportional to the activity of the source. The radiation exposure of nuclear medicine staff may be determined both by external irradiation (when radiopharmaceuticals are manipulated for preparation and administration, when patients are examined for post-therapeutic assessment, when health care is provided in emergency situations after the patient has been irradiated, etc.) and by internal irradiation (due to ingestion of nuclides via contamination of the skin and hands, accidental punctures during manipulation and administration, or inhalation of volatile radiopharmaceuticals, e.g. ^{131}I radioiodine).

In order to reduce the irradiation as far as possible during daily practice, nuclear medicine staff should use appropriate techniques and procedures and adhere to relevant regulations. The following list provides an overview and explanation of issues which nuclear medicine staff should take into account in order to reduce the irradiation to their own benefit and that of the other members of the medical team:

- Experience is invaluable and may ameliorate the exposure: an experienced technologist will perform procedures more quickly and with a lower likelihood of accidents (e.g. misadministration, contamination).
- It should be ensured that appropriate steps are followed for the different procedures. All necessary information, including documentation and blood samples, should be obtained from patients prior to administration of the therapeutic radionuclide. It is also mandatory to provide the patient with all the necessary information about the procedure and to ensure that the patient understands all aspects of the procedure and has no further questions or doubts; in this way technologists can minimise contact with patients after the administration.
- Technologists should wear appropriate protective equipment when entering controlled areas and during the manipulation, preparation and administration of radiopharmaceuticals. This equipment includes gloves, a single-use protective coat, mask, single-use shoes and special glasses
- To reduce irradiation of the hands, it is very useful to manipulate unshielded sources or radioactive vials using long forceps or tongs; this is in accordance with the "inverse square law", according to which if the distance from the radiation source is doubled, the radiation intensity will be decreased by a factor of 4. In the same way, during post-therapeutic assessment it is useful for technologists to maintain the maximum possible distance.
- It is mandatory always to manipulate the sources with appropriate shielding. Most

therapeutic radiopharmaceuticals are beta (β^-) emitters, so the best way to shield the source is to use low Z materials in order to reduce the probability of producing bremsstrahlung X-rays (which are more penetrating than β^- particles). Perspex is suitable for this purpose. When high activities are used, and in therapeutic administrations this is a common situation, or when, in addition to β^- particles, the radionuclide emits gamma (γ) photons, it is useful to have a mixed shielding from Perspex and lead [6]. It is important that, when necessary, mobile shielding walls are used to offer protection against the radiation emitted by the patient (this depends on the energy and, implicitly, the radionuclide used and the activity administered).

Surveillance of personnel exposure is very important; thus, all members of staff should wear personal dosimeters and be monitored in order to ensure that the limits established by national regulations are respected. It is also important for technologists to wear finger dosimeters during procedures that involve source manipulation and administration. The ideal dosimeter should be: independent of radiation energy and geometry of the irradiation, capable of distinguishing doses from different types of radiation (β, γ, X), capable of detecting a large range of energies, easy to use, low cost, immediately readable, small, robust and independent of environmental conditions. Common types of personal dosimeter are film badges, thermoluminescent dosimeters and electronic personal dosimeters using as detectors G-M tubes or silicon solid-state diodes. When there is a risk of internal contamination, measurements of internal contamination may be performed.

- In order to prevent any unnecessary exposure and to keep the exposure of personnel as low as possible, it is important that scheduled environmental measurements are performed at representative points in the department to assess the environmental radiation level. Surfaces should be kept clean and decontamination procedures should be appropriately performed.

- Nuclear medicine staff should be suitably trained so that when accidental contamination occurs, they respect stipulated procedures in order to minimise the radiation exposure to themselves and others.

- When health care procedures are necessary after therapy, the nursing or medical staff should be instructed regarding radiation protection (e.g. permissible time and distance in proximity to the radioactive patient, special care regarding the risk of contamination with radioactive saliva or urine).

- No pregnant person should work in areas where the exposure is higher than 1 mSv over the period of pregnancy; no breastfeeding person should work in areas where there is risk of internal contamination.

The patient and his/her family (or members of the public who will come into contact with the patient)

According to legal and guidance documents considered in this chapter, any therapeutic administration of radionuclides must be justified. For this purpose, clinicians follow dedicated protocols and clinical guidelines for pathologies that may be treated by metabolic radionuclide therapy.

It is well known that no therapeutic administration should be performed in a pregnant patient. In the case of a breastfeeding person, the therapy can be performed under certain circumstances, respecting constraints relating to breastfeeding and taking into account special concerns regarding radiation protection of the child (e.g. the exposure limit of the child should not exceed 1 mSv).

From a radiation protection point of view, the nuclear medicine staff must be aware of several aspects relevant to avoidance of unnecessary exposure or minimisation of exposure of the patient and persons who come into contact with the patient after administration of the therapy. The technologist should pay special attention to these aspects; he/she and the medical team have the responsibility of instructing the patient and of making the patient aware of the importance of these aspects of radiation protection.

The patient must be prepared appropriately for the therapy. When necessary, the patient should be in the fasting condition (for oral administration of the radiopharmaceutical, to avoid malabsorption, e.g. for ^{131}I radioiodine therapy). Contraindications to certain pharmaceuticals, substances, treatments or food are to be respected (in the case of radioiodine therapy, administration/use of the following should be avoided: thyroid hormones, iodinated contrast media, antiarrhythmic medications such as amiodarone, iodine-containing disinfectants, food containing iodine in excess).

The nuclear medicine staff member will instruct the patient on certain measures that may be taken in order to minimise the effect of radiation on non-target organs, e.g. to eat sour candies or lemon for the salivary glands, and to be appropriately hydrated in order to ensure good clearance of the radiotracer and to minimise the effects of the radiation on the kidneys and urinary system.

The patient and his family should understand all aspects of the therapeutic procedure and all the necessary conditions regarding visits, contact with other persons and hygienic measures and should be ready to respect them.

Some procedures are performed during hospitalisation and some under out-patient conditions. Usually, for radioiodine therapy, any administration of radioiodine that exceeds 30 mCi (1.1 GBq) is performed during hospitalisation; however, some publications and studies assert that higher activities (3.7–5.5 GBq) can be administered on

an outpatient basis with adapted radiation protection guidelines and proper oversight by professionals [7]. In other types of radionuclide therapy, hospitalisation is not necessary, but the patient should remain under medical surveillance for up to several hours.

The decision to perform the therapy on an out-patient basis or to discharge a hospitalised patient after therapy can be taken only if dose constraints and dose limits for family members or close persons and the public will not be exceeded due to residual activity. The values to be observed are established by competent authorities and national regulations [8]. In Europe, the situation regarding treatment delivery on an out-patient basis and time of discharge varies from country to country. In some countries the activity of radioiodine that may be administered on an out-patient basis is up to 30 mCi, while in others even hyperthyroidism is treated during hospitalisation of the patient.

During the hospitalisation, the patient will be instructed how to use the toilet (e.g. the toilet should be flushed 2-3 times, and men should sit down to avoid spillage), how to maintain personal hygiene in order to minimise contamination (hands should be washed with soap and water after using the toilet), to wear footwear when leaving the bed and not to leave the room unnecessarily.

A hospitalised patient should be discharged only if he or she will be able to respect the instructions regarding radiation protection, taking into account socio-economic and environmental factors like the living space, the number of rooms, the quality of sanitary installation, the number of family members etc. [8].

In the majority of therapeutic procedures, including those involving radionuclides that emit only beta (β^-) particles (e.g. metastatic bone pain palliation with ^{89}Sr), the patient needs to give special attention only to urine contamination (clothes and toilets) in order to ensure the radiation protection of other persons [9]. The situation in respect of radioiodine therapy is more complex, and the patient should respect some other instructions after discharge:

- The patient should stay as far as possible from other persons at home (more than 1 m and for extended periods of time, more than 2 m).
- The patient should urinate sitting down, flush the toilet 2-3 times after urinating, and wash the hands afterwards.
- Direct contact with children should be avoided, and a greater distance should be maintained from them; in addition, arrangements should be made for children to be cared for in another house by other individuals for the first 2 days (if this is not possible for psychological reasons, contact should be as brief as possible).

- While physical contact with adults is not contraindicated, it should be restricted to about half an hour per day (hugging and sex).
- The patient should sleep alone, with beds at least 2 m apart; beds in adjacent rooms should not be against the same wall.
- Regarding elderly persons, those over 60 years old will be encouraged to take only those measures that are easy for them.
- In the case of a pregnant partner, the sleeping instructions outlined above should be respected in order to keep the dose to the unborn child as low as is reasonably achievable
- Breastfeeding must be stopped before therapy and should not be restarted after returning home
- Conception should be avoided for 4 months after therapy
- For short visits (up to a few hours), visitors should keep a safe distance and avoid direct contact with the patient; visits by young children and pregnant women are discouraged.
- Cutlery, crockery and towels must not be used by other persons (after washing they are safe).
- During the first week, public transportation should be restricted to a maximum of 2 hours per trip; as far as possible, the patient should maintain a suitable distance from other passengers, and the passengers should also change seats during the trip.
- Social events should be avoided.
- While at work, a distance of 2 m should be maintained from other individuals most of the time; if the work involves contact with children under 10 years old, the patient must stay off work; similarly, if the work would be affected by ionising radiation (e.g. development of photographic plates, radioimmunoassay), the patient should stay at home.

The length of time for which patients should follow these instructions has been estimated in different ways. One of these estimations has been made as a function of the effective dose measured at 1 m distance from any point of the patient's body [8]:

- At an effective dose rate of <40 μSv h-1, corresponding to an estimated residual activity of <800 MBq, the recommended period for compliance with instructions is 3 weeks.
- At an effective dose rate of <20 μSv h-1, corresponding to an estimated residual activity of <400 MBq, the recommended period for compliance with instructions is 2 weeks.

- At an effective dose rate of <10 μSv h-1, corresponding to an estimated residual activity of <200 MBq, the recommended period for compliance with instructions is 1 week.

- At an effective dose rate of <5 μSv h-1, corresponding to an estimated residual activity of <100 MBq, the recommended period for compliance with instructions is 4 days.

- At an effective dose rate of <3 μSv h-1, corresponding to an estimated residual activity of <60 MBq, the recommended period for compliance with instructions is 24 hours.

Radiation protection is a very important aspect of metabolic radionuclide therapy and it must be ensured not only that the patient benefits from the therapy but that the procedure is done properly, thereby minimising exposure of the patient, the medical staff, the patient's family and the public.

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Section II

Preamble on a Multiprofessional Approach in Radionuclide Metabolic Therapy

Giorgio Testanera and Arturo Chiti

Introduction

Whilst the science of nuclear medicine continues to be further perfected and described within the literature, a significant limitation in translating this knowledge into practice is associated with the ways in which people work together to deliver a service which integrates and collaborates effectively with relevant medical and non-medical disciplines. Put simply, the science can be faultless but the practice can be deficient because of human limitations. As nuclear medicine has evolved, it has grown closer to those it provides services to. Clear examples of this include oncology for radiotherapy planning (PET/CT) and radionuclide therapy for treatment or palliation of benign and malignant pathology. In both instances, personnel external to nuclear medicine have become centrally involved in the organisation and delivery of key aspects of the nuclear medicine service to improve the pathway and enhance the outcome whilst addressing patients' needs more sensitively. With these considerations in mind, in this preamble we recognise the importance of effective inter-professional working both within and external to the nuclear medicine department and highlight some key human-related factors that need to be considered for the delivery of a successful multidisciplinary externally integrated service.

Nuclear medicine comprises a broad professional mix. Each professional group has a specific formative training programme and subsequently holds a range of responsibilities within the department. Whilst considerable variations in individual responsibilities exist between and within countries, one thing all nuclear medicine departments have in common is the continued need for a diverse range of professional groups. This professional range is necessary to deliver a service which draws expertise from different bodies of knowledge.

Daily practice is a synergy between medical specialists, nurses, technologists, radiopharmacists and physicists, with every professional figure covering fundamental elements of the work flowchart, from radiopharmaceutical preparation to reporting.

In diagnostic nuclear medicine the goal is to have an appropriate report on high-standard quality images, while in radionuclide therapy the goal is to achieve appropriate treatment of the disease through delivery of a radiation dose at the desired cytotoxic level, with the defined endpoints being cure, disease control (stabilisation) or palliation. Likewise it is fundamental to avoid or minimise toxic effects (spare normal organs), both in the acute time frame and as long-term complications [1]. These topics are discussed in more breadth and depth in dedicated chapters of this book.

Facility and personnel

The facilities required depend on national legislation for the emission of beta- and beta- and gamma-emitting therapy agents. If required by law, the patient should be admitted to an approved isolation facility

comprising an appropriately shielded room and en suite bathroom facilities. Radioprotection issues are critical not only due to patient emission but also because of the relatively long half-life and the higher possibility of contamination.

The facility in which treatment is administered must have appropriate personnel and radiation safety equipment; procedures must be available for waste handling and disposal, handling of contamination, monitoring personnel for accidental contamination and controlling contamination spread [2].

It is really important for all the personnel involved to have a good knowledge of the facility and of the principles and legislation underlying the facility structure in order to be able to interact efficiently.

Facilities are considered not only the shielded hospital rooms, but also the radiopharmacy laboratory for radiopharmaceutical preparation, specific patient circuits within the department and the nuclear medicine diagnostic department in which pre- and post-treatment dosimetry imaging is performed.

Patients and personnel

Patients are the main subject of all radionuclide therapy procedures and it is important that staff behave correctly in order to ensure that they are introduced into a friendly and easy-to-understand environment. Illness and radioactivity are two of the most scary events for people living within the "Western culture" and this has to be borne in mind in patient management. Treatment must be explained to the patient by the physician, but in addition all personnel who deal with the patient (nurses, technologists) must be aware of the procedure that he or she is undergoing in order to be able to answer questions properly. Radiation safety measures must be orally explained and presented to the patient in written form (leaflet). The ways in which these rules are explained will influence patient compliance with them. It is also important not to ask patients to do impossible things [3].

Patients and personnel have to follow the same goals of effective therapy and respect for radiation safety procedures within a good practice environment.

Personnel and personnel

Generally speaking, each professional group has a *lead* person and together these people manage the service. A medical lead (doctor) specialised in nuclear medicine is necessary and holds medical responsibility for the service. The service usually also has a manager; often the manager is a nuclear medicine technologist, physicist or radiographer. As mentioned earlier, nuclear medicine is now integrated more closely with other disciplines (e.g. oncology) and these disciplines will also have their professional groups and managerial systems.

The delivery of a successful patient-focussed service will require good team working [4]. To achieve this, all team members will require varying levels of skill and knowledge about other professional groups, in relation to their areas of expertise and the roles they can fulfil. One way of achieving effective inter-professional working is through inter-professional education. Leadership skills are also vital so that work gets done efficiently and all those involved contribute effectively. In the rest of this preamble we shall consider what team working, leadership and inter-professional working/education are and why they are so important.

Some examples of team working procedures directly related to radionuclide therapy are as follows (these examples are not meant to be exhaustive, but only to illustrate concepts expressed in situations encountered in daily practice):

- *Clinical audit*: Carried out by physicians but with the cooperation of nurses, since the hospitalisation must be geared to specific patient needs and special care may be required to ensure patient comfort.

- *Pre-therapeutic scans*: Performed by the technologist, after indication by a physician, in order to simulate the biodistribution of radiopharmaceuticals using a diagnostic activity. This is very important in order to guarantee a high-standard scan and to identify possible abnormalities in patient uptake that can change the choice of therapeutic modality (e.g. owing to unexpected metastasis). The technologist must be aware of the diagnosis and prognosis of the patient as these are prerequisites for ensuring that the scan is performed adequately.

- *Pre-therapeutic dosimetry*: Performed by a physicist together with the technologist, after indication by a physician, using a tracer activity in order to assess individual kinetics and plan effective treatment within the dose limits for radiosensitive organs. Good practice is fundamental since small errors in instrument calibration and measurements with the probe and gamma camera may lead to wide differences in therapeutic dose estimation. Technologist cooperation is fundamental to find time slots in the diagnostic schedule for performance of dosimetry calculation, and coordination with nurses is required for scheduling of blood sampling for analysis of activity in the blood.

- *Administration*: The radiopharmaceutical is prepared by radiopharmacists and given by a nurse, technologist or radiographer with appropriate skills, depending on national regulations. Generally, physicians act as a support but they also can be the main actors. All those involved, including the patient, must be aware of the radiopharmaceutical characteristics, the dose to be administered, possible adverse events and the level of radiation risk.

- *Hospitalisation*: Nurses monitor patients' early symptoms and make patients as comfortable as possible without forgetting radiation protection and contamination risks. Suitable advice and explanations must be given to patients to ensure that they have a correct approach to the environment and respect for radiation protection rules. Physicists will cooperate with patients in minimising risk and teaching them the best way to deal with patient emergencies without increasing personnel exposure to radiation.

- *Post-therapy dosimetry and follow-up*: Physicists must perform evaluations and controls before discharging patients. The technologist's role is to scan the patient with the gamma camera to evaluate biodistribution. The technologist must know the administered dose and patient audit to perform a good scan for the indication requested. The patient needs to know the appropriate radiation safety procedures to be followed at home, and it is important to have a printed leaflet available as a sound means of explanation.

As stated above, legislation regulating radionuclide therapy may vary greatly between countries, and competencies, skills and knowledge of professional groups may differ accordingly.

The need for good inter-disciplinary working has been recognised for many years, and centres of excellence have been established to enhance inter-professional practice and facilitate/publish research [5]; a multitude of articles about this subject have been published in the medical, nursing and allied health literature. Underpinning this is a growing realisation that inter-professional education supports good inter-professional working, and consequently medical, nursing and allied health curricula have evolved to accommodate this; the relationship between inter-professional education and inter-professional collaboration in practice is well documented [6,7]. Various definitions have been proposed on what constitutes inter-professional education, but an appropriate one is that put forward by the Centre for the Advancement of Inter-professional Education: "when two or more professions learn with, from and about each other to improve collaboration and the quality of care… and includes all such learning in academic and work-based settings before and after qualification, adopting an inclusive view of professional" (2006).

Inter-professional learning is not simply about learning alongside other professionals in a classroom or lecture theatre. It concerns learning with other professionals to understand much more about them with the intention of improving collaboration and mutual respect and ultimately the quality of patient care. However, the importance of team skill development within hospitals seems to be culturally sensitive, so much so that while some countries (e.g. the United States) attach high importance to team

working abilities, other countries have not yet recognised their value. Numerous textbooks have been published on team working, and a tremendous amount of journal literature exists on this topic, too [8].

It is important that, besides theories, the focus is kept on treating the patient successfully with the lowest dose possible and with the least possible radiation risk for operators.

Involvement of different medical specialists

Medicine is increasingly becoming a multidisciplinary science, and this enhances the quality of care provided to patients. Radionuclide therapy is no exception, and agreement among disciplines must be sought on why, when and how the use of radionuclide targeted techniques can be of value. Different diseases can be successfully treated with nuclear medicine techniques, and different specialists should be involved in patient management depending upon the disease under consideration. Most patients who can benefit from radionuclide therapy are suffering from cancer, but it should not be forgotten that nuclear medicine therapy helps many patients affected by hyperthyroidism and diseases of the joints. The clinical scenario always requires careful evaluation of all the possible therapeutic strategies that a nuclear medicine physician can apply to his or her patients, and cases which do not fit into existing guidelines should always be discussed within multidisciplinary boards. In this context, some discussion about leadership may arise.

Leadership is a poorly understood concept and often people misguidedly directly associate leadership solely with management roles [9,10]. It is true to say that managers *should* be leaders; it is also true to say that leaders do not need to be managers – indeed, most leaders are not managers [11]. Leadership is about getting things done with and through other people: it concerns influencing others to do things. The purpose of leadership training is clear – effective leadership has been proven to enhance productivity, staff loyalty and performance, and many other important factors. Many theories exist about leadership but perhaps the most pertinent for nuclear medicine would be transformational leadership [12], as this is ideally suited to peer leadership. It is important to recognise the concept of peer leadership within and external to nuclear medicine as for many aspects of work it is the team and specific team members who take responsibility rather than one individual. For instance, when nuclear medicine articulates with oncology for performance of radionuclide therapy procedures, the oncology team "work with" the nuclear medicine team to deliver the joint service in order to achieve the required outcomes. It might be that neither nuclear medicine nor oncology is "in charge", but together they apply their talents to achieve outcomes. Making sure these teams work effectively together can be difficult to achieve as conflict of role can arise and confusion can ensue about who should do what and who is capable of doing what. Transformational leadership theory sits well in this context.

EANM

As you read our book on radionuclide metabolic therapy we hope you will remember that effective inter-professional working is essential for the delivery of an efficient and successful service.

At this point we acknowledge that the issues raised in our preamble have significant bodies of knowledge associated with them and we do not claim to be experts in these fields. In this preamble we appreciate that we have only skimmed the surface of the theory and practice that would support this, but we anticipate that in the next Technologist's Guide an expert in inter-professional working will be invited to contribute an evidence-based chapter.

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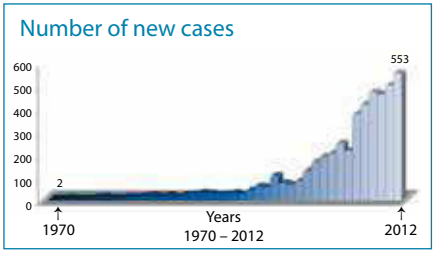
The thyroid gland

The thyroid gland is located in the anterior cervical area. It has two lobes, one on each side of the trachea, and an isthmus, which lies between the right and left thyroid lobes. The internal jugular vein, the vagus nerve, the common carotid artery, the four parathyroid glands and the recurrent laryngeal nerves are the most important anatomical elements situated in the thyroid area [1].

The major role of the thyroid gland is the synthesis and release of thyroxine (T_4) and triiodothyronine (T_3) from the follicular cells and of calcitonin from the parafollicular thyroid cells. These hormones influence heart rate, blood pressure, body temperature, nervous system, digestive system, weight and calcium level in the body [2]. The thyroid hormones act on every metabolic path, and normal thyroid function is reflected in the equilibrium of the human body. The regulation of thyroid function is achieved through the hypothalamic-pituitary-thyroid axis negative feedback mechanism.

Epidemiology of thyroid cancer

Thyroid cancer is the most frequent endocrine tumour, and especially during the last decade it has displayed one of the most rapidly increasing incidences among human cancers. According to data published by the National Cancer Institute (NCI), in 2013 about 45,000 women and 15,000 men will be diagnosed with thyroid cancer in the United States [3]. Various studies have confirmed that the incidence of this pathology is continuing to rise [4-7], with a clear preponderance of cases in females. Thyroid cancer accounts for 0.5-1.5% of all childhood tumours and represents the most common malignant head and neck tumour in young people. Compared with cases in adults, the epithelial-derived differentiated thyroid cancers (DTC), which include papillary (PTC) and follicular (FTC) thyroid cancers, occurring in children are more aggressive, are discovered in advanced stages and are associated with higher rates of recurrence [8]. Figure 1 shows the trend in the incidence of thyroid cancer in the database of the Institute of Oncology, Cluj-Napoca, Romania.



Database of the "Ion Chiricuță" Institute of Oncology (IOCN), Cluj-Napoca, Romania, Dr.Piciu D.

Figure 1: Incidence of thyroid cancer between 1970 and 2012 at the "Ion Chiricuță" Institute of Oncology (IOCN), Cluj-Napoca, Romania.

Causes of thyroid cancer

Endemic goitre

Endemic goitre (or "thyropathic endemic dystrophy") results in the chronic hypersecretion of thyroid stimulating hormone (TSH), which acts as a trigger in the appearance and development of thyroid cancer. A low-iodine diet and iodine deficiency are associated with a particular form of differentiated thyroid cancer, so-called follicular thyroid cancer.

Ionising radiation

Ionising radiation is one of the most studied causes of thyroid cancer, which scientific and clinical communities accept is directly related to a personal history of irradiation.

The human environment accounts for up to 85% of the annual human radiation dose, the sources being construction materials, food, drink, soil and the cosmos. Human activities account for the remaining 15%, the predominant source being medical procedures (14% of total); only a small amount of exposure is due to fallout from past testing of nuclear weapons, though nuclear accidents have been associated with a clear increase in the incidence of thyroid cancer [9].

Chronic stimulation of TSH

As mentioned above, chronic TSH stimulation is considered a trigger for the appearance of metaplasia. This condition is also important in the follow-up of patients with DTC, where the replacement dose of thyroid hormone must produce suppression of TSH in order to decrease the probability of disease recurrence.

Environmental factors

Environmental risk factors include radiation from soil, water, drinks, construction materials and professional exposure, as well as low-iodine diet and intake.

Immunological factors

The association of chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) with thyroid cancer is well known. This pathology is frequently associated with thyroid nodules; the long evolution of nodular thyroid and the occurrence of chronic thyroid insufficiency may lead to cancer.

Genetic factors

Genetic mutations are responsible for the development of medullary thyroid carcinomas (MTC) in more than 25% of cases. If the abnormal gene, usually located in codon 634 of chromosome 10, runs in the family, then the individual may be at very high risk of developing MTC. Such persons should consider approaching a medical practitioner for information on serum calcitonin tests and genetic testing. People with certain inherited medical conditions, including Gardner's syndrome and familial polyposis (genetic disorders in which large numbers of precancerous polyps develop throughout the colon and upper intestine), are also at higher risk of PTC. Cowden disease, a rare inherited disorder that causes lesions on the face, hands and feet and inside the mouth, also increases the risk of developing thyroid cancer and breast cancer. In addition, mutations of BRAF genes, which may be determined even from the cytology specimen, are related to DTC.

Symptoms of thyroid cancer

The symptoms of thyroid cancer frequently are not expressed for many years during the evolution of the disease. A nodule in the cervical area is the most common presenting feature. A complete clinical examination is able to suggest the diagnosis of thyroid pathology, but the positive diagnosis of thyroid

cancer is sometimes very difficult. The guidelines published by clinicians and scientists have sought to optimise working practice and procedures in order to assist in diagnosis.

Only local compression and invasion are findings specific to thyroid cancer. The following symptoms may be present owing to thyroid dysfunction but they are not specific to thyroid carcinoma:

- Respiratory insufficiency
- Hoarseness
- Deglutition difficulties
- Tremor
- Sweating
- Diarrhoea/constipation
- Anxiety, depression, lethargy
- Heat/cold intolerance
- Coarse skin
- Weight loss/weight gain
- Pretibial oedema
- Muscle weakness
- Increased/reduced heart rate
- Dry hair
- Swallowing difficulties
- Rarely, pain in the anterior cervical area

These signs and symptoms may very seriously affect the patient's status.

Diagnosis of thyroid cancer

Clinical examination

The location of the thyroid gland in the anterior neck region makes it very easy to inspect the organ so as to determine the presence or absence of disease. A large goitre may cause tracheal deviation. Palpation of the cervical lymph nodes should be done carefully, taking into account the known pathways of lymphatic drainage: lateral cervical, supraclavicular and submental. Inspection of the gland may reveal enlargement, asymmetry and a full, bounding pulse. The physician may observe mobility of the gland and difficulties in swallowing. Palpation will reveal the texture (soft/firm), the surface (smooth/seedy/lumpy) and the volume (increased in different grades or decreased/atrophic). The presence of regional pathological lymph nodes should be noted, as should spontaneous pain or pain on palpation, mobility over the neck structures and mobility upon swallowing. During the clinical examination it is important to note any history of irradiation and possible inherited associated pathologies.

Thyroid ultrasound

Thyroid ultrasound is a widespread technique that is used as a first-line diagnostic procedure for detecting and characterising nodular thyroid disease (more than 46% of thyroid nodules greater than 1 cm are not detected by palpation). There are some special patterns on an ultrasound image that suggest malignant transformation, the most important being a solid nodule, with peri- and intranodular circulation, a taller-than-wide shape (sensitivity, 40.0%; specificity, 91.4%), a spiculated margin (sensitivity, 48.3%; specificity, 91.8%), marked hypoechogenicity (sensitivity, 41.4%; specificity, 92.2%), microcalcification (sensitivity, 44.2%; specificity, 90.8%), and macrocalcification (sensitivity, 9.7%; specificity, 96.1%) [10].

Fine-needle aspiration biopsy

Fine-needle aspiration biopsy (FNAB) is routinely recommended for all nodules exceeding 1 cm in maximum diameter. Its sensitivity has been reported to be 83%, with an associated specificity of 72–100% [11].

FNAB is a simple, rapid, cost-effective diagnostic method used in the evaluation of the thyroid nodule. According to the latest studies [12], the use of various immunohistochemical markers in cytological samples (BRAF, RAS, RET/PTC etc.) might increase the accuracy of the positive diagnosis.

Serum hormonal tests

Current guidelines [13,14] recommend that serum TSH be used as the first-line test for detecting both overt and subclinical hypo- or hyperthyroidism in ambulatory patients with stable thyroid status and intact hypothalamic/pituitary function. Thyroid hormone tests, [T_4, T_3, free T_4 (FT_4) and free T_3 (FT_3)] are conducted to determine the cause of an abnormal TSH test and to check how well treatment of thyroid disease is working. In practice, measurement of FT_4 and FT_3 is a more reliable test of thyroid function than measurement of total hormone levels.

The tissue-specific origin of thyroglobulin (Tg) is used as a tumour marker for DTC. Because Tg protein is tissue specific, the detection of Tg in non-thyroidal tissues or fluids (such as pleural fluid) indicates the presence of metastatic thyroid cancer (except struma ovarii). Current guidelines do not routinely recommend preoperative serum Tg measurement. Serum Tg measurements performed at 4-6 weeks after surgery have been shown to be of important prognostic value. Antithyroglobulin antibodies interfere with the accurate measurement of serum Tg. Serial antithyroglobulin antibody monitoring necessitates the use of the same method each time, because assays vary in sensitivity, specificity and absolute values.

Thyroid scintigraphy

Thyroid scintigraphy uses radioactive tracers for imaging of the thyroid gland and for functional assessment during thyroid uptake of the radiopharmaceutical. Different tracers are in use for different purposes. Thyroid scintigraphy is not the first-line method for the evaluation of thyroid nodules but it has a very well established place in the diagnostic protocol. Whole body radioiodine scintigraphy is the most important imaging method during the follow-up of DTC.

Computed tomography, magnetic resonance imaging and positron emission tomography

These modalities are not usually indicated in the evaluation of thyroid nodules and thyroid cancers; rather, they are reserved for specific well-documented situations.

Overall, clinical examination, TSH determination, thyroid ultrasound and FNAB are generally sufficient in permitting correct assessment of thyroid nodules and cancer.

Classification of thyroid tumours

Well-differentiated malignant neoplasms (85% of thyroid cancers):

- Papillary thyroid carcinoma (PTC)
- Follicular thyroid carcinoma (FTC)

Poorly differentiated malignant neoplasms:

- Medullary thyroid carcinoma (MTC)
- Anaplastic thyroid carcinoma

Other thyroid tumours:

- Teratoma
- Primary lymphoma and plasmacytoma
- Ectopic thymoma
- Angiosarcoma
- Smooth muscle tumours
- Peripheral nerve sheath tumours
- Paraganglioma
- Solitary fibrous tumour
- Follicular dendritic cell tumour
- Langerhans cell histiocytosis
- Secondary tumours of the thyroid

The TNM Staging System

The most common system used to describe the stages of thyroid cancer is the American Joint Committee on Cancer (AJCC) TNM Staging for Thyroid Cancer [15], where *T* indicates the size of the main (primary) *tumour* and whether it has grown into nearby areas, *N* describes the extent of spread to nearby (regional) lymph *nodes* and *M* indicates whether the cancer has spread (*metastasised*) to other organs of the body. (The most common sites of spread of thyroid cancer are the lungs, the brain, the liver and the bones.)

T categories for thyroid cancer (other than anaplastic thyroid cancer)

Note: All categories may be subdivided:

- (s) solitary tumour
- (m) multifocal tumour (the largest focus determines the classification)

TX: Primary tumour cannot be assessed

T0: No evidence of primary tumour

T1: Tumour 2 cm or smaller, limited to the thyroid

T1a: Tumour 1 cm or smaller, limited to the thyroid

T1b: Tumour larger than 1 cm but not larger than 2 cm, limited to the thyroid

T2: Tumour between 2 and 4 cm in greatest dimension, limited to the thyroid

T3: Tumour more than 4 cm in greatest dimension, limited to the thyroid; any tumour that displays minimal extrathyroidal extension (e.g. extension to the sternothyroid muscle or perithyroid soft tissues)

T4a: Tumour of any size that has grown extensively beyond the thyroid gland into the nearby tissues of the neck, such as the larynx, trachea, oesophagus or recurrent laryngeal nerve (also called moderately advanced disease)

T4b: Tumour of any size that has grown either back toward the spine or into nearby large blood vessels (also called very advanced disease)

T categories for anaplastic thyroid cancer

All anaplastic thyroid cancers are considered T4 tumours at the time of diagnosis.

T4a: Tumour still within the thyroid

T4b: Tumour has grown beyond the thyroid

N categories for thyroid cancer

NX: Regional (nearby) lymph nodes cannot be assessed

N0: No spread to nearby lymph nodes

N1: Cancer spread to nearby lymph nodes

N1a: Spread to pretracheal, paratracheal and prelaryngeal lymph nodes

N1b: Spread to other cervical lymph nodes or to lymph nodes behind the throat (retropharyngeal) or in the upper mediastinum

M categories for thyroid cancer

M0: No distant metastasis

M1: Spread to other parts of the body, such as distant lymph nodes, brain, internal organs and bones

Thyroid cancer staging

Papillary or follicular thyroid cancer in patients younger than 45 years old

All people younger than 45 years old having these types of cancer are considered to have stage I cancer if they have no distant spread, and stage II cancer if they have distant spread:

Stage I (any T, any N, M0)

Stage II (any T, any N, M1)

Papillary or follicular thyroid cancer in patients aged 45 years old and older

Stage I (T1, N0, M0)

Stage II (T2, N0, M0)

Stage III:

- T3, N0, M0
- T1 to T3, N1a, M0

Stage IVA:

- T4a, any N, M0
- T1 to T3, N1b, M0

Stage IVB (T4b, any N, M0):

Stage IVC (any T, any N, M1)

Medullary thyroid cancer

Age is not a factor in the staging of medullary thyroid cancer

Stage I (T1, N0, M0)

Stage II:

- T2, N0, M0
- T3, N0, M0:

Stage III (T1 to T3, N1a, M0)

Stage IVA:

- T4a, any N, M0
- T1 to T3, N1b, M0

Stage IVB (T4b, any N, M0)

Stage IVC (any T, any N, M1)

Anaplastic (undifferentiated) thyroid cancer

All anaplastic thyroid cancers are considered to be stage IV, reflecting the poor prognosis of this type of cancer.

Stage IVA (T4a, any N, M0)

Stage IVB (T4b, any N, M0)

Stage IVC (any T, any N, M1)

Prognostic factors

The majority of thyroid cancers are not aggressive and have an excellent prognosis. Prognostic factors include:

- Age
- Sex
- Histological type
- Histological grade
- Tumour size
- Extrathyroidal extension
- Distant metastases
- Lymph node involvement
- Multicentricity
- Incomplete resection

Depending on histology and stage, different treatment approaches are adopted for thyroid carcinoma. There are multiple guidelines for diagnosis and therapy, many of them published by national and international committees of experts in endocrinology, endocrine surgery, nuclear medicine and oncology. All of these algorithms have been reviewed frequently with the intention of minimising suboptimal diagnosis, surgery or irradiation and providing the best option for multimodal treatment.

Surgical Treatment

Surgery is the most important treatment option in thyroid cancer management. It consists in total thyroidectomy, total lobectomy or prophylactic total thyroidectomy in MTC. Lymphadenectomy in thyroid cancer is well defined regarding the ablation of the pretracheal lymph node group (level VI, Delphian lymph nodes) and the selective resection of lateral-cervical lymph nodes. The type of surgical procedure is dictated by the type of tumour and the risk category, as follows [14]:

Differentiated thyroid carcinoma (DTC) – nodules with undefined cytology from FNAB:

- undefined solitary nodule <4 cm – total lobectomy
- undefined solitary nodule >4 cm or personal history of irradiation or familial history of thyroid cancer – total thyroidectomy
- undefined multiple nodules or bilateral nodules – total thyroidectomy

Differentiated thyroid carcinoma (DTC) – nodules with suggestive cytology for malignancy:

- thyroid cancer >1 cm – total thyroidctomy
- total lobectomy only if:
  - tumour <1 cm
  - low risk histology
  - unifocal
  - intrathyroid papillary carcinoma, without previous irradiation and without lymph node metastases or local invasion.

The type of lymphadenectomy depends on the tumour type, tumour size and presence of lymph node metastases.

Medullary thyroid carcinoma (MTC) is treated by total thyroidectomy and level VI lymph node dissection; uni- or bilateral cervical

lymph node resection is also recommended depending upon presence of the sporadic or hereditary form, tumour size and lymph node involvement.

Anaplastic thyroid carcinoma requires total thyroidectomy and level VI lymph node dissection, assuming that the staging indicates these to be appropriate; frequently, however, this cancer is classified as being at a stage unsuitable for surgical resection.

Thyroid hormone treatment

Synthetic levothyroxine is typically administered in a dose of 2-2.5 µg/kg body weight; according to the risk group and time since therapy, the dose might be suppressive, with the aim of maintaining the TSH level below 0.1 mIU/L.

Radioiodine therapy

Radiopharmaceutical

Iodine-131 (^{131}I) sodium iodide capsules are used for oral administration, with a specific activity of 1.11 GBq, 1.85 GBq, 2.59 GBq, 3.7 GBq or 5.55 GBq at calibration time, as clearly stated by the producer.

Principle

^{131}I-sodium iodide is administered systemically for selective irradiation of post-surgical thyroid remnants of DTC or other suitable cases of DTC not treated by surgery, or for the irradiation of iodine-avid metastases.

Recommendations

The European Thyroid Association (ETA) [14] recommendations are:

1. Very low risk group – no indication for postoperative ^{131}I
   - Unifocal differentiated microcarcinoma (≤1 cm)
   - No extension beyond the thyroid capsule
   - No lymph node metastases
   - Complete surgery
2. Low-risk group – probable indication – no consensus
   - Less than total thyroidectomy, no lymph node dissection
   - Age <18 years
   - Unfavourable histology, T1 >1 cm, T2, N0, M0
3. High-risk group – definite indication
   - T3, T4, N1, M1
   - Incomplete surgery
   - High risk of recurrence

The American Thyroid Association (ATA) [13] categorised their recommendations into seven ratings (A–F, plus I for recommendation neither for nor against) according to the strength of the available medical evidence. For assessment of risk recurrence, they proposed a three-level stratification into low-, intermediate- and high-risk groups.

According to the ATA, radioiodine ablation is recommended for:

- Patients with stage III or IV disease
- All patients with stage II disease who are younger than 45 years
- Most patients with stage II disease who are 45 years old or older
- Selected patients with stage I disease who have higher risk factors, i.e. multifocal (>2 foci) disease, nodal metastases, extrathyroid and vascular invasion and/or aggressive histology.

ETA/ATA recommendations for management of metastatic and recurrent disease

For local and regional recurrence:

- Surgery and ^{131}I
- External beam therapy of 40-45 Gy in 25-30 sessions only if surgery is not possible and there is no ^{131}I uptake

For distant metastases:

- Lungs: 3.7-7.4 GBq every 4-8 months during the first 2 years
- Bones: surgery and ^{131}I, external beam therapy
- Brain: surgery and external beam therapy, ^{131}I only after external radiotherapy
- Doses are repeated until the disease is cured
- Radioiodine therapy is stopped if there are signs that the tumour is no longer iodine avid

Risk of second malignancies:

- ETA – the risk of second malignancy is significantly higher at a dose above 22.2 GBq ^{131}I [14].
- ATA – the risk of second malignancy is dose related, and long-term follow-up studies demonstrate a very low risk. There appears to be an increased risk of breast cancer, but it is unclear whether this is a result of screening, radioiodine therapy or other factors.

Protocol

There are multiple choices for establishing the necessary dose for radioiodine therapy, but administration of a fixed dose of ^{131}I is the simplest and most widely used method.

The indications for radioiodine are as follows:

a) *Remnant ablation*. The dose for remnant ablation may be 1.1, 1.85, 2.59 or 3.7 GBq, according to the volume of the tissue, the uptake and the level of Tg.

b) *Lymph node metastases* may be treated with 3.7–6.475 GBq of ^{131}I. Cancers that extend through the thyroid capsule and have been incompletely resected are treated with 3.7-7.4 GBq.

c) Patients with distant metastases are usually treated with 7.4 GBq of ^{131}I, which typically will not induce radiation sickness or produce serious damage to other structures but may exceed generally accepted

safety limits for the blood in the elderly and those with impaired kidney function.

d) Diffuse pulmonary metastases are treated with 5.55 GBq or less of ^{131}I to avoid lung injury, which may occur when more than 2.96 GBq remains in the whole body 48 h after the treatment.

The administered activity of radioactive iodine therapy should be adjusted for paediatric patients.

After the administration, the patient remains in a fasting condition for two more hours and after that he/she is advised to hydrate consistently and to use "chewing drops" to stimulate saliva production and thereby reduce the impact of irradiation on the salivary gland.

The administration of ^{131}I for the treatment of DTC is typically performed under hospitalisation and patients are discharged in accordance with national radioprotection regulations; however, in some countries the treatment may be done on an ambulatory basis even at doses of ^{131}I higher than 1.1 GBq.

All patients receive paper and electronic information about the diagnosis, the treatment options, follow-up, side-effects and personal indications about individual medication.

The rooms must have separate washing and toilet facilities and the patient is under continuous surveillance by the staff, on separate cameras. Upon discharge, the patient is advised how to minimise the radiation risk to other persons and for what period of time, depending on the dosimetry measurements at the time of discharge.

Post-treatment whole-body ^{131}I scan

Whole-body radioiodine imaging should be performed several days (1-3) following treatment to document ^{131}I uptake by the tumour and to assess the extent of the disease.

Special recommendations:

- Do not use CT with contrast media for staging; it is reserved for specific situations where the ^{131}I therapy is not scheduled.
- Avoid ^{131}I whole-body scan before radioiodine treatment unless distant metastases are suspected and an important active thyroid remnant must be removed by surgery.
- Do not use any medication (blocking agents with iodine, amiodarone etc.) that may influence the radioiodine uptake.
- Use the lowest efficient radioiodine activity.
- At discharge it is necessary to give the patient information regarding radioprotection issues.

A total response and disease-free state are indicated by the absence of tumour mass on clinical examination and ultrasound, absence of symptoms, undetectable Tg in the presence of high TSH and absence of anti-Tg antibodies.

Strict follow-up is very important for early detection of disease recurrence and rapid institution of appropriate treatment.

External beam radiotherapy

External beam radiotherapy (EBRT) has only a limited indication in DTC, being appropriate when the tumour is inoperable or there is local invasion without a favourable response to radioiodine therapy. Similarly, in MTC, EBRT is limited to inoperable tumours and cases with regional invasion. In anaplastic thyroid carcinoma, by contrast, EBRT is frequently used owing to the very severe outcome of the disease and the lack of other therapeutic options.

Chemotherapy

Thyroid carcinoma is widely considered to be radio- and chemoresistant. In DTC, chemotherapy is reserved for those situations in which the tumour loses affinity for radioiodine, while in MTC it is used in some forms of abdominal metastasis. Anaplastic thyroid carcinoma shows rapid and aggressive growth, and response rates to systemic chemotherapy are very limited.

Clinical trials

When DTC shows continued evolution, but no longer responds to radioiodine and presents a negative ^{131}I whole-body scan, new drugs undergoing clinical trials might represent a reasonable treatment choice.

The role of supporting staff in administering radionuclide therapy

Patient preparation

Patients must have undergone total or near-total thyroidectomy and have a confirmed pathological diagnosis of DTC.

For successful radioiodine therapy, the TSH value must exceed 40 mIU/L. This value may be obtained:

- At 4-6 weeks after surgery in the absence of thyroid therapy replacement
- After 2-4 weeks of thyroid hormone withdrawal, in the case of replacement thyroid hormone therapy;
- After administration of recombinant TSH in two intramuscular injections of 0.9 ml solution on two consecutive days, if the patient is under hormonal treatment.

It is important to be familiar with the TSH stimulation procedures and to be able to verify that the patient has understood and consented to the procedure. The recombinant TSH stimulation method will involve a range of clinical professionals in ensuring accurate dose preparation and administration.

Patients must fast before therapy and must be checked carefully by all the staff. It must be ensured that the patient is not taking any of an extensive inventory of long-term medications that might interfere with iodine uptake. During the preceding 3 months, the

patient must not have received blocking agents or iodinated contrast media used in X-ray examinations. Dietary restrictions consist in avoidance of iodised salt, seafood, nuts and other foods rich in iodine for 1 week prior to therapy.

Precautions

In the case of female patients of childbearing potential, a routine pregnancy test must be done within 72 h prior to the administration of ^{131}I. No radioiodine therapy may be administered in pregnant patients.

All institutional and departmental documentation must be explained and signed before therapy in order to limit the exposure after iodine administration.

In order to avoid or reduce the stunning effect, pretherapy ^{131}I whole-body scan is not routinely recommended. It is possible to:

- Use ^{123}I or low doses (74 or 111 MBq) of ^{131}I
- Use a shortened interval (of not more than 72 h) between the diagnostic ^{131}I dose and the therapy dose.

A close relationship between all staff members involved in the diagnostic and treatment of this pathology is essential in achieving an optimal outcome for patients.

Patient surveillance

Patient surveillance in the period following radioiodine administration is an issue relevant to physicians, nurses, technologists and others. Radiation protection-related problems are very important for both patients and staff, and have already been discussed in Chapter 4 of this book.

Contamination and vomiting, as well as various prostheses and metallic clips (which may be contaminated by the iodine from the bloodstream), are factors that may influence the accuracy of scanning results [16] and therefore it is very important that staff pay attention to such circumstances.

Whole-body scanning (WBS) – technical issues

^{131}I-NaI is absorbed from the gastrointestinal tract after oral administration. The process of organification consists in trapping of ^{131}I in the thyroid gland and in all DTC cells disseminated in the body.

The whole-body acquisition allows data to be acquired from a patient who is larger than the field of view of the gamma camera. The patient's bed is moved into/out of the gantry during acquisition of the image.

The scan is performed at 24, 48, 72 h or sometimes even 5-7 days after administration of the radioiodine capsule, the time interval depending on the activity of the radioiodine dose and the amount of remnant tissue. The patient's position for scanning is supine, with slight neck extension. Scanning technique entails use of the following:

- Gamma camera (single head or dual head)
- Calibration and valid quality control tests
- Large field rectangular head
- High-energy general-purpose (HEGP) collimator
- Anterior-posterior (AP) and posterior-anterior (PA) scanning over the patient's body, as close to the patient as possible, ensuring that sufficient distance is maintained in order to avoid any influence on resolution
- Acquisition: whole body
- Selected energy: 364 keV
- Window: 15–20%
- Matrix: 1,024 × 256
- 750,000–1,000,000 counts/image
- Acquisition of lateral or oblique-lateral images (optional)
- Special PC programs for processing the images.

Figure 2 shows the normal distribution of the radiopharmaceutical in the body: there is uptake in the thyroid remnant, the mouth and salivary glands, the stomach, the digestive tract and the urinary bladder.

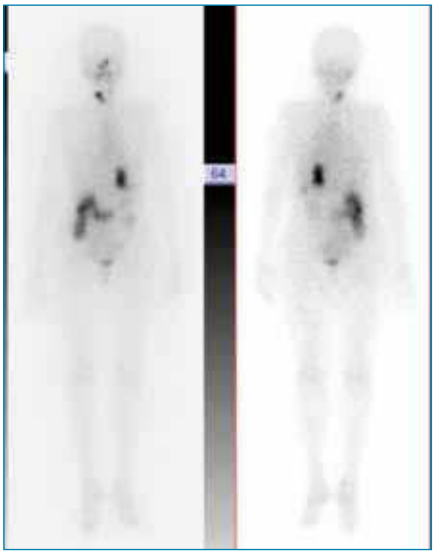


Image from the Department of Nuclear Medicine of the "Ion Chiricuță" Institute of Oncology (IOCN), Cluj-Napoca, Romania, Dr.Piciu D.

Figure 2: ^{131}I WBS at 24 h post therapy.

It is essential to obtain the best possible image, yielding the most accurate information on uptake and distribution of radioiodine in the patient's body. As the technologist is the first member of the clinical staff to observe the image showing radioiodine distribution, he or she must be well prepared and aware of possible artefacts and radioiodine contamination. Figure 3, showing high uptake in

the ocular areas due to contact lens contamination, illustrates how a mistake may occur and the importance of recognising artefacts and taking appropriate corrective action.

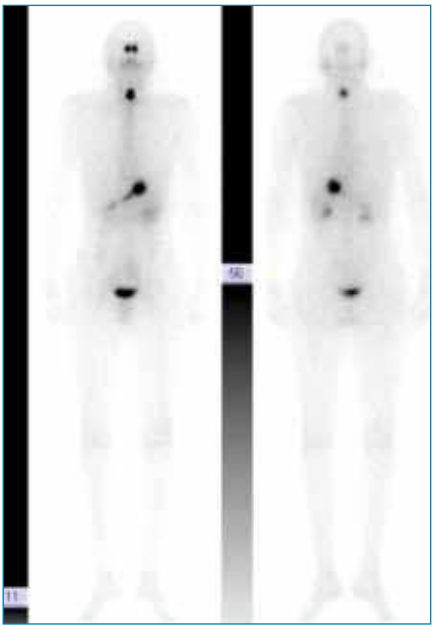


Image from the Department of Nuclear Medicine of the "Ion Chiricuță" Institute of Oncology (IOCN), Cluj-Napoca, Romania, Dr.Piciu D.

Figure 3: ^{131}I WBS post therapy: high uptake is seen in the ocular areas due to contact lens contamination.

Figures 4 and 5 further serve to illustrate the sort of mistake that may arise if inadequate precautions are taken to limit possible contamination. Figure 4 shows a ^{131}I WBS at 48 h post therapy that demonstrates thyroid remnant uptake in the thyroid area; in addition, pathological uptake is evident in the lower right lobe of the lung. This image was highly suggestive for a macronodular right lung metastasis. Because the value of Tg (28.5 ng/L, N.V. <0.1 ng/L in athyreotic patients) was not very high, as is usually the case in patients with lung metastasis, we supposed that either the lung tumor was not related to the thyroid pathology or that this was a metastasis of the thyroid carcinoma with low expression of Tg. Before testing other pathologies, it was important to double check the possibility of radioiodine contamination of the patient. In this second inspection we found that the patient had placed a handkerchief in the pocket of the disposable robe. Figure 5 was obtained immediately after changing the disposal robe, and we observed that the uptake from the right lung has disappeared.

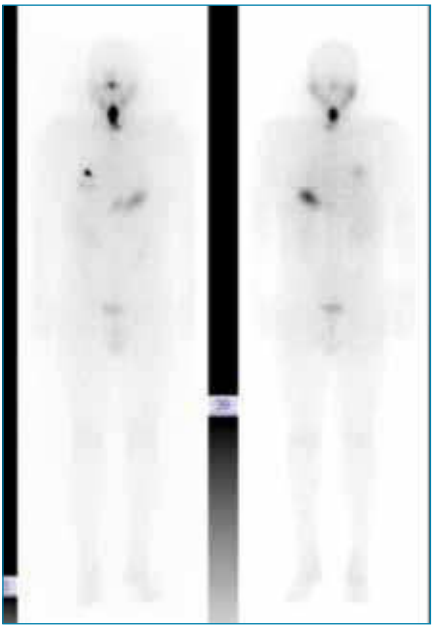


Image from the Department of Nuclear Medicine of the "Ion Chiricuță" Institute of Oncology (IOCN), Cluj-Napoca, Romania, Dr.Piciu D.

Figure 4: ^{131}I WBS at 48 h post radioiodine therapy: there is suspicion of a right lung metastasis.

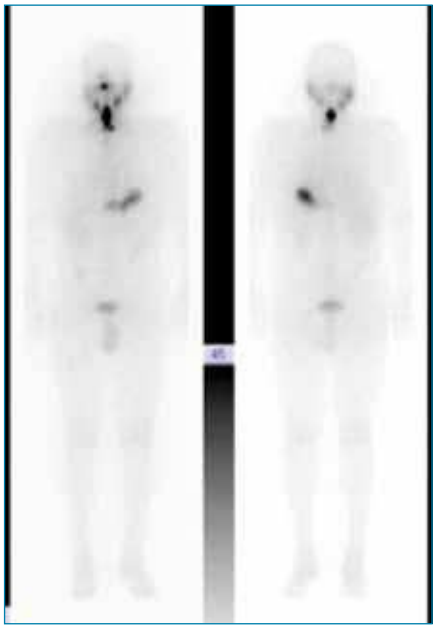


Image from the Department of Nuclear Medicine of the "Ion Chiricuță" Institute of Oncology (IOCN), Cluj-Napoca, Romania, Dr.Piciu D.

Figure 5: Same patient as in Figure 4. ^{131}I WBS at 48 h post radioiodine therapy. After changing the disposable robe, the contamination responsible for the apparent metastasis was eliminated.

Radioprotection issues

Clinical staff must know and respect the radiation protection measures relating to staff protection, handling of radiopharmaceuticals and patient safety. Chapter 4 in this book describes extensively the radioprotection issues related to radioiodine therapy. The three basic requirements that must be respected in daily medical practice involving the use of ionising radiation are justification, optimisation and adherence to the International Commission on Radiological Protection (ICRP) dose limits.

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2. Radionuclide Therapy in Benign Thyroid Disease

Doina Piciu

Introduction

Radioiodine (iodine131, 131I) was the first radiopharmaceutical to be used in humans for the treatment of benign conditions of the thyroid gland, the first procedure being performed during the 1940s.

A frequent indication for radioiodine therapy is hyperthyroidism, which is a consequence of excessive thyroid hormone action. Patients with large non-toxic goitre, including even those with a euthyroid status, may benefit from a reduction in thyroid volume after radioiodine therapy (shrinkage effect).

The further treatment options for hyperthyroidism include antithyroid drugs and surgery, and the choice of therapy depends upon the specific circumstances. Medical treatment (drugs) is frequently the first-line therapy, with the primary intention of stabilising symptoms and allowing for a proper assessment of definitive therapeutic strategies. During the next 3-6 months, according to disease evolution and the recurrence or otherwise of hyperthyroidism upon withholding of medication, surgery or radioiodine therapy may be proposed. There are, however, centres in the world, mainly in the United States, where radioiodine is started as first-line therapy. Surgery is usually reserved for large, compressive, unaesthetic goitres and for those patients with thyroid nodules in which there is a high index of suspicion of future malignant transformation.

In patients with hyperthyroidism, the aim of the ^{131}I treatment is to achieve a non-hyperthyroid status, which can be euthyroid or hypothyroid, the latter being subsequently treated by thyroid hormone substitutive medication, such as levothyroxine (LT_4).

Indications and contra-indications for ^{131}I therapy

Indications for ^{131}I therapy are:

- Graves' disease (autoimmune hyperthyroidism)
- Toxic multinodular goitre
- Solitary hyperfunctioning nodule
- Non-toxic multinodular goitre
- Goitre recurrence after surgery
- With special precautions, amiodarone-induced hyperthyroidism

Contra-indications for ^{131}I therapy may be absolute or relative. *Absolute contra-indications* are pregnancy and breastfeeding; the physician may, however, advise the radioiodine treatment after termination of pregnancy and cessation of breastfeeding if the patient's condition is life threatening. *Relative contra-indications* are uncontrolled hyperthyroidism and active thyroid orbitopathy (especially in smokers).

Clinical staff, including all those involved with patient care, should take appropriate steps to determine whether any contra-indications exist. When they do exist, the physician should be informed prior to the commencement of radionuclide therapy.

Facility requirements

In some countries the national regulations dictate that radionuclide treatments may be conducted only in in-patients while in others they may be permitted on an ambulatory out-patient basis. The clinical facility in which thyroid disease is to be treated with radionuclides must have appropriate authorisation. It must also have appropriate personnel, radiation safety equipment and clear, well-defined procedures for handling and disposal of waste. This facility may be an endocrinology department or a nuclear medicine department or any other specialised unit that respects the above requirements.

The involvement of technologists in radionuclide therapy procedures varies significantly, from no involvement to leading administration procedures. At the minimum they should have knowledge and skill in the correct use of the equipment and the radiation safety of the facility.

Patient preparation

- Written informed consent must be obtained from the patient before the procedure commences. Special recommendations and radioprotection information must also be discussed/given to patients before commencement.

- Depending upon national regulations, recommendations relating to conception may have to be provided. Generally, it is suggested that after ^{131}I therapy, contraception should be used for 4 months.

- In female patients of childbearing potential, a routine pregnancy test should be performed before the administration of ^{131}I.

- Antithyroid drugs must be stopped 5–7 days before radioiodine therapy.

- Beta-blockers, e.g. metoprolol, atenolol and propranolol (drugs used to manage heart problems) should be stopped 24 h before therapy.

- Propylthiouracil (a drug to reduce thyroid metabolism) should be stopped at least 2 weeks before therapy.

- In patients with Graves' ophthalmopathy, if the patient is already taking steroid therapy, oral prednisolone (a drug used to treat auto-immune and inflammatory conditions) is administered. It is not routine to start corticotherapy.

- In patients with thyrotoxicosis induced by amiodarone (an anti-arrhythmic drug) or in those receiving compounds that contain iodine (e.g. radiographic contrast agents), radioiodine can be administered as definitive therapy if the drug has been stopped sufficiently long for the excess iodine load to be eliminated – at least 3–6 months.

Assessment of disease

- Laboratory testing, including free thyroxine (FT_4), free triiodothyronine (FT_3), thyroid-stimulating hormone (TSH), anti-thyroid

peroxidase antibodies (anti-TPO) and anti-thyrotropin receptor antibodies (TRab).

- ^{99m}Tc thyroid scintigraphy or a radioactive iodine uptake test (RAIU, with scanning 24 h after intake of the radioactive iodine) can be undertaken according to availability. Uptake measurements are not usually required when fixed activities are used.

- Determination of the thyroid target volume can be done using ultrasonography, while evaluation of intrathoracic extension in those with a large goitre can be achieved using magnetic resonance imaging or computed tomography (without contrast agents).

- Fine-needle aspiration biopsy (FNAB) is performed when nodules meet criteria suggestive of malignancy.

- In patients with Graves' ophthalmopathy, the status of thyroid eye disease activity is established by an experienced ophthalmologist.

- For children between 5 and 15 years of age, radioiodine therapy may be considered. The side-effects should be clearly discussed by all staff involved in the treatment of a young patient with Graves' disease.

Radiopharmaceutical and administration

Radioiodine is available in solid (capsules) and liquid forms, both of which can be used for oral administrations.

The *fixed dose method* is usually based on an estimation of the size of the gland, which can be achieved by ultrasound. Frequently the recommended activity is 3.7-5.55 MBq/gram of thyroid, adjusted with the 24-h ^{131}I RAIU (radioiodine uptake). In patients with autonomous nodules, the activity currently prescribed varies between 200 and 800 MBq, with the intention of achieving an irradiation dose of 200-300 Gy at nodule level.

The *calculated dose method* might be used in the selection of a more accurate dose of radioiodine for treatment. There are multiple methods for dose calculation, but the simplest formula is as follows:

$$\text{MBq} = (V \times 25 \times \text{Gy}) \div [(\text{RAIU (24h)} \times T_{ef}]$$

where MBq = the calculated activity in MBq, V = the gland volume estimated at ultrasound in ml (cm^3), Gy = the estimated dose at thyroid level, RAIU (24h) = % of thyroid uptake at 24 h, T_{ef} = effective half-time, and 25 is a constant.

Those involved with performing or assisting with radionuclide therapy procedures must be able to use and calculate this and similar basic formulas.

Side-effects of ^{131}I therapy

Patients with a large goitre may notice transient swelling of the goitre and dyspnoea. In some patients a thyroid storm may develop. This rare condition must be treated with intravenous infusion of antithyroid drugs,

corticosteroids and beta-blockers. This situation is extremely rare and does not represent a reason for not recommending the therapy.

Hypothyroidism is the main side-effect of radioiodine treatment. Its rate varies and its incidence continues to increase over time, so that life-long follow-up is essential. According to published literature, the rate of hypothyroidism at 1 year after radioiodine therapy is very similar to the rate following the surgical approach.

Administration of prednisone (a drug used to treat allergic reactions) helps prevent exacerbation of ophthalmopathy, and this is now the standard approach in patients who have clinically active ophthalmopathy at the time of treatment.

The determination of periorbital inflammatory tissue by nuclear testing with ^{99m}Tc-DTPA may identify the cases that will benefit from steroid treatment.

Follow-up after radioiodine treatment

As mentioned above, regular review of thyroid function tests in patients who have undergone radioiodine treatment for thyroid disease is essential to assess the efficacy of the treatment and for timely detection of development of hypothyroidism. The level of serum TSH increases slowly, so determination of TSH is less useful for monitoring during the first 3-6 months, when determination of FT_4 should be used instead. In those with persistent hyperthyroidism, radioiodine treatment can be repeated after 6–12 months. Annual laboratory tests (including TSH) are necessary throughout life, even in patients with euthyroidism after ^{131}I therapy.

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Ruth Berhane Menghis, Brian A. Lowry, Christopher Mayes and Sobhan Vinjamuri

Definition and classification of neuroendocrine tumours

Neuroendocrine tumours (NETs) are a rare, slow growing and heterogeneous group of tumours that originate from the diffuse neuroendocrine system and the confined neuroendocrine system. The diffuse and confined neuroendocrine systems are represented by the pituitary, the parathyroid and the adrenal medulla, as well as the endocrine islets in the pancreatic tissue, and the disseminated endocrine cells in the digestive and respiratory tracts [1].

NETs are classified according to their embryological origin into tumours of the foregut (oesophagus, lungs, stomach, duodenum and pancreas), midgut (appendix, ileum, caecum and ascending colon) and hindgut (distal large bowel and rectum) [2]. This classification does not, however, take into consideration the biological differences of NETs. Optimal and revised current practice is to describe NETs according to their location of primary origin (e.g. duodenum and caecum) and to include information on biological activity which results in hormone secretion or symptomatic presentation (e.g. vipoma, gastrinoma and insulinoma).

The first WHO classification of NETs was published in 1980. In this classification the term "carcinoid" was used to describe most tumours. In order to standardise terminology, this classification was updated in 2000, in 2004 and in 2010. The 2010 updated classification is based on tumour histopathology (well differentiated/poorly differentiated), proliferative activity (G1, G2, G3) and TNM staging [3].

Pathology

At presentation the vast majority of tumours are either benign or relatively slow growing (well differentiated) or retain many multipotent differentiation features [4]. Such features include the possession of neuroamine uptake mechanisms and/or specific receptors at the cell membrane, such as somatostatin receptors (SSTRs), which can be used for the identification, localisation and therapy of NETs. However, NETs can also present with an aggressive behaviour and become highly malignant. The latter are described as poorly differentiated NETs.

SSTRs are G protein-coupled receptors with a widespread distribution in the human nervous system and different tissues in the body, including the pancreatic islets, stomach, lungs, kidneys and prostate. Five SSTR subtype genes have been cloned and characterised. They have been code named sst1, sst2, sst3, sst4 and sst5 [5].

Of particular interest is the fact that a large number of NETs express SSTRs and this forms the foundation for the functional imaging carried out in nuclear medicine. Of the five major subtypes of SSTR, SSTR2 and SSTR5 are the ones most commonly expressed in NETs; however, there is considerable varia-

tion in SSTR subtype expression among the different tumour types and among tumours of the same type [6].

It is also particularly important to evaluate the proliferation index of neoplastic cells by measuring the percentage of tumour cells with Ki-67 positivity. Ki-67 is an antigen expressed during the G_1 and M phases of the cell cycle. Determination of the Ki-67 plays an important role and allows selection of the most appropriate and effective treatment, reserving chemotherapy for NETs with a high proliferative index which are likely to respond better when treated with antiblastic drugs [7]. In contrast, NETs with a low Ki-67 respond less well to chemotherapy and are more responsive to treatment with somatostatin analogues, either cold somatostatin or possibly radiolabelled analogues (radiometabolic therapy) [8].

Presentation

Clinically, NETs can be symptomatic (i.e. "functioning") or silent (i.e. "non-functioning"). The functioning NETs can give rise to clinical syndromes, such as the one called "carcinoid syndrome", which is characterised by nausea, flushing and diarrhoea. Other clinical manifestations include wheezing or asthma-like symptoms as well as pellagra-like skin lesions. These symptoms arise due to specific production, storage and secretion of polypeptides, amines and hormones, like serotonin. Cardiac involvement can occur as a result of fibrosis involving the endocardium, primarily on the right side.

Non-functioning NETs are not associated with any specific syndrome and are more difficult to detect than functioning NETs; for this reason, patients generally present late, with large primary tumours and advanced disease. In the case of non-functioning NETs, there can be some degree of hormonal secretion, but the secretion may be at subclinical levels or there may be secretion of inactive compounds. Non-specific symptoms such as weight loss, abdominal bleeding and pain can be related to increased tumour mass producing mass effect symptoms and/or metastases [9].

Diagnosis

The diagnosis of NETs is best carried out by a multidisciplinary approach and is based on clinical symptoms, hormone levels, histological characterisation, and radiological and functional nuclear medicine imaging assessment.

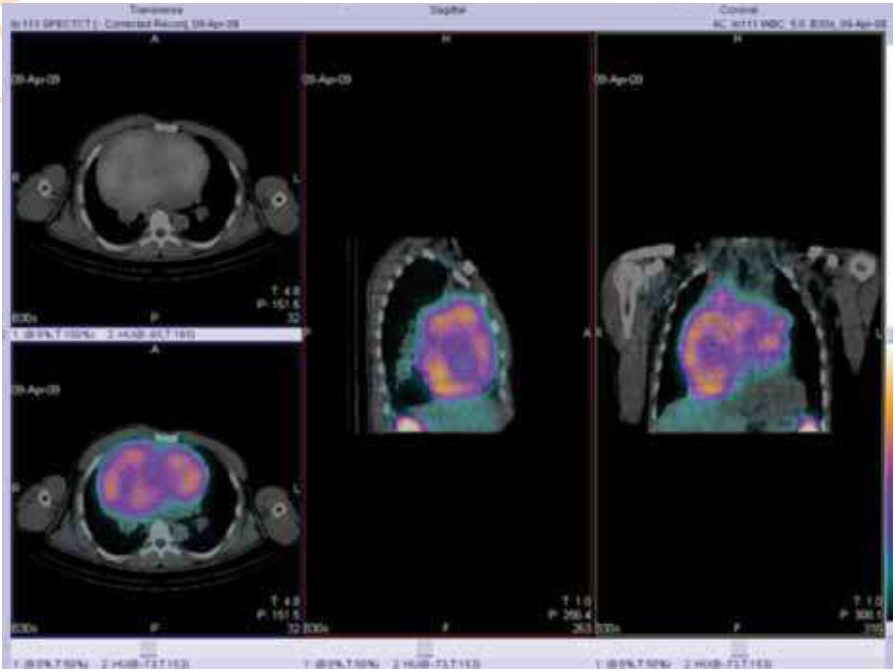
Nuclear imaging has played an important role in the diagnosis, staging and follow-up of NETs and, as mentioned above, has allowed appropriate and optimal functional assessment of NETs. Scintigraphic imaging with indium-111 (^{111}In)-labelled SST (Octreoscan®) has been a useful tool in diagnosing SSTR-positive tumours for decades (Fig. 1). A recent development which marked an important step forwards in the

diagnostic work-up of NETs is the introduction of novel somatostatin-based positron emission tomography (PET) tracers labelled with generator-produced radiometal gallium-68 (^{68}Ga).

Visualisation of NETs is obtained on ^{68}Ga-DOTA-peptide PET/CT scans as PET tracers such as ^{68}Ga-DOTA-peptides bind to the SSTRs overexpressed on the surface of NET cells. Several different DOTA-peptides (DOTATOC, DOTANOC and DOTATATE) have been used in the clinical setting for either diagnosis or therapy (Fig. 2). Basically the difference among these compounds is due to different peptides having different affinity for SSTR subtypes.

Many studies have found a high target/background ratio which results in better image contrast and a higher sensitivity for ^{68}Ga-DOTATOC PET/CT than for somatostatin receptor scintigraphy (SRS) [10, 11]. The study with the largest patient population (84 patients with NETs) reported DOTATOC to have a superior sensitivity (97%) compared with CT (61%) and SRS (52%) for the detection of NET lesions, with special value in the detection of small tumours and lesions localised in the nodes [12].

Moreover, further studies have been carried out to compare ^{68}Ga-DOTATOC with conventional imaging to assess the accuracy of PET for the detection of bone lesions. In 51 patients with well-differentiated NETs, PET with ^{68}Ga-DOTATOC performed better than CT or SRS for the early detection of secondary bone NET lesions (sensitivity of 97% and specificity of 92%) [13].



Images by courtesy of Prof. Sobhan Vinjamuri

Figure 1: Octreoscan® image obtained with ^{111}In in a patient with thymic carcinoid.

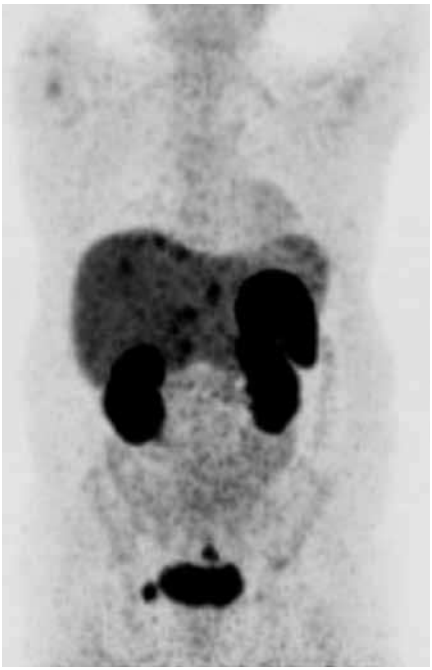


Image by courtesy of the Imperial College Hospital London

Figure 2: ^{68}Ga-DOTATATE scan in a patient with metastatic NET.

Therapy

Therapeutic management of NETs after thorough diagnostic work-up includes medical and surgical strategies. The therapeutic recommendations are mainly based on retrospective studies, and the optimisation of diverse management strategies is best achieved by multidisciplinary assessment and consensus-based therapy [14].

The optimal tumour therapy is curative treatment, and the primary treatment goal for patients with NETs is in fact complete resection of tumour. The main secondary goals are symptom control and limitation of tumour growth where possible. Surgery to remove the primary malignancy and adjacent involved lymph nodes is currently the only possible cure and it represents traditional first-line therapy. Curative surgery is, however, not an option for patients presenting with metastases at diagnosis, which are the majority.

When curative surgery is not feasible owing to metastases, patients are offered medical management to relieve symptoms, especially diarrhoea and flushing, and to a lesser extent to suppress tumour growth. An important class of drugs offered in this setting is the somatostatin analogues, which are endogenous inhibitors of various hormones secreted by the endocrine system. They exert their effect by binding with high affinity to the five SSTR subtypes (SSTR1–5) on secretory endocrine cells [15].

Radiolabelled somatostatin analogues are a fairly new treatment modality for patients with SSTR-positive tumours and with inoperable or metastasised endocrine gastro-entero-pancreatic tumours. Radiopharmaceuticals used for diagnostic purposes can be modified for therapeutic use by substituting a gamma-emitting radioisotope with a beta-emitting one. Thus, SSTR analogues used for diagnostic scintigraphy labelled using ^{111}In are replaced by the radiometal, yttrium-90 (^{90}Y) or lutetium-177 (^{177}Lu).

The rationale for the targeted therapy is the selective irradiation of tumoral cells by means of transportation of radioactivity inside the tumour cell, following internalisation of the complex formed by the SSTR and the beta-emitting particle. Suitable radionuclides are ^{90}Y, a pure, high-energy beta emitter (2.27 MeV), ^{177}Lu, a medium-energy beta emitter (0.5 MeV) with a low abundance, and ^{111}In [16].

^{111}In is a gamma-emitting isotope with a half-life of 2.8 days. The energy of this gamma-emitting isotope ranges from 171 to 245 keV, making it suitable for scintigraphic imaging.

^{177}Lu is a beta- and gamma-emitting isotope with a maximum energy of 0.49 MeV, a tissue penetration range of 2 mm and a half-life of 6.7 days. The gamma emission enables performance of imaging and dosimetry calculations at the same time. Its short tissue penetration range allows targeted therapies for small lesions and its longer half-life makes it suitable for cases where a longer "tumour residence time" is a clinical requisite.

^{90}Y is a pure beta-emitting isotope with high energy (2.3 MeV), a half-life of 2.67 days and a tissue penetration range of 11 mm. Its high therapeutic potential derives from the emission of high-energy beta particles causing damage to large tumours. The absence of gamma ray emission, however, makes imaging and dosimetric calculation with ^{90}Y difficult. The latter is an important factor for therapeutic planning.

Radionuclides for therapeutic purposes should emit beta particles because it is these particles which have greater therapeutic potential since have sufficient energy to cause cell damage and deliver higher radiation doses to a larger part of the tumour without penetrating very far into the surrounding tissue [17].

The first radiopharmaceutical used in *peptide receptor radionuclide therapy* (PRRT) was ^{111}In-DTPA-octreotide, already used in the medical setting as a diagnostic agent with activities ranging between 10 and 160 GBq [18, 19]. The therapeutic efficacy of ^{111}In-DTPA-octreotide was initially promising but several studies arrived at the conclusion that ^{111}In-coupled peptides are not ideal for PRRT because of the small particle range and therefore short tissue penetration and poor energy delivery to tumour cells.

Limitations of ^{111}In were overcome when researchers came up with a modified somatostatin analogue, [Tyr3]octreotide, with a higher affinity for SSTR2, and a different chelator, DOTA instead of DTPA (which was used in ^{111}In therapy), to ensure more stable binding of the intended beta-emitting radionuclide, ^{177}Lu or ^{90}Y.

Clinical applications, contra-indications and limitations of PRRT

Targeted radionuclide therapy offers several advantages compared with the conventional management options offered for NETs. Selective tumour localisation allows

treatment to be administered systemically while minimising potential toxicity to non-target, healthy tissues. The fact that potential toxicity to healthy tissue is spared means that targeted therapies are usually better tolerated than other, systemic treatments such as chemotherapy and deliver higher absorbed radiation doses to the tumour than can be achieved by external beam irradiation. This applies mostly to NETs, which are relatively radioresistant compared with other solid cancers. This kind of therapy relies on the administration of appropriately radiolabelled somatostatin analogues and is intended to control symptoms due to hormonal secretion. Indeed, symptomatic improvement may be achieved with all ^{90}Y- and ^{177}Lu-labelled somatostatin analogues that have been used for PRRT. However, several studies that have assessed objective responses have yielded encouraging results as well. Kwekkeboom et al. reported that despite differences in protocols, complete plus partial responses in different studies with ^{90}Y-octreotide have ranged from 10% to 30%. According to the same authors, the overall objective tumour response rate with ^{177}Lu-octreotate, comprising complete and partial responses, was almost 30% [20].

A prerequisite for PRRT is the demonstration that tumoral lesions have sufficient uptake when a diagnostic ^{111}In-octreotide or ^{68}Ga-labelled somatostatin analogue scan is carried out. Adequate uptake of the above-mentioned tracers is an essential indicator that therapeutic levels of internal radiation could potentially be delivered by administration of ^{177}Lu-octreotate or ^{90}Y radiopeptide therapy. The intensity of uptake is assessed visually and considered adequate if lesion uptake is of greater intensity than that of normal liver. Once adequate uptake has been confirmed, further suitability criteria include the confirmation of a histopathologically proven, relatively well differentiated NET with a Ki-67 score <10 [8].

The kidney is the major critical organ during therapy with ^{90}Y or ^{177}Lu. Once filtered by glomeruli, radiolabelled peptides are reabsorbed by proximal tubular cells and retained in the interstitium [21]. Another critical organ to be taken into consideration is the bone marrow.

In summary, the inclusion criteria for PRRT are:

- Adequate tumour uptake on octreotide scan or ^{68}Ga-DOTA-peptide PET/CT
- ECOG performance status of 2 or less
- Life expectancy of at least 6 months

Absolute contra-indications for PRRT are:

- Pregnancy and lactation

Relative contra-indications for PRRT are:

- Severe liver impairment
- Renal impairment
- Impaired haematological function
- Severe cardiac impairment

Pre-therapeutic evaluation

PRRT uses radiolabelled somatostatin analogues with high affinity for SSTR2, which is expressed by the majority of NETs. Currently the most frequently used radiopharmaceuticals for PRRT of NETs are ^{90}Y-DOTA-Tyr^3-octreotide (^{90}Y-DOTATOC), ^{90}Y-DOTA-Tyr^3-octreotate (^{90}Y-DOTATATE) and ^{177}Lu-DOTA-Tyr^3-octreotate (^{177}Lu-DOTATATE).

Adequate tumour uptake on ^{111}In-DTPA-octreotide (^{111}In-pentetreotide) scintigraphy (Octreoscan®) is an essential prerequisite when considering PRRT as a therapeutic option. Novel somatostatin-based PET imaging techniques such as ^{68}Ga-DOTATOC or ^{68}Ga-DOTATATE are also used to evaluate adequate tumour uptake before PRRT. In the pre-therapy imaging evaluation setting, false negatives may be due to the small size of lesions (knowledge of the spatial resolution of the imaging modality used is important) or poorly differentiated forms, which express fewer receptors.

Other imaging modalities that can be considered before radionuclide therapy administration are chest X-ray, CT or MRI of the lesion and echocardiography (the latter can be considered in patients in whom carcinoid heart disease is suspected).

Further pre-therapy evaluation for PRRT consists in reviewing the blood tests in order to exclude patients with important renal, hepatic and haematological impairment. Of vital importance is the determination of Ki-67 and correct histopathological evaluation of the tumoral lesion, as well as correct biochemical assessment, in order to better categorise the patient.

As mentioned above, radionuclide therapy is contraindicated in pregnant and lactating women and patients with less than 6 months' life expectancy. Patients with carcinoid heart disease should be monitored closely because these patients are at high risk of right-sided heart insufficiency.

Therapeutic procedure

Prior to therapy administration, each patient has to undergo a consultation with the nuclear medicine physician in order to obtain a thorough medical history, perform a physical examination, confirm appropriateness for treatment and acquire formal written informed consent.

Targeted therapy is administered intravenously in subsequent cycles (usually three or four) in order to reach an adequate cumulative activity to effectively irradiate the tumour. According to several dosimetric studies, to obtain the disappearance of tumoral lesions or, at least, a reduction in lesion size, an absorbed dose of at least 70-80 Gy must be provided. Such an absorbed dose can be delivered by giving the patient a cumulative activity of at least 20 GBq of ^{177}Lu-DOTATATE [22]. Based on a prospective phase I-II study, Bodei et al. reported cumulative activities of up to 29 GBq of ^{177}Lu-DOTATATE to be well tolerated. In this study, cumulative renal

absorbed doses ranged from 8 to 37 Gy with no major acute or delayed renal toxicity. A median decrease in creatinine clearance of 27.9% was recorded after 2 years, with higher reductions in patients with hypertension and diabetes [23].

An example of the precautions taken to reduce the renal absorbed dose is to give patients an intravenous infusion of positively charged amino acids, such as lysine and/or arginine, 30 min before administration of ^{177}Lu or ^{90}Y and in the 4 h following therapy. The amino acid infusion aims to optimally hydrate the patient and competitively inhibit the renal proximal tubular reabsorption of the radiopeptide [24]. This precaution has been shown to reduce the absorbed dose to the kidneys by between 9% and 53% [22].

As nausea and vomiting are some of the common side-effects of radionuclide therapy, an intravenous injection of an anti-emetic is also administered. The radiopeptide is then administered in a saline bag through slow intravenous infusion. As ascertained by phase I studies, the recommended dose per cycle of ^{177}Lu-DOTATATE is about 5.5-7.4 GBq, while the cumulative dose is around 22.2-29.6 GBq [25]. The subsequent doses can be fixed or escalated according to patient response and post-therapy image evaluation.

The unsealed source should be administered in designated facilities incorporating appropriate lead shielding, en suite washing facilities and radiation monitoring equipment.

The cycles are separated by at least 8-12 weeks, such intervals being necessary to ensure adequate recovery from any haematological or other toxicity.

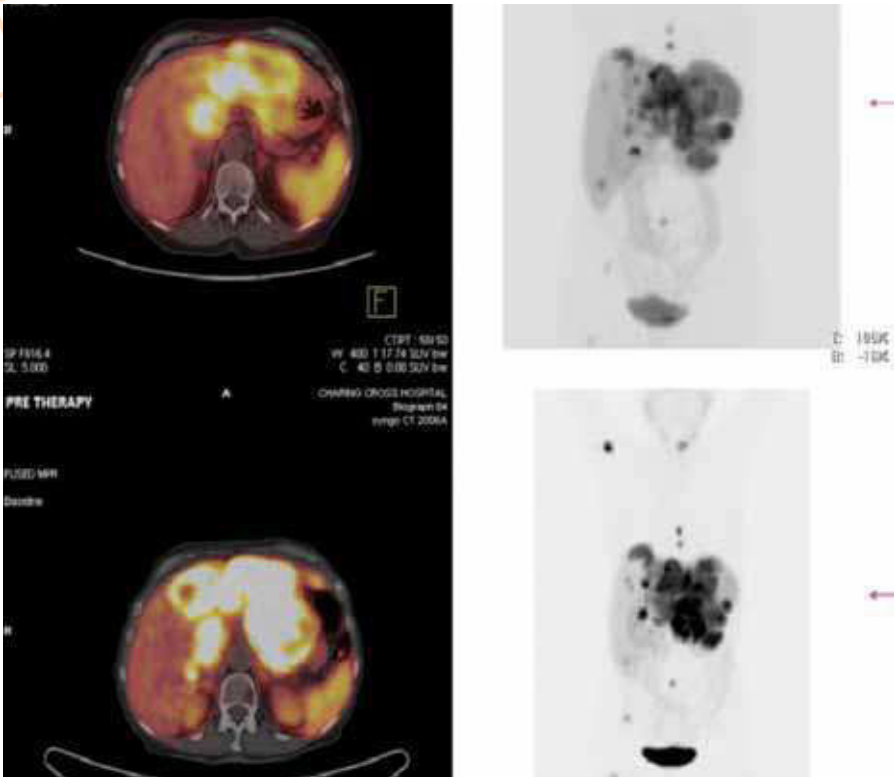
The side-effects of radionuclide therapy can be divided into acute side-effects and more delayed effects caused by radiation toxicity. The most common acute effects, occurring at the time of injection or up to a few days after therapy, include nausea, vomiting and increased pain at tumour sites [26]. These side-effects are generally mild, are minimised by a slow infusion and can be prevented or reduced by symptomatic treatment. Severe toxicity includes liver, kidney or haematological failure and may occur as a result of the radiation absorbed dose in healthy organs.

Post-therapy evaluation

Follow-up of patients who undergo targeted radiopeptide therapy consists in anatomical, functional, biochemical and clinical response evaluations.

The anatomical response is evaluated by means of radiological imaging (Fig. 3), most notably CT or MRI. The image response criteria used when applying CT are based on the RECIST criteria (Response Evaluation Criteria in Solid Tumors), according to which response can be subdivided into:

- CR (complete response)
- PR (partial response)
- PD (progressive disease)
- SD (stable disease)



Images by courtesy of Imperial College Hospital London

Figure 3: Pre- (bottom) and post-PRRT therapy (top) imaging in a patient with metastatic NET.

Functional imaging modalities with somatostatin analogues labelled with ^{111}In or ^{68}Ga play an important role in the follow-up of patients treated with radionuclide therapy. More comprehensive information may be gained by evaluating factors such as tumour uptake intensity, together with the image response on CT.

Clinical response evaluation is carried out in symptomatic patients. Any change in the frequency or intensity of the symptoms is recorded by the patient in a special diary and subsequently evaluated by a doctor.

In conclusion, treatment with ^{90}Y- or ^{177}Lu-labelled somatostatin analogues has been associated with considerable symptomatic improvement and, to a lesser extent, disease stabilisation with limited side-effects that are mainly related to reduction in kidney function [20].

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4. Radionuclide Therapy in Hepatocellular Carcinoma

Nadine Silva and Maria do Rosário Vieira

Epidemiology

Each year, the number of new cases of cancer and cancer-related deaths increases. It is estimated that there are 10.9 million new cancer diagnoses and 6.7 million cancer-related deaths around the world each year [1]. Liver cancer is the sixth most common cancer worldwide, with 749,000 new cases per year, and is the third leading cause of cancer-related deaths, with 695,245 cases annually [2]. Hepatocellular carcinoma (HCC) represents more than 90% of primary liver cancers [1].

The worldwide distribution of HCC is related to the prevalence of risk factors [3,4]. The highest incidence rates, approximately 85%, occur in East Asia and sub-Saharan Africa [1], and the dominant risk factor in these geographical areas is chronic hepatitis B virus (HBV) infection [3]. In the United States and France, the prevalence of HCC is related to cirrhosis due to alcohol abuse [3], while in Spain, Italy and Japan the primary risk factor for HCC appears to be hepatitis C virus (HCV) infection [3].

The incidence of HCC is increasing worldwide, and it is estimated that by 2020, the incidence in Europe will be 78,000 new cases annually [1].

Risk factors

The predominant risk factors are HBV infection, HCV infection, alcoholism and aflatoxin intake [1,3,4]. It is estimated that 54% of HCC cases are related to HBV infection, while 31% are related to HCV infection and almost 15% are due to other causes [1].

All the aforementioned risk factors can induce a process of chronic inflammation that is capable of causing hepatocyte necrosis and further regeneration, leading to collagen deposition and cirrhosis [4]. One-third of cirrhotic patients will develop HCC [1]. Patient survival is related to cirrhosis, as it is a progressive disease and influences the success of treatments [1].

Since the risk factors are recognised and HCC is typically initially "silent", often being diagnosed at an advanced stage, it is important to enter patients at higher risk of developing HCC into surveillance programmes in order to detect tumours early [1,4,5]. The overall 5-year survival rate for HCC is below 10%, and without treatment the 5-year survival rate is less than 5% [5,6].

Diagnosis

Nowadays, the goal is to diagnose tumours sized less than 2 cm with the purpose of applying potentially curative procedures [1,4].

Alpha-fetoprotein (AFP) is a serum glycoprotein that may be increased in HCC [4,7]. However, serum levels of AFP remain normal in about 30% of HCC patients [7] and some other tumours may be associated with elevated serum AFP. Despite this, increased AFP values can be helpful in identifying patients with a higher risk of HCC [4,7].

It is possible to detect HCC at an early stage with ultrasound (US), but also with dynamic imaging techniques such as four-phase computed tomography (CT) or dynamic contrast-enhanced magnetic resonance imaging (MRI) [1,4,8].

Liver biopsy is not necessary if clinical, laboratory and radiography are positive for HCC [7] but is recommended for tumours occurring in non-cirrhotic livers [1].

Therapeutic approach

The therapeutic approach to HCC will depend on the tumour size, the extent of liver disease and the presence of metastases [9]. Staging the disease is the first step in achieving an appropriate therapeutic approach. There are several potential curative therapies, such as surgical resection, liver transplantation and percutaneous ablation [4,5].

Surgical resection is the first-line treatment option for patients with well-defined and solitary liver tumours, as well as good liver function [4]. Selected candidates may have a positive outcome with resection, with a 5-year survival rate of 30-50% [1]. Unfortunately, this is an option for only 10-20% of HCC patients, and recurrence after resection is a possibility [1,3,9]. In cases of recurrence, patients need to be re-staged and treatment based upon the results of that re-staging [1].

Liver transplantation offers less risk of recurrence, with the same chance of survival. On the other hand, the waiting list is often several months and this may lead to tumour progression, resulting in exclusion from the transplantation list [4].

For both of the aforementioned approaches there are some neo-adjuvant therapies which may be helpful by delaying disease progression, such as transarterial chemoembolisation (TACE) and transcatheter embolisation (TAE) [1,4].

Local ablation by percutaneous ethanol injection or radiofrequency achieves good responses in patients with tumours less than 2 cm, with a 90% complete response rate [1].

Although there are options which provide a high complete response rate for HCC at early stages, there is a lack of effective options for unresectable HCC associated with liver disease [3]. For most such patients, treatment options are palliative [9].

HCC has a poor response to systemic chemotherapy [3,6,9]. TACE and TAE are the most commonly used options for patients with intermediate stage HCC [1,4]. Although these procedures can achieve partial responses in 15-55% of patients, both are often associated with mild to moderate adverse events, such as abdominal pain, fever, nausea and vomiting [1,3].

Some patients with advanced stage HCC may benefit from therapy with sorafenib, which is the only systemic approach with demonstrated value in the management of HCC [1].

External beam radiation therapy has a limited role in the treatment of HCC as for patients with normal liver function the maximum tolerated dose is 30-35 Gy, which is below the required dose for tumoricidal effect [3].

Radionuclide therapy is an approach which aims to deliver radioactive substances, such as iodine-131 (^{131}I)-Lipiodol or yttrium-90 (^{90}Y) microspheres, by the use of intra-arterial percutaneous techniques [1,10]. Radioembolisation techniques are based on tumour hypervascularisation, as most unresectable liver tumours receive their blood supply almost totally from the hepatic artery, whilst the normal liver parenchyma receives its blood supply mainly through the portal vein [1,10,11]. This differential flow between tumour and normal tissue allows the administration of high-energy and low-penetration radionuclides in order to obtain highly selective tumour uptake while delivering tolerable doses to the normal liver tissue [1,10-12].

Radioembolisation with ^{90}Y-microspheres

Some positive outcomes from cohort studies [1] indicate that radioembolisation with ^{90}Y-microspheres is an option for patients with an intermediate or advanced tumour stage. Patients with intermediate and advanced stage disease showed median survival times of 17.2 and 12 months, respectively [1].

This therapeutic approach is a reported option not only for HCC patients, but also for patients with secondary hepatic tumours from colorectal cancer, pancreatic cancer and neuroendocrine tumours, due to the unique inflow characteristics of these tumours [13-15]. This local liver-directed therapy may reduce tumour burden, provide palliation and increase survival, while having a low toxicity profile [3].

Physical characteristics of ^{90}Y

^{90}Y is a beta particle emitter which has no gamma photon emission (Table 1) but does have secondary bremsstrahlung radiation emission [10,16]. This secondary emission does not imply burdensome radiation safety precautions because it does not exceed 1 mSv for twhe general public [12].

Emission	Pure beta emission (β-)
Mean energy (MeV)	0.9367
Decay product	Zirconium-90 (stable)
Physical half-life (h)	64.2
Average penetration range (mm)	2.27
Maximum penetration range (mm)	11.3
Production	Nuclear reactor ^{89}Y(n,p)^{90}Y

Table 1: Biophysical characteristics of ^{90}Y [10-12,17]

Radiolabelled microspheres

Currently, two types of ^{90}Y-microsphere are available: resin microspheres (SIR-Spheres; Sirtex Medical, Lane Cove, Australia) and glass microspheres (TheraSphere; MDS Nordion, Kanata, Ontario, Canada) [10,12]. These

two types of microsphere have different production methods, but also different characteristics, as shown in Table 2.

Characteristics	Glass microspheres	Resin ricrospheres
No. of spheres per dose (range)	3-8x10^6	30-60x10^6
Specific activity per sphere (Bq)	2500	50
Activity available (GBq)	3, 5, 7, 10, 15, 20	3
Size (µm)	20-30	20-60
Splitting one vial for two or more patients	Not possible	Possible
Solution used for suspension of the spheres	Saline (0.9%)	Sterile water
Associated impurities	^{88}Y, ^{152}Eu, ^{154}Eu, ^{57}Co, ^{60}Co	^{88}Y

Table 2: Summary of general characteristics of glass and resin microspheres (adapted from Giammarile et al. [10], Murthy et al. [17] and Vente et al. [18])

Glass microspheres are obtained by neutron bombardment of the glass matrix of the spheres, in which ^{89}Y is embedded; in this way, ^{89}Y is converted to radioactive ^{90}Y and the radioisotope cannot be leached from the glass [11,12]. This procedure may enhance the production of detectable amounts of impurities, such as ^{88}Y, ^{152}Eu, ^{154}Eu, ^{57}Co and ^{60}Co, but dose calculations have shown that these impurities do not exceed the medical event limits [12].

Resin microspheres are produced by the chemical incorporation of ^{90}Y in the carboxylic group after the production of the microspheres [10]. Trace amounts (up to 0.4% of the administered dose) of ^{90}Y may be present and excreted by urine during the first 24 h. Resin microspheres have been shown to have detectable amounts of ^{88}Y [12].

Both types of microsphere are biocompatible, non-biodegradable devices and are not excreted or metabolised. These devices decay to infinity, delivering 94% of their radiation in 11 days [17].

Radiation safety considerations

Patients treated with ^{90}Y-microspheres will have the activity confined to the liver, though some may have shunting activity in the lungs or the gastrointestinal tract. As ^{90}Y is a pure beta emitter, the only considered dose to an individual likely to be in contact with the patient is the bremsstrahlung radiation [12].

Patient instructions are only required if the dose to other individuals is likely to exceed 1 mSv [12]. For health care workers, no burdensome radiation safety precautions need be taken: the shielding of this radiopharmaceutical is achieved by the use of plastic and acrylic materials and lead should be avoided due to the bremsstrahlung radiation production that may arise [12].

As some free ^{90}Y may be excreted by urine during the first 24 h after administration (particularly with the resin microspheres), instructions may be issued with a view to ensuring careful bathroom hygiene [10,12].

Contra-indications and eligibility criteria

Pregnancy and breastfeeding are two absolute contra-indications to this therapy, as with almost all nuclear medicine-related procedures. Another important absolute contra-indication, for radioprotection reasons, is a life expectancy of less than 1 month [10].

There are relative contra-indications that should be analysed specifically for each patient. Lab tests are required, generally to assess liver function, renal function, pulmonary disease and contra-indications to hepatic artery catheterisation [9,10]. It is also important to determine the extension of the disease as disseminated extrahepatic malignant disease and extensive intrahepatic disease are relative contra-indications [10].

For each type of microsphere there are specific contra-indications, which are reported in Table 3.

SIR-Spheres®	TheraSphere®
Abnormal excretory liver function tests	Severe hepatic dysfunction
Ascites	Tumour volume ≥70% of the target liver volume or multiple tumour nodules ("bulky disease")
Abnormal hepatic vascular anatomy (if it would induce radiopharmaceutical reflux to other organs)	Abnormal hepatic vascular anatomy (if it would induce radiopharmaceutical reflux to other organs)
Lung shunt fraction ≥20% (determined by ^{99m}Tc-MAA scintigraphy)	Lung shunt fraction which results in delivery of ≥610 MBq
Extrahepatic malignant disease	Infiltrative tumour type
Portal vein thrombosis	

Table 3: Specific contra-indications to each type of microsphere (adapted from Giammarile et al. [10])

Dosimetry and administered dose

In order to calculate the necessary activity to deliver the required dose to the tumour, either dosimetric or empirical methods may be used. For SIR-Spheres®, empirical models are proposed that are based on the estimated tumour involvement of the liver [10,16]. This method implies that the greater the tumour burden, the higher the dose to the tumour, as reported in Table 4 [10,16].

Tumour involvement (%)	Recommended activity (GBq)
<25%	2.0
25-50%	2.5
>50%	3.0

Table 4: Recommended activity for SIR-Spheres®, accordingly to tumour involvement [10,16]

Another empirical model suggested for SIR-Spheres® relates to the body surface area (BSA), using Eq. 1 to calculate the activity to be delivered to the patient [10]:

$$A(GBq) = (BSA - 0.2) + \frac{tumor\ volume}{total\ liver\ volume} \quad (1)$$

The dosimetric models, which consider the lung shunt fraction (LSF), are usually used for TheraSphere® [10,16]. The delivered dose for TheraSphere® is between 80 and 150 Gy [16]. With glass microspheres the activity required to deliver the prescribed dose is calculated using Eq. 2 [16]:

$$A(GBq) = \frac{[Dose(Gy)]\ [Liver\ mass(kg)]}{49.8} \quad (2)$$

Whichever type of microsphere is used, the vendors recommend adjustments in order to reduce the fraction of activity shunting to the lungs (the LSF). For TheraSphere, the dose to the lungs should be less than 30 Gy [10,16]. For SIR-Spheres®, the adjustments are shown in Table 5 [10].

LSF	Reduction in the administered activity (%)
<10%	No reduction
10-15%	20%
15-20%	40%
>20%	The technique is contra-indicated

Table 5: Adjustment in the administered activity according to LSF, for SIR-Spheres® [10]

In order to detect and quantify LSF, technetium-99m (^{99m}Tc)-labelled albumin macroaggregate (MAA) scintigraphy is performed [10]. The LSF is determined using Eq. 3 [10]:

$$Lung\ Shant\ fraction = \frac{lung\ counts}{lung + liver\ counts} \quad (3)$$

Procedure

As mentioned previously, a pre-therapy evaluation must be performed in order to assess patient eligibility for this specific treatment. This evaluation consists in a complete history and physical examination, chest radiography and assessment of pulmonary function, liver sonography or CT, evaluation of serum liver enzymes, complete blood count, coagulation testing, determination of creatinine levels and assessment of tumour markers [9-11].

Positron emission tomography (PET)/CT with fluorine-18 (^{18}F) fluorodeoxyglucose (FDG) can be performed to exclude extrahepatic disease and also to evaluate the extension of hepatic disease. Usually, HCCs have very low-grade FDG uptake, or even no uptake,

unless the tumour is of an aggressive type; nevertheless, ^{18}F-FDG uptake has prognostic value and is used to check the therapeutic outcome [10,19].

A CT scan allows accurate calculation of the liver volume, which is essential for dose calculation [10,11].

Angiography by high-speed multi-slice CT is usually performed 4-6 weeks before the therapy with ^{90}Y-microspheres [11]. Angiography visualises the hepatic arterial anatomy and the haemodynamics of the hepatic circulation [11]. Anatomical variations are assessed, as is the presence or absence of portal venous thrombosis [10]. Angiography also permits the placement of coils in order to occlude aberrant hepatic arteries and embolise collateral vessels, to ensure that the microspheres remain confined to the liver [11]. Coil embolisation of the gastroduodenal artery may be of use in preventing shunting activity to the gastrointestinal tract [10].

During angiography, a catheter is placed in the hepatic artery or in any branch of the hepatic artery (depending on the hepatic arterial anatomy or on selective treatment options) [10,11]. This procedure allows intra-arterial administration of ^{99m}Tc-MAA, which have a comparable size to ^{90}Y-microspheres. Thus, scintigraphic acquisition is performed as soon as possible after the administration of 75-150 MBq of ^{99m}Tc-MAA. Planar views (anterior and lateral) of the upper abdomen, anterior chest image and hepatic SPECT are acquired [9-11]. Visual evaluation of lung and gastrointestinal shunt and lung shunt quantification are performed, which may lead to dose adjustment. Assessment of the tumour uptake within the liver is also performed [10]. It is important to note that imaging with ^{99m}Tc-MAA may entail visualisation of the thyroid, stomach and urinary bladder because of free pertechnetate [10].

After LSF assessment and evaluation of the presence or absence of gastrointestinal shunt and of whether patients are sufficiently well to undergo the therapy, dose calculation proceeds [10]. ^{90}Y-microsphere administration is carried out in the interventional radiology department as it involves intra-arterial catheter manipulation. Administration is performed by a nuclear medicine physician using the vendor's device and with gentle infusion in order to prevent backflow of the radiopharmaceutical [10].

A few hours after administration, in order to locate the administered activity, bremsstrahlung planar images (anterior and right lateral) may be acquired using a gamma camera with an energy peak of 100 keV and a wide-energy window in order to increase sensitivity [20]. Alternatively, 30-min PET images may be acquired, which have the advantage of better spatial resolution [10]. These images are essential to assess the administered activity, as this may be unexpectedly located outside the liver despite the findings on ^{99m}Tc-MAA scintigraphy and the previous liver embolisation [20]. They are also important in

localising the activity in order to prevent and manage side-effects if there is extrahepatic activity [20].

Side-effects and follow-up

The overall incidence of complications and side-effects after the therapy is low [17]. Even though prophylactic hepatic embolisation is performed in order to prevent shunting and to guarantee maximum tumour uptake, some side-effects may be experienced by patients because inadvertent deposition of ^{90}Y-microspheres is a possibility despite angiographic occlusion techniques [9]. Commonly, patients experience fatigue, nausea, abdominal pain, fever and transitory elevation of the transaminases [10]. Some other possible side-effects occur at lower rates (2-8%), such as chronic abdominal pain, radiation gastritis, gastrointestinal ulceration, upper gastrointestinal ulceration, haemorrhage, pancreatitis, radiation pneumonitis and radiation-induced liver disease [9,10]. In addition to careful assessment of extrahepatic shunting, appropriate selection of patients is essential to minimise side-effects [9,17].

Post-therapeutic follow-up is performed in order to detect any possible side-effects but also to evaluate tumour response. It is conducted 30 days after the therapy and at 2- to 3-month intervals thereafter [10].

^{131}I-Lipiodol therapy

Treatment with intra-arterial injection of ^{131}I-Lipiodol was developed in the 1990s and has yielded valuable clinical results and demonstrated good tolerance by patients [21]. Compared with ^{90}Y-microspheres, ^{131}I-Lipiodol is approximately 10 times less expensive [19].

^{131}I-Lipiodol is an option in patients with portal vein thrombosis and those who have already been surgically treated. ^{131}I-Lipiodol is also under study for application in patients with liver metastases and as a neoadjuvant therapeutic before resection and liver transplantation [10].

Physical characteristics of ^{131}I

^{131}I is a beta emitter but it is also characterised by high gamma ray emission (Table 6). This allows image acquisition but constrains the administered activity owing to radiation exposure [10,21].

Emission	**Beta, gamma**
Mean energy (MeV)	β (0.61, 89% abundance), γ (0.36, 81% abundance)
Decay product	Xenon-131 (stable)
Physical half-life (days)	8.04
Average penetration range (mm)	β: 0.9 mm
Maximum penetration range (mm)	β: 2.4 mm
Production	Nuclear reactor

Table 6: Biophysical characteristics of ^{131}I [10,19,21]

131I-Lipiodol

This radiopharmaceutical is available in a commercial form as Lipiocis (IBA, Brussels, Belgium) [10]. Lipiodol is an oil compound with 38-40% iodine fatty acid ethyl esters of poppy seed oil [10,19]. This compound contains stable iodine-127 (^{127}I), and by a simple isotopic change it is substituted by ^{131}I [10,19].

After intra-arterial injection, ^{131}I-Lipiodol migrates towards the tumour region. There may be some unspecific uptake in non-malignant endothelial cells, but this compound is highly selective for malignant cells [10,19]. It is estimated that 24 h after the administration, more than 75% of Lipiodol is trapped in the liver, though the remainder reaches the lungs [10,19,22]. The tumour/non-tumour uptake ratio is about 15-20:1 and it tends to increase with time, possibly because of the lack of macrophagic cells in the tumour, leading to slow Lipiodol clearance from the tumour [19].

Other tissues show very little uptake of this compound, this being true even of the thyroid gland [22].

Radiation safety considerations

Because of the gamma emission of ^{131}I, hospitalisation is required in order to safeguard individuals likely to come into contact with the patient [22]. This hospitalisation can be from 4 days to a week, in a shielded room [22,23]. Discharge will depend on the measured remaining activity, and this limit is usually less than 1 mSv to other individuals.

It is important to note that ^{131}I-Lipiodol is eliminated mainly via the urinary tract (30-50% of the administered activity at day 8) [19]. A small amount of the activity is eliminated in faeces (<3% at day 5) [19]. In this respect, it is important to verbally instruct the patient on effective bathroom hygiene to prevent contamination.

Thyroid gland blockage with stable iodine or potassium perchlorate is usually not recommended [10].

The health facility in which the procedure is performed must be fully equipped in order to guarantee radiation safety for both staff and patients (i.e. shielding rooms, adequate protection during transportation of the patient within the institution, implementation of appropriate contamination procedures and suitably trained staff) [10].

Contra-indications and eligibility criteria

Pregnancy and breast-feeding are again two absolute contra-indications to this therapy. Another important absolute contra-indication, for radioprotection reasons, is a life expectancy of less than 1 month [10].

There are relative contra-indications that should be analysed individually for each patient. Lab tests are required, generally to access liver function, renal function, pulmonary disease and contra-indications to hepatic artery catheterisation [10]. It is also important to determine the extension of the disease, as disseminated extrahepatic malignant

disease and extensive intrahepatic disease are relative contra-indications [10].

Appropriate patient selection with respect to hepatic reserve and overall functional status will maximise the therapeutic outcome and minimise the risk to normal hepatic parenchyma [10].

Administered dose

The administered activity of ^{131}I-Lipiodol is 2.22 GBq, which corresponds to a hepatic dose of approximately 50 Gy [10]. Although this is a fixed activity, it is possible to adjust it according to tumour load if necessary [10].

Radiopharmaceutical preparation must be performed in an adequately ventilated cabinet in the Nuclear Medicine Department in order to prevent iodine aerosol inhalation [19].

As this compound is a viscous oil, it might offer some resistance to syringe dispensing and catheter injection [10].

Procedure

As previously mentioned, a pre-therapy evaluation must be performed in order to assess the patient's eligibility for this specific treatment. This evaluation consists in a complete history and physical examination, pulmonary function assessment, three-phase contrast CT, gadolinium-enhanced MRI, assessment of extent of extrahepatic disease, evaluation of serum liver enzymes, complete blood count, coagulation testing, determination of creatinine levels and assessment of tumour markers [10,19].

As previously mentioned, PET/CT with ^{18}F-FDG may be of use, especially in order to evaluate extrahepatic disease [10,19].

Angiography is performed to assess the hepatic vascular anatomy and to place an intra-arterial catheter. Due to anatomical variations the catheter may be placed in other, distally located hepatic branches [10,19,23].

The activity is administered slowly in the catheter to prevent reflux and consequent retrograde flow into the gastroduodenal artery [10,23]. This procedure is done under fluoroscopic control [10,23]. After the administration, the patient is taken to the shielded room [19,22,23].

Whole-body scintigraphic images are acquired one week after the administration of ^{131}I-Lipiodol. A CT scan may be performed based on the high iodine content of the radiopharmaceutical as this dispenses supplementary contrast administration [10,23].

Some patients may benefit from one or several treatments [19] that can be performed 2, 5, 8 and 12 months after the first injection [10].

Side-effects and follow-up

Serious adverse effects are rare [19,22]. Early side-effects, which occur rarely, may be moderate and temporary pyrexia (29%),

moderate and temporary alteration on biological liver test (20%) and hepatic pain on injection (12.5%) [10,19,22]. The delayed side effects, which occur more rarely, are moderate and reversible leucopenia (7%) and interstitial pneumopathies (2%) [19].

Follow-up should be performed using the same modalities as have been employed to assess the disease (three-phase CT, MRI, PET/CT, lab tests) and this should be done 1 month after therapy and then at 2- to 3-month intervals [10,19].

References Section II, Chapter 4

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5. Radioimmunotherapy in Lymphomas

Aurore Rauscher, Caroline Bodet-Milin, Amandine Pallardy, Alain Faivre-Chauvet, Françoise Kraeber-Bodéré

EANM

Introduction

Radioimmunotherapy (RIT) is a targeted therapy whereby irradiation from radionuclides is delivered to tumour targets using monoclonal antibodies (MAbs) directed against a tumour antigen. Over the last 20 years, RIT has progressed significantly, with the development of new humanised mAbs, stable chelates for labelling and pretargeting techniques [1]. The cytotoxic mechanisms of RIT involve both radiobiological and immunological processes. B-cell non-Hodgkin lymphoma (NHL) cells express well-characterised antigens, are highly radiosensitive, respond to cold mAbs and represent a relevant indication for RIT. NHLs can be classified into more than 25 histological subtypes according to the World Health Organisation (WHO) classification, and can be separated into aggressive (65% of NHLs) and indolent forms (35%) [2]. Diffuse large B-cell NHL (DLBCL) is the most common type of aggressive NHL (31%), and follicular lymphoma (FL) is the most common type of indolent NLH (22%). FL generally shows indolent progression with response to chemotherapy, but always relapses. Survival ranges from 5 to 15 years. The prognosis of DLBCL is different, with 50-60% of patients being cured. Treatment of disseminated NHL includes multi-agent chemotherapy, with the possibility of high-dose chemotherapy coupled with stem cell transplantation in high-risk young people (<60-65 years). The introduction of rituximab (MabThera, Rituxan, Roche Ltd., Genentech, Basel, Switzerland), a monoclonal chimeric anti-CD20 antibody, resulted in an improvement in outcome in patients with aggressive or indolent B-NHL when it was combined with different chemotherapy regimens (R-chemotherapy), as compared with use of chemotherapy alone [3]. Involved-field radiation can be proposed for limited stage FL or treatment of residual masses of DLBCL. Today, one product targeting the CD20 antigen has been approved in Europe for RIT: ^{90}Y-ibritumomab tiuxetan, (Zevalin, Spectrum Pharmaceuticals, Henderson, NV, USA). Another product targeting CD20 is available in the United States: ^{131}I-tositumomab, (Bexxar, GlaxoSmithKline). RIT can be integrated into clinical practice using non-ablative doses for treatment of FL patients. Different RIT protocols are being assessed in clinical trials in FL or other lymphoma subtypes: myeloablative or high-dose treatment, RIT as consolidation after chemotherapy, RIT in first-line treatment, fractionated RIT and other MAbs especially targeting antigens other than CD20.

Clinical application and contra-indications/ limitations to RIT

Clinical application

RIT can be integrated into clinical practice using non-ablative activities for the treatment of patients with relapsed or refractory FL or as consolidation after induction chemotherapy in the front-line treatment of FL patients.

Contra-indications

Exclusion criteria for treatment with Zevalin® are:

- Pregnancy and continuing breast-feeding
- Known hypersensitivity to ^{90}Y-ibritumomab tiuxetan, yttrium chloride, other murine proteins or any of their components
- Children and adolescents under 18 years of age
- Marked bone marrow suppression (<1.5 x 10^9/L leucocytes; < 100 x 10^9/L thrombocytes)
- Greater than 25% of bone marrow infiltration by lymphoma
- Previous external beam radiation involving >25% of the active bone marrow
- Prior bone marrow or stem cell transplantation
- Detectable human anti-murine antibody (HAMA), depending on titre

The peripheral blood cell count should not be lower than the limits stated above. While lower blood counts do not constitute an absolute contraindication, they do increase the risk of severe and prolonged bone marrow suppression.

Therapeutic procedure

Radiopharmaceutical

Approved name: ^{90}Y- ibritumomab tiuxetan or Zevalin®

Yttrium-90 is a beta-emitter, with a physical half-life of 64 h, a maximum particle energy of 2.27 MeV and a maximum range of 11 mm in soft tissue.

Preparation procedure

Zevalin® is supplied as a kit for the preparation of ^{90}Y-radiolabelled ibritumomab tiuxetan. The kit contains one antibody vial with 3.2 mg ibritumomab tiuxetan (1.6 mg/mL), one 2-mL sodium acetate vial, one 10-mL formulation buffer vial and a 10-mL empty reaction vial. The kit must be stored at 2-8°C and should not be frozen. The radioactive component, ^{90}Y, must be obtained separately upon order from the manufacturer. Only carrier-free ^{90}Y of pharmaceutical grade quality must be used for antibody labelling, since metal contamination has a detrimental effect on the labelling efficiency.

Labelling must be performed only by qualified staff (radiopharmacist, chemist or technician with qualification in radiopharmacy) with appropriate authorisation for the use and manipulation of radionuclides. Appropriate facilities for shielding, calibration and quality control should be in place. Proper aseptic technique and precautions for handling radioactive materials must be employed during the preparation procedure. Vial rubber stoppers must be cleaned with a suitable alcohol swab and sterile syringes must be used. Waterproof gloves, protective shields for syringes and containers, forceps and tongs as gripping tools must be used for the preparation. Owing to the 9.2 mm

length of ^{90}Y beta emission [4], at least 1-cm-thick Perspex or lead-loaded Perspex shields should be used during labelling.

The first step consists in the addition to the reaction vial of a 1.2-fold excess of sodium acetate solution compared with the yttrium volume. The second step involves aseptically transferring 1,500 MBq of ^{90}Y to the reaction vial and mixing the solution by inversion (or 'rolling' the vial). Then 1.3 mL ibritumomab tiuxetan solution, previously brought to room temperature, is transferred to the reaction vial, and after mixing the reaction solution is left at room temperature for 5 min. A labelling time longer than 6 min or shorter than 4 min or foam formation during the mixing will result in inadequate radiolabelling. In order to chelate free ^{90}Y and inhibit radiolysis of the radiolabelled antibody, an appropriate volume of formulation buffer that contains human serum albumin and DTPA is added to the reaction vial; this results in a combined total volume of 10 mL.

The final formulation after radiolabelling contains 2.08 mg ibritumomab tiuxetan in a total volume of 10 mL. After radiolabelling, immediate use is recommended, but the solution may be stored at 2°-8°C (in a refrigerator). At these temperatures and protected from light, it can be used up to a maximum of 8 h.

Quality control

The radiochemical purity of the prepared ^{90}Y-radiolabelled Zevalin must be checked before administration. Instant thin-layer chromatography (ITLC) is recommended for this purpose with sodium chloride solution (0.9%) as mobile phase. DTPA-^{90}Y is carried by the solvent and has a chromatographic ratio (Rf) of 1, and radiolabelled antibody remains at the deposit with an Rf of 0. The radiochromatogram may be analysed in different ways: by cutting the ITLC into two parts and counting each part in an appropriate counter, by using a radiochromatograph or by using a phosphorimager. Radiochemical purity is calculated as follows:

% RCP = net count bottom half / total count x 100

Common sources of error in quality control are drop size and dead-time error during measurement of the ITLC strips. If the average radiochemical purity is less than 95%, the preparation must not be administered.

Method of administration

Before Zevalin® infusion, the activity in the 10-mL syringe must be measured using a calibrated ionisation chamber under the appropriate geometric-, volume- and material-specific (plastic needles, glass vials) conditions of calibration.

The prepared solution must be given as a slow intravenous infusion over a minimum of 10 min. The infusion must not be administered as an intravenous bolus. Zevalin® may be infused directly by stopping the flow from an infusion bag and administering it directly into the line. A 0.2- or 0.22-µm low-protein-binding filter must be on line between the

patient and the infusion port. The line must be flushed with at least 10 mL of sodium chloride 9 mg/mL (0.9%) solution after the infusion of Zevalin®.

Administration schemes

Zevalin® is administered 6-8 days after a predose of 2 x 250 mg of rituximab, to improve biodistribution and tumour targeting. The whole therapy requires only two outpatient visits. No dosimetry study is required. When a dosimetry study is performed for research purposes, the first dose of cold MAb is injected with 185 MBq of ^{111}In-ibritumomab tiuxetan. The injected activity depends on body weight and platelet count. The therapeutic dose is 14.8 MBq/kg (11.1 MBq/kg in patients with a platelet count of 100,000 to 149,000/mm^3) to a maximum total activity of 1,184 MBq [5].

Pre-therapeutic evaluation

Evaluation prior to RIT should be carried out as proposed in the EANM guideline (6) and should include:

- A clinical examination.
- Careful recording of the patient's history, including information on previous therapies, in particular external beam radiation therapy involving active bone marrow and stem cell transplantation.
- A representative (>2 cm long cylinder) bone marrow biopsy from the iliac crest: The biopsy must have been performed no earlier than the last point in time at which disease progression was detected or in any case a maximum of 3 months before the scheduled RIT.
- Exclusion of pregnancy and confirmation of cessation of breast feeding.
- Recording of current medications, especially those affecting haematological function.
- Determination of blood profile, prothrombin time (INR) and serum creatinine and bilirubin levels within 1 week prior to RIT: RIT should not be performed if these values are above 2.5 times the upper normal limits for the local laboratory.
- Estimation of life expectancy (life expectancy >3 months, Karnofsky index >70%): Patients with a life expectancy of less than 3-4 weeks or rapid disease progression are unlikely to benefit from RIT.

Post-therapeutic assessment

Safety

Haematological toxicity is the major side-effect of RIT, and depends on bone marrow involvement and prior treatment [6, 7]. After a dose of 14.8 MBq/kg of Zevalin®, a reduction of 30-70% in leucocyte and platelet counts from baseline levels is possible, sometimes occurring very rapidly. Grade 4 neutropenia, thrombocytopenia and anaemia have been reported in 30%, 10% and 3% of patients, respectively, with the nadir in counts occurring 7-9 weeks after Zevalin® injection, i.e. later than after chemotherapy. Median time to complete recovery of blood count (haemoglobin >12 g/dL, platelets >150,000/μL and leucocytes >4,300/μL) is 99 days for FL patients [8]. After RIT, weekly blood tests from the second post-RIT week are recommended, until baseline levels have been reached [9]. If levels drop faster than expected, shorter-term controls should be instituted. If the platelet count falls below 30 x 10^9/L, levels should be checked at least three times per week. Platelet transfusions and growth factors should be administered if indicated. The patient should also be informed of the increased risk of infection and bleeding.

Non-haematological toxicity is generally low, including asthenia, anorexia, fever, nausea, headache, chills, arthralgia and myalgia. Allergic reactions have been observed during MAb infusion, in particular after the first rituximab injection prior to Zevalin administration. It is important to highlight that RIT is well tolerated by older patients and represents a strong treatment choice in this group. Immunogenicity with human anti-mouse and human anti-chimeric antibody production has been observed, ranging from 1% to 63% between studies.

Secondary myelodysplastic syndrome or acute myelogenous leukaemia has been reported in 1-3% of cases [7]. The risk appears to be increased in patients previously treated with several lines of chemotherapy or radiotherapy. A cytological and genetic analysis of bone marrow could be proposed for heavily pre-treated patients prior to beginning RIT. In the long-term analysis of the International Radioimmunotherapy Network, the rate of secondary solid tumours was 0.8%, including breast cancer, prostate cancer, glioblastoma and non-small-cell lung cancer [8].

Efficacy

In a study of 143 patients with relapsed or refractory FL or transformed B-cell NHL, Zevalin® appeared more efficient than rituximab, yielding significantly higher overall response (OR) and complete response (CR) rates (80% vs 56%, p=0.002, and 30% vs 16%, p=0.04, respectively) [10]. Patients refractory to rituximab had a 74% OR and those with thrombocytopenia had an OR of 83% [11]. Mean time to progression (TTP) in responders was 12.6 months. OR was observed in 50% of patients with bulky lymphoma. Chemotherapy, administered in patients treated with RIT, was not associated with higher toxicity [12]. In a meta-analysis involving relapsed NHL patients treated with Zevalin® in four

clinical trials, long-term responses (TTP >12 months) were seen in 37% of patients [13]. At a median follow-up time of 53.5 months, the median TTP was 29.3 months. A third of these patients had been treated with at least three previous therapies, and 37% of them had not responded to their last therapy. The estimated 5-year overall survival was 53% for all patients treated with Zevalin and 81% for long-term responders.

The FIT (First-Line Indolent Trial) randomised phase III trial showed the benefits of Zevalin® as consolidation in previously untreated FL patients [14]. After completing induction therapy, patients were randomised to receive either a standard dose of Zevalin® (n=208) or no further treatment (n=206). Induction therapies included CVP/COP (n=106), CHOP and CHOP-like (n=183), fludarabine combinations (n=22), chlorambucil (n=39) and rituximab–chemotherapy combinations (n=59). A high conversion rate from partial response (PR) to CR of 77% was observed after RIT, leading to a high CR rate of 87% after RIT. The improvement in response was associated with an increase in progression-free survival of more than 2 years in the RIT consolidation arm as compared to the control arm.

After RIT, response should be assessed 3 months after Zevalin® injection using the international guidelines on lymphoma response criteria. The quality of response may still be improved beyond 3 months after RIT.

Conclusion

The anti-CD20 radiolabelled antibody ^{90}Y-ibritumomab tiuxetan (Zevalin®) is approved in Europe for the treatment of patients with relapsed or refractory FL or as consolidation after induction chemotherapy in the front-line treatment in FL patients. In relapsing refractory FL and transformed NHL, RIT as monotherapy induces a CR rate of around 30%, with a possibility of durable remissions. RIT consolidation after induction therapy significantly improves the quality of the response. Dose-limiting toxicity of RIT is haematological, depending on bone marrow involvement and prior treatment. Non-haematological toxicity is generally low.

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Section II

6. Radionuclide Therapy of Refractory Metastatic Bone Pain

Brian A. Lowry, Ruth B. Menghis, Christopher Mayes and Sobhan Vinjamuri

Introduction

In recent years there has been improvement in treatment strategies in many types of cancer and survival rates have improved. Many of the more common cancers metastasise to bone and a significant number of patients may therefore experience pain from such lesions. Patients are often fearful of metastatic bone pain, and report it as their worst symptom. If it is not well controlled, it can be the factor which most reduces their quality of life. The majority of patients respond well to conventional analgesia using the widely accepted World Health Organisation (WHO) pain ladder approach, and there is a role for bisphosphonates in many types of cancer [1]. However, some patients have pain which is not controlled well by conventional analgesia, and may have an unacceptable level of side-effects from it.

In some cancers, disease-modifying treatments may also help with bone pain, and the effects of chemotherapy may provide pain relief in some cases. In more difficult cases, external beam radiotherapy (EBRT) can be highly effective, especially in localised disease. When patients have metastases that are more widespread, EBRT can be used to treat a wide field, but toxicity may begin to outweigh the beneficial effects [1]. As it is a systemic treatment, treatment with radionuclide therapy is likely to be most useful in patients with multi-site disease. Due to the fact that the treatment is targeted to tumour, the potential toxicity is relatively reduced [1].

Radiopharmaceuticals

Bone metastases may involve mainly osteoblastic cells, leading to a sclerotic type lesion, or mainly osteoclasts, which will result in lytic lesions. Often there is a mixture of the two. There are virtually no bone metastatic lesions that do not have at least an element of osteoblastic activity, meaning that substances involved in bone re-mineralisation, such as calcium and phosphate, will be preferentially taken up there [2]. The exact mechanism of action of the radionuclides used for this type of therapy is not fully understood, but it is thought to be related to the reduction of inflammatory processes at the interface between neoplastic and normal bone, resulting in reduced mechanical pressure effects on the periosteum [3].

The ideal radiopharmaceutical for bone metastases – often termed "bone seeking" – is one which is preferentially taken up by the sites of metastatic bone damage and retained there for a prolonged period. Beta particle emission is preferable, but recently alpha emitters have been used and are likely to be used more widely in the future. The presence of gamma emissions may be helpful in enabling imaging of the distribution of the radiopharmaceutical in the body, but may present radiation protection problems. They should deposit energy over a path length similar to that of the tumour deposit size and decay to a stable daughter product [2]. The range of the particle in tissue may influence its suitability for a particular situation – more bulky tumours may be better treated with a

radionuclide with a longer range. The physical half-life of the radionuclide should be approximately the same as the biological half-life of the radiopharmaceutical [1]. The physical properties of the commonly used radionuclides are shown in Table 1.

	Half-life	Maximum energy	Mean energy (MeV)		Maximum range	Gamma emission (keV)
Strontium-89	50.5 d	1.4	0.583	β	7 mm	None
Rhenium-186	3.7 d	1.07	0.362	β	5 mm	137
Rhenium-188	16.9 h	2.1	0.764	β	10 mm	155
Samarium-153	1.9 d	0.81	0.229	β	4 mm	103
Radium-223	11.4 d	5.78		α	<10 µm	154

Table 1: Properties of radionuclides used in bone pain palliation [2].

There are three main ways in which a radiopharmaceutical may be taken up in a bone metastasis [2]. The first is to use the normal physiology of bone remineralisation, where a substance with chemical properties similar to calcium will be taken up by the osteoblasts and incorporated into the bone structure. Examples of these are strontium-89 and radium-223. A second way is to incorporate the radionuclide into a molecule which will be taken up at sites of increased bone turnover. Samarium-153 is used as part of an ethylene diamine tetramethylene phosphonic acid (EDTMP) complex which is taken up by the osteoblasts and incorporated into hydroxyapatite (similar to the way that technetium-99m labelled methylene diphosphonate (^{99m}Tc-MDP) is used in bone imaging). The rhenium isotopes rhenium-186 and rhenium-188 can be combined into a complex molecule called 1-1-hydroxyethylidene diphosphonate (HEDP), which, in contrast to most bone-seeking radiopharmaceuticals, is thought to be taken up by the osteoclasts. The third way is to use a tumour-specific radiopharmaceutical, such as iodine-131, which is taken up by functioning thyroid tissue and therefore by metastases from thyroid cancer; this is considered in Chapter 4.

Strontium-89

Strontium-89 (^{89}Sr) is a beta-emitter with a long half-life. The beta particles have a relatively long range. It is used in the

radiopharmaceutical form ^{89}Sr chloride. The maximum range of the beta particles in tissue is relatively long, at 7 mm. It is handled by the body in a manner similar to calcium and is therefore taken up by bone which is more metabolically active. It is renally excreted and the glomerular filtration rate of the patient should be considered. It has mainly been used to treat metastatic bone pain from hormone-resistant prostate cancer and has been found to give pain relief in 60-70% of patients. The onset of pain relief is typically around 10-14 days and the duration of pain relief may be prolonged, at up to 15 months. Its toxicity is usually in the form of myelosuppression, which typically occurs in the first 6 weeks post treatment and reverses over the next 6 weeks [2].

Rhenium-186

Rhenium-186 (^{186}Re) is a beta emitter with a half-life of 3.7 days and also has gamma emissions which permit imaging. The range of the beta particles is 5 mm. It has been used in prostate cancer and breast cancer and most patients report pain relief within about 2 days of administration. It causes temporary myelosuppression with a nadir in counts at around 4 weeks and recovery in 8 weeks [1].

Rhenium-188

Rhenium-188 (^{188}Re) is also a beta emitter. It has a shorter half-life of 16.9 h and may produce more rapid pain relief than other radiopharmaceuticals. Its beta particles have a relatively long range, 10 mm, which may be useful for some clinical applications. It also causes myelosuppression [1].

Samarium-153

Samarium-153 (^{153}Sm) emits lower energy beta particles with a range of only 4 mm. A high proportion of the radiopharmaceutical is quickly taken up by bone – preferentially at sites with increased osteoblastic activity. The gamma emissions have potential for imaging. There is typically a quick pain relief response in most patients – within about one week – with the duration being in the order of 8 weeks. Myelosuppression may occur, with a nadir in blood counts at around 6 weeks [1].

Radium-223

Radium-223 (^{223}Ra) has been the subject of considerable interest recently. It is an alpha particle emitter and the energy will therefore be deposited over a short range: less than a tenth of a millimetre. It is a calcium mimetic and will therefore be taken up by the osteoblasts and incorporated into hydroxyapatite at sites of increased bone turnover [4]. A relatively low number of "hits" to a cell by alpha particles will result in cell death, so there is potential for an alpha-emitting radiopharmaceutical to efficiently kill tumour cells without having a significant impact on the bone marrow.

Clinical applications

The most established indication for radionuclide therapy for bone pain is in prostate cancer, and ^{89}Sr has been found to be effective in achieving pain relief in 65-75% of patients. A sub-group of patients may even report complete pain relief [5,6]. ^{89}Sr has also been

used both instead of EBRT and as an adjuvant to it, showing pain relief in most cases [2]. ^{153}Sm has also been used with good effect in metastatic prostate cancer [2]. ^{223}Ra, with the trade name Alpharadin®, has been used with very promising results in hormone-resistant prostate cancer and, at the time of writing, a trial called Alpharadin in Symptomatic Prostate Cancer (ALYSMPCA) is soon going to be formally published. The initial data show significant reductions in the pain reported by patients and their use of opioid analgesia. A significant survival benefit has also been found [7]. The radiopharmaceutical is now going through licensing procedures and is likely to be brought into widespread clinical use over the next few years.

In breast cancer, ^{89}Sr, ^{186}Re and ^{188}Re have all been used and found to be effective in achieving pain relief in most patients [6]. Significant reduction in pain was found in a small study using ^{186}Re-(Sn)-HEDP. A trial which included breast cancer patients found that ^{153}Sm-EDTMP yielded a significant reduction in pain and opioid use [8].

Toxicity and limitations

The most important consideration for patient safety with bone-seeking radionuclide therapy is the effect on the bone marrow. Almost all patients will have some myelosuppression [1], which in most cases will be relatively mild and transient. The timing of myelosuppressive effects varies with the radiopharmaceutical used, as mentioned above, but typically the nadir in blood counts is around 4 weeks and recovery occurs at around 8 weeks post treatment [2]. Patients with significant bone marrow involvement will be at higher risk of haematological toxicity and this should be considered before treatment. Toxicity may be increased in patients with subclinical disseminated intravascular coagulation (DIC), which is often present in advanced stage cancer patients, particularly those with prostate cancer [1].

A significant number of patients may experience a short-term increase in pain, a phenomenon known as "pain flare". This is more common with rhenium treatments. There do not appear to be any clinical features that identify patients likely to experience pain flare [2].

Contra-indications and situations requiring caution

As with many medical radiation exposures, pregnancy is an absolute contra-indication and should be excluded according to local protocol.

Patients with bone metastases are at risk of developing spinal cord compression, where a metastatic deposit in the spine enlarges sufficiently to exert mechanical pressure on the nervous tissue. Treatment with bone-seeking radiopharmaceuticals can potentially worsen this and it is therefore a contra-indication. Any health professionals dealing with such patients should be alert to the symptoms of this condition, which include worsening back pain (particularly pain outside the

lumbar region), limb weakness, sensory loss in a dermatomal distribution and bowel and/or bladder dysfunction. A patient with symptoms or signs suspicious of spinal cord compression will require urgent medical review.

As the radiopharmaceuticals are predominantly renally cleared it is important to consider the patient's renal function. A patient with poor renal function will receive a higher effective dose due to more radiopharmaceutical remaining present in the body for longer. Acute kidney injury will be a contraindication to bone-seeking radionuclide therapy and the patient will require stabilisation before it can be considered. The presence of vesico-ureteric flow obstruction and/or bladder outflow obstruction, of particular concern in prostate cancer, may cause an increased dose to those organs and surrounding structures; this may need assessment and possibly intervention before treatment [1]. Urinary incontinence, again a common scenario in prostate cancer, may cause problems with radioactive contamination.

Pre-therapeutic evaluation

The indication for treatment with bone-seeking radionuclides is therefore metastatic bone pain that is not controlled with conventional analgesia and is limiting activities of daily living. The patient group presenting for nuclear medicine therapy is likely to include those in whom other treatments, such as bisphosphonates, hormonal treatment and EBRT, have failed. It should be noted that evidence shows that patients in somewhat earlier stages of the development of bone metastases, with relatively limited and localised disease, may gain more benefit from radionuclide treatment [3]. Bearing in mind the time frames for onset of pain relief and its duration, consideration should be given to which radionuclide is most suitable. A radionuclide with a shorter half-life may give a quicker response, but with a shorter duration in a patient with relatively rapidly progressing disease. A radionuclide with a longer half-life may be appropriate to achieve a longer duration of effect in other patients. Patients with a short life expectancy may not be suitable for therapy with some of the longer-lived radionuclides, particularly ^{89}Sr.

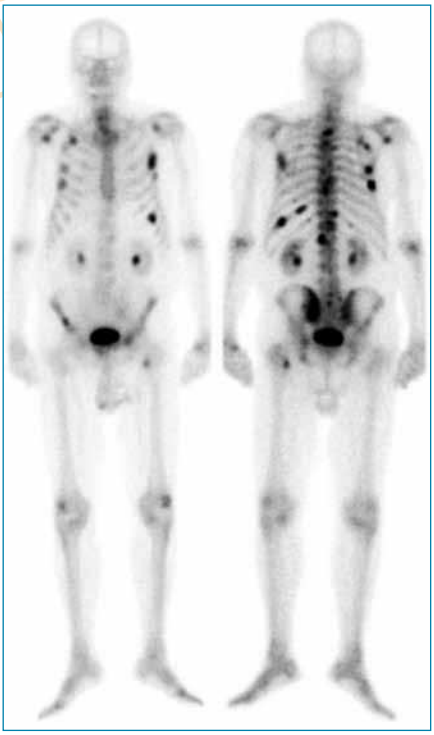
A suitably qualified medical practitioner should obtain sufficient medical history and perform an appropriate examination prior to therapy. Enquiries should be made about symptoms suggestive of conditions which would contra-indicate radionuclide therapy. Medication history should be looked at to see whether there are any medicines which may affect radiopharmaceutical uptake or cause interactions. It should be borne in mind that many patients will take "over the counter" medicines which do not require prescriptions. Many may also be taking "complementary therapies" such as herbal substances and food supplements.

Test	Reason for test	Results raising concern
Full blood count (FBC)	To assess risk of myelosuppression	Pancytopenia Neutropenia Anaemia Thrombocytopenia
Urea and electrolytes (U&E)	Renal function glomerular filtration rate	Dehydration Reduced glomerular filtration rate (GFR) Acute kidney injury
Biochemical profile	Calcium status	Hyper- or hypocalcaemia
Coagulation screen	Risk of DIC	Signs of DIC

Table 2: Pre-therapeutic blood tests [1].

Bearing in mind the myelosuppressive side-effects which are likely, and the importance of renal function, it is necessary to obtain the results of suitable blood tests before radionuclide therapy, as summarised in Table 2. Patients with pre-existing problems in their haematological status will be at increased risk of more serious adverse events after therapy. Results outside the normal ranges may mean the treatment is contra-indicated. A centre performing radionuclide therapy should draw up a protocol based on existing guidelines and evidence and patients will need medical assessment of their results before treatment.

Consideration of the mode of action of radionuclide therapy tells us that it will be successful where pain is being caused by metastatic deposits with osteoblastic activity – although it can also help where there is predominantly osteoclastic activity. A standard radionuclide bone scan with ^{99m}Tc-MDP should be performed prior to therapy and a history of the sites of pain taken. An example of a bone scan with metastases is shown in Fig. 1; if the patient concerned describes pain in the back and ribs, the therapy will have a good chance of success. These pain sites can then be "mapped" to areas of increased uptake on the bone scan. Treatment success is likely when areas giving pain are well matched to regions of increased osteoblastic activity. When a patient indicates pain from a site which does not show increased uptake on a bone scan, it should be considered that the pain may be due to a cause other than metastatic disease. Possibilities include osteoporotic collapse, degenerative arthropathy such as osteoarthritis and pain from internal organs, e.g. due to obstruction in the urinary system [1]. It is important for imaging of all modalities to be reviewed before therapy.



From archives of the Nuclear Medicine Department, Royal Liverpool and Broadgreen University Hospitals NHS Trust

Figure 1: ^{99m}Tc-MDP bone scan showing bone metastases due to prostate cancer.

Therapeutic procedure

The therapy should be explained to the patient, and provision of written information is highly recommended. There may be misconceptions in the patient population about the use of radionuclides, and considerable explanation may be required regarding the mode of action of the therapy and its possible benefits and risks. The palliative nature of the therapy should be emphasised as many patients have unrealistic expectations of cancer treatment. Radiation protection regulations and requirements and arrangements, as discussed in Chapter 3, will need to be gone through in detail. Individual information should be given regarding the potential time required for pain reduction to be noticed and the possible duration of pain reduction, according to the radionuclide used [3]. The possibility of a pain flare should be mentioned. Informed consent should be obtained and the authors would recommend a specific consent form to be signed by the patient.

Therapy should be carried out in a department with suitable facilities which meet the local regulations as discussed in Chapter 3. The therapy should be supervised by a physician who has sufficient knowledge and experience and administered by a suitably qualified practitioner. Medical physics support is invaluable. Radiopharmaceuticals should be administered according to the manufacturer's instructions. An intravenous cannula or butterfly should be used and great care should be taken to avoid extravasation [3].

Post-therapeutic assessment

Considering the possibilities of toxicity post therapy, clear arrangements are required for patient follow-up and it must be agreed in advance who will be taking responsibility for this. Information regarding the therapy

and follow-up plans should be conveyed immediately after its administration to the patient's supervising physician, e.g. an oncologist or urologist, and to the general practitioner.

It will be important to monitor the patient for haematological toxicity and this will again depend on the radionuclide used. Such monitoring will involve periodic blood tests – typically every 1-2 weeks – for up to 6 weeks in the case of ^{186}Re and ^{153}Sm, and up to 16 weeks for ^{89}Sr [3]. The patient should be told to be alert to potential symptoms suggesting more serious toxicity, such as lethargy and pyrexia. A pain flare may require temporarily increased analgesia.

In patients who respond to therapy, particularly with shorter-acting radionuclides, re-treatment may be suitable. The period between therapy should be consistent with the radionuclide, e.g. around 8 weeks for ^{153}Sm and 12 weeks for ^{186}Re [3].

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Section II

7. Radiosynovectomy

Christopher Mayes, Brian A. Lowry, Ruth Berhane Menghis and Sobhan Vinjamuri

Introduction

Radiosynovectomy (also known as radiosynoviorthesis) is an established, powerful therapeutic technique that provides targeted therapy to combat synovial inflammatory processes in individual joints and so minimises the damage and chronic arthritic disease that follows. It was first described by Fellinger in 1952 [1] and is the subject of EANM guidelines published in 2003 [2]. However, even 2003 is a long time ago in medicine, and although the technique itself has not changed massively, the advances in medical technology outside the field of nuclear medicine provide new challenges and opportunities that need to be taken into account as we practise this therapy.

Indications for radiosynovectomy

Arthropathies for which radiosynovectomy is indicated are shown in Table 1.

Rheumatoid arthritis
Haemophilic arthritis
Spondyloarthropathy, e.g. reactive or psoriatic arthritis
Persistent synovial effusion
Persistent effusion following prosthesis
Other inflammatory joint disease (e.g. Lyme disease, Behçet's disease)
Undifferentiated arthritis with synovitis, synovial thickening or effusion
Calcium pyrophosphate dihydrate (CPPD) arthritis

Table 1: Arthropathies that are indications for radiosynovectomy

Overview of synovitis and arthritis

Synovitis

Synovitis is the inflammation of the connective tissue lining the ligaments that make up the joint capsule, the synovium. The synovium secretes the thick synovial fluid that lubricates the joint.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is one of the most common auto-immune diseases. It affects more women than men and has a prevalence of approximately 1% in the whole population. RA increases the numbers of synovial lining cells with colonisation by fibroblast growth and intensive vascularisation. This leads to hyperplastic synovial tissue growth (pannus) that erodes cartilage, subchondral bone, the capsule and ligaments.

Synovial lining cells are colonised by lymphocyctes and plasma cells. T cells produce lymphokines, such as tumour necrosis factor, and mature B cells produce immunoglobulins, such as rheumatoid factor.

In the early stages, pain increases with stiffness and swelling, and reduced movement is possible. Later stage disease involves progressive joint destruction and deformation. Baker's cyst is also a common development in the disease.

Traditionally RA has been a major source of referrals for radiosynovectomy, but drug management has improved in the last 20 years and this is reducing RA referrals for both surgical interventions and radiosynovectomy in Western countries [3].

Drug therapies for RA. New drug regimens have improved the management of the disease in recent years. Non-steroidal anti-inflammatory drugs are used to relieve pain and stiffness in early disease by inhibiting cyclo-oxygenase (COX) but do not influence the radiographic progression of the disease.

Systemic corticosteroids improve symptoms and do reduce damage. Intra-articular corticosteroid injections are widely used and can produce rapid and sometimes sustained relief in target joints.

Disease-modifying anti-rheumatic drugs (DMARDS) are a group of systemic drugs that require sustained use, but do slow the progression of RA. Methotrexate and sulfasalazine are of this type and they can be used effectively in combination therapies with other DMARDs and biological response modifiers (BRMs). BRMs include tumour necrosis factor (TNF) blockers and monoclonal antibodies which act on the immune system, e.g. rituximab.

This improved management of RA means the injury to many patients' joints has been successfully reduced or at least postponed. There are new products and combinations that are fortunately reducing the need for patient referral for radiosynovectomy. This reduction in demand does not mean that radiosynovectomy has been replaced, however. Furthermore, the new drug regimens are systemic and have significant side-effects. There are concerns about anti-TNF therapy regarding a possible dose-dependent increase in serious infection and malignancies, especially skin cancers [4-6], so targeted therapies may continue to have an important role for some patients.

Reactive arthritis

Reactive arthritis is another autoimmune disease that is triggered by an infection in another part of the body, e.g. by food poisoning or chlamydial infection.

Psoriatic arthritis

Psoriatic arthritis, which causes destruction of joints, can be as severe as RA but will attack fewer joints and thus is suitable for targeted radiosynovectomy.

Osteoarthritis

Erosion of the normal covering of the cartilage allows the breaking off of tissue, irritation of the synovium and osteophyte formation. Synovitis can be treated with radiosynovectomy but the underlying cartilage disease cannot. Radiosynovectomy has been shown to be useful in osteoarthritis, especially in younger patients with early disease, whose joints show little radiographic damage [7].

Haemophilic arthritis

Haemophilia is an X chromosome-linked disorder caused by a deficiency of factor VIII or factor IX due to mutation of the respective clotting factor genes. This is a rare disease with an estimated frequency of 1 in 10,000 births. It generally affects males on the maternal side and, although this can usually be traced down family lines, as many as one-third of all cases are the result of spontaneous mutation where there is no prior family history.

In haemophilia, between 70% and 80% of bleeding occurs internally into joints, especially the hinged joints: ankles, knees and elbows. Best medical practice in caring for patients is detailed in the World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia [8], published in 2013, which recommend prophylactic clotting factor replacement: "Prophylaxis prevents bleeding and joint destruction and it should be the goal of therapy to preserve normal musculoskeletal function." The importance of the musculoskeletal system is highlighted in the guidance. Target joints are defined as joints in which three or more spontaneous bleeds have occurred within a 6-month period and "with repeated bleeding, the synovium becomes chronically inflamed and hypertrophied". Synovectomy is the recommended action to deactivate the synovium as quickly as possible and preserve joint function. Non-surgical radiosynovectomy is the treatment of choice.

These guidelines support radiosynovectomy because research has consistently shown that bleeding episodes are significantly reduced following radiosynovectomy. In a 2012 review [9], 75% of patients were said to benefit from a reduction in articular bleeding. Furthermore, reduction in bleeding is not the only benefit, with pain, range of motion, clinical synovitis and the size of the synovium all showing great improvement [10].

Contra-indications to radiosynovectomy

Pregnancy, breast-feeding, ruptured Baker's cyst of the knee, local skin infection and massive haemarthrosis are absolute contra-indications to radiosynovectomy. Relative contra-indications include age less than 20 years, evidence of significant cartilage loss and extensive joint instability.

Radiopharmaceuticals for radiosynovectomy

EANM guidelines [2] propose three radionuclides that are available in Europe for use in radiosynovectomy; their physical properties are summarised in Table 2.

	Yttrium-90 (^{90}Y)	Rhenium-186 (^{186}Re)	Erbium-169 (^{169}Er)
Use	Large	Medium	Small
Half-life (days)	2.7	3.7	9.4
Max. beta energy (MeV)	2.27	1.07	0.34
Max. beta particle range (soft tissue) (mm)	11	3.7	1.0
Mean beta particle range (soft tissue) (mm)	3.6	1.1	0.3
Gamma ray energy	None	137 keV	None

Table 2: Radionuclides available for radiosynovectomy

The radiopharmaceuticals used in radiosynovectomy are in the form of colloidal particulates that are small enough to be phagocytised and trapped in the inflamed synovial membrane. The particles must be large enough to resist escape from the joint by absorption into the lymphatic system before they have been phagocytised. Particle sizes are thus in the range of 2-10 µm. The beta particles emitted create free radicals that cause apoptosis and thus ablation of the inflamed synovial membrane.

The colloids available are: ^{90}Y as yttrium citrate, ^{186}Re as rhenium sulphide and ^{169}Er as erbium citrate. The activities and recommended volumes injected for each joint are detailed in Table 3.

Joint	Radiopharmaceutical	Activity (MBq)	Volume (ml)
Knee	^{90}Y citrate	185-222	1
Hip	^{186}Re sulphide	74-185	3
Shoulder	^{186}Re sulphide	74-185	3
Elbow	^{186}Re sulphide	74-111	1-2
Wrist	^{186}Re sulphide	34-74	1-1.5
Ankle	^{186}Re sulphide	74	1-1.5
Subtalar	^{186}Re sulphide	37-74	1-1.5
Metacarpophalangeal	^{169}Er citrate	20-40	1
Metatarsophalangeal	^{169}Er citrate	30-40	1
Proximal interphalangeal	^{169}Er citrate	10-20	0.5

Table 3: Joint activities and injection volumes.

The radiosynovectomy procedure

National legislation requirements vary between countries for administration of radioactive agents. In-patient treatment may be required and although this may not be legally demanded, because immobilisation must follow radiosynovectomy, procedures may require that less able patients stay in hospital. Appropriately shielded accommodation and toilet facilities may therefore be necessary.

Radiosynovectomy demands an aseptic injection so appropriate clean areas and sterile protocols are needed during administration.

Knees are the joints most often treated and these are the only joints that can be injected without imaging. Confirmation of the correct intra-articular placement of the needle is possible by aspiration of synovial fluid. For other joints, imaging, e.g. by mobile image intensifier or ultrasound, is necessary to ensure safe positioning of the needle for injection.

Staffing requirements

Radiosynovectomy requires a multi-disciplinary team to be run efficiently. In addition to the nuclear medicine medical, technological, nursing and physics staff, a rheumatologist or orthopaedic surgeon will probably supply the expertise in synovial puncture. In the case of haemophilic patients, haematologists will have ensured prophylactic clotting factor cover.

Patient preparation

Previous intra-articular glucocorticoid injection will have been unsuccessful in patients referred for radiosynovectomy. Recent radiographs of joints to be treated will be reviewed prior to the procedure. Other imaging techniques may be useful: Scintigraphic assessment of soft tissue and active inflammation is often carried out using ^{99m}Tc-MDP/HDP/HEDP. Ultrasound is useful to evaluate synovial structure and thickness and exclude ruptured Baker's cyst. Magnetic resonance imaging may also be useful.

Knees with Baker's cysts can be treated by skilled practitioners [11]. The cyst may be reduced using external pressure or synovial puncture and aspiration of the main joint. The danger of rupture and escape of the radiopharmaceutical must be assessed by the clinician.

Arthroscopy or surgery must not have been performed during the 2–6 weeks preceding radiosynovectomy.

The minimum interval between repeat radiosynovectomy is 6 months.

Consent

Informed written consent must be obtained prior to radiosynovectomy. Written and verbal information must be given to the patient and this should include:

1. Between 60% and 80% of patients benefit from the therapy.
2. Response is unlikely within 14 days of injection and may not be noticeable for 1 month.

3. There is a risk of a temporary increase in synovitis.

4. Potential complications of treatment are:
   a) Due to joint puncture: local haemorrhage, bruising, infection (very rare) and future malignancy.
   b) Theoretical risk of exposure to beta-emitting radiation, including radiation necrosis (rare) and future malignancy.
   c) Risk of post-injection pyrexia or radiopharmaceutical allergy (very rare).

Administration

Radiosynovectomy is an aseptic technique. It must therefore be performed under full aseptic conditions by suitably qualified medical, nursing and technical staff. Skin preparation may have included the removal of excess hair. After clinical examination a sterile field is created around the joint to be treated using towels.

There follows a brief description of the procedure using the example of the knee as the target joint: The exposed skin of the injection site is disinfected. Local anaesthesia is advisable before the joint puncture. Intra-articular puncture of the knee may be achieved using a 20-gauge 7.6-cm needle on a slightly flexed knee proximal and lateral to the superolateral angle of the patella. Local anaesthetic can be injected first subcutaneously through this needle (this also ensures that skin-punch cylinders are not carried into the joint).

Once the needle has been advanced into the joint, aspiration of synovial fluid will confirm the correct position of the needle. Radiopharmaceutical must not be injected unless intra-articular placement has been ensured by aspiration. As already mentioned, joints other than the knee must have imaging confirmation of position, e.g. by mobile image intensifier; this is particularly important as the joint may be misshapen by the disease process and small joints with little fluid make the aspiration test impracticable.

In a joint with effusion, aspiration of excess fluid is useful so long as enough fluid is left to distribute the radiopharmaceutical in the joint space. If no effusion is present, 10 ml or more of saline may be useful to achieve good dispersion. The radiopharmaceutical is then injected and it is recommended that this be followed by use of long-acting glucocorticoids to reduce any acute synovitis and improve treatment response.

The needle is finally flushed with saline, before and during withdrawal, to reduce the chance of leakage of radioactivity down the needle track.

Once the needle has been removed, a skin dressing is applied to the puncture site and this is followed by joint immobilisation (splinting) for 48 h. For a knee this may consist of a thigh-leg plaster/ resin cast. Immobilisation reduces the transport of particles through the lymphatics to the regional lymph nodes.

Many centres will carry out scintigraphy of the treated joint to demonstrate that accurate intra-articular dispersion of the radiopharmaceutical has been achieved (Fig. 1). For ^{90}Y bremsstrahlung radiation is imaged; the gamma rays from ^{186}Re can be imaged directly.

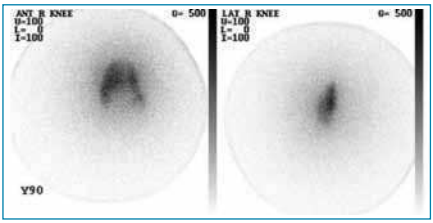

Image courtesy of Department of Nuclear Medicine, Royal Liverpool and Broadgreen University Hospitals NHS Trust. UK.

Figure 1: Post-radiosynovectomy imaging following successful administration of ^{90}Y into the knee joint, demonstrating an even distribution and no leakage of radiopharmaceutical [12].

Post-radiosynovectomy care

Patients must understand the importance of immobilisation. Radiation protection advice, which may need to be in writing for legal reasons, must be given to the patient to reduce unnecessary radiation exposure to family members and the public. If the patient is a hospital in-patient, staff must be instructed in radiation safety.

Radioactive urinary excretion is greatest during the first 2 days after the procedure. Rigorous hygiene will avoid contamination. Incontinent patients should be catheterised prior to radiopharmaceutical administration and the catheter should remain in place for 3-4 days and the collection bag emptied frequently. The risk and benefits of the procedure must be assessed in these difficult cases.

Women should avoid pregnancy for 4 months after treatment.

At 6-8 weeks after radiosynovectomy, patients should be reviewed for treatment response, assessment of synovial inflammation and possible radionecrosis. Assessment should be repeated at 3-4 months and 12 months.

Pain reduction typically occurs within 3 weeks of injection and the treatment has probably failed if no response has been detected after 6 months. Patients who fail to respond to the first injection may respond to a second attempt after a delay of 6 months. If two procedures fail to achieve any response, further radiosynovectomy should not be attempted.

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8. Nursing Implications for Patients Undergoing Radionuclide Metabolic Therapy

Ana Gorgan, Nicoleta Lupu and Claudiu Peştean

General aspects of nursing

Concepts and models

Nursing has many definitions, but may most appropriately be considered to comprise the diagnosis and treatment of human reactions to actual or potential health problems [1]. There are many conceptual models of nursing, the differences between them relating to the definition of nursing and its purpose, the definition of the patient, the definition of state of health and the definition of the environment which interacts with the patient [1]. Central to nursing conceptual models is the role of the individual, the individual's family and the community in maintaining and/or recovering the state of health [2].

Most concepts and models emphasise the necessity of a holistic approach to ensure that all the needs of patients and the context in which their health and well-being are grounded are taken into consideration.

Nursing, as an integrated part of the social assistance system, includes health assistance, disease prevention and health care for all types of disease (physical or mental) and disability at any age. Nurses focus on individual, familial or group reactions against the disease. They need to respond to the real or potential health problems of individuals or a community. Nursing interventions, as a response to the reactions against disease, range from individual interventions aimed at recovering the individual's health, to the development of specific policies designed to preserve the health of the population in the long term, as pointed out by the International Council of Nurses. The World Health Organisation and the International Council of Nurses define nursing as part of the health system [3].

Nursing, as a profession, involves various activities that can be complex and specialised or simple, such as the gesture of holding a patient's hand. Nursing is a mix of science and art: it requires theoretical knowledge about health care, applied in daily practice with ability by skilled personnel. Nursing activities are aimed in four main directions: health maintenance, disease prevention, health recovery and assistance in the event of disability or even death.

According to Virginia Henderson, author of the first scientific theory about health care needs and a key figure in laying the basis for modern nursing, nursing means helping the individual to find his or her route to health or recovery, taking into consideration that the individual should have the strength, the will and the knowledge to do this [4]. The conceptual nursing model established by Virginia Henderson is based on 14 fundamental patient needs. According to this model, maintenance of the individual's independence, or at least a certain level of independence, allows that individual to satisfy his or her fundamental needs.

The individual should be considered holistically, including the following dimensions: bio-physiological, psychological,

sociocultural and spiritual. Environment factors should also be taken into consideration because they may produce imbalances and consequently adversely affect the independence of the individual.

The state of disease represents a disruption of the equilibrium between the organism and the environment, which is an alarm signal expressed as physical and/or psychological distress, a difficulty or maladjustment to a new situation, temporary or permanent. This imbalance represents a negative event or experience for the individual.

The conceptual nursing model, through its perspective, offers a systematised methodology to identify the health problems of the patient and to elaborate a nursing plan which will reduce the patient's dependency. It also offers modalities for the implementation of this plan and for the evaluation of its efficacy upon completion.

The conceptual nursing model offers several advantages:

- It identifies the specific problems of the patient. In this way it is possible to establish general and specific objectives that will enable recovery from these problems. To accomplish these objectives, specific interventions are applied according to nursing skills and knowledge. The patient and his or her family are included in the health care team.
- The identification of the patient's needs improves communication between the members of the health care team.
- The nursing process uses consistent and orderly records relating to all aspects of nursing. These records allows quantification of all health care activities and, in this way, evaluation of the quality of health care provided.

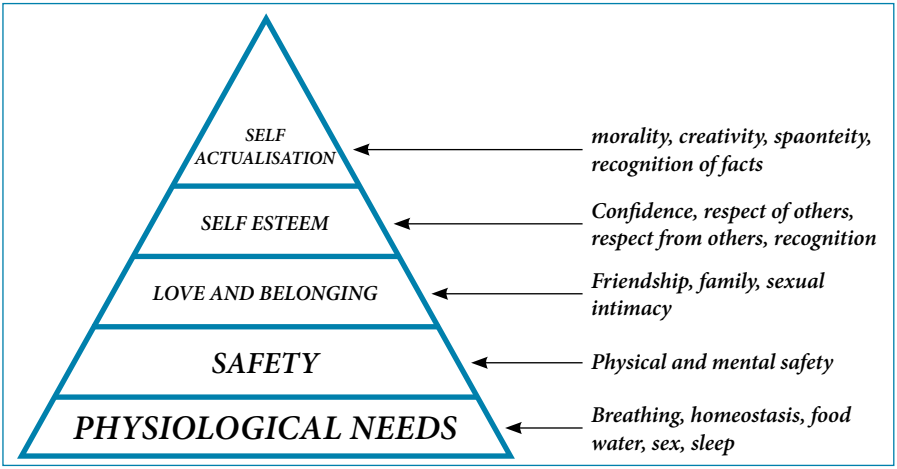
The nursing process

The nursing process has five phases:

The analysis. This entails the gathering of all necessary information to identify the actual or potential health problems, and for this purpose, an objective and impartial attitude is required. The information obtained can be subjective (when collected from the patient or his family) or objective (when it derives from measurable conditions).

Nursing diagnostics (the analysis from a clinical point of view of the individual's response to actual or potential health problems). This consists in identifying the patient's health problem and formulating and validating a nursing diagnosis. Formulation of a diagnosis consists in correlating the health problem to its cause or aetiology. One example concerns the impact of restrictions on contact with other persons on positive relations with others; this is a potential nursing diagnosis for a patient undergoing radioiodine therapy for differentiated thyroid carcinoma,

which for radiation protection reasons requires certain restrictions on contact with family or visitors. As multiple nursing diagnoses may be identified in the same patient, their prioritisation is essential; for this purpose reference may be made to the so-called Maslow hierarchy, a structural model of need categories based on priorities (Fig. 1).



Buxbaum BS, Mauro E, Norris CG, eds. Illustrated manual of nursing practice, 2nd edn. Springhouse: Springhouse Corporation; 1994.

Figure 1: Maslow's hierarchy, adapted after Illustrated manual of nursing practice, 2nd edn. [1]

The nursing plan. The nursing plan consists in the elaboration of all objectives to be accomplished and also all the nursing interventions necessary to achieve these objectives. For a nursing plan to be objective, it has to be realistic: objectives too difficult to accomplish should be avoided since they can discourage patients. The nursing plan must be individually adapted, as every patient is different, and should be designed without unclear terms.

Implementation of the nursing plan. This consists in enactment of the sum of the planned interventions.

Evaluation of the nursing plan. The results are analysed and compared with the established objectives. Correction of the nursing plan is done if necessary.

The nursing applied to patients undergoing radionuclide metabolic therapy

Radionuclide metabolic therapy is a specific and complex therapeutic alternative. The approach is multidisciplinary and nursing care plays a well-defined role in the process of healing. Besides carrying out the specific duties associated with health care, the nurse has the role of teaching the patient about different aspects relating to his or her suffering, thereby assisting the patient in accepting and defeating the illness.

The pathologies in which radionuclide metabolic therapy can be applied are diverse, but most are oncological diseases. The disease, its symptomatology and also its therapy may affect the patient's needs, from the vital ones to those with low priority. Nursing interventions are extremely important in recovering or improving the patient's state of health.

In the following we will approach radionuclide metabolic therapy not from the perspective of pathology, but from the perspective of the altered patient's needs and the nursing care to be applied.

Alteration of respiratory function

Example: patients with primary or secondary lung tumours. Potential nursing interventions include monitoring of breathing, consciousness surveillance, prevention of complications, maintenance of an appropriate climate and environmental conditions, maintenance of an adequate position, administration of medications and evaluation of their effects, preparing and using instruments for oxygen therapy, preparing the patient (physically and psychologically) and the materials for investigations (e.g. pleural puncture, bronchoscopy, tomography), helping in mobilisation and transport and teaching the patient how to cough.

Inadequate circulation/alteration of cardiovascular function

Example: some cases of hyperthyroidism or neroendocrine tumours secreting adrenaline/noradrenaline. Potential nursing interventions include monitoring of blood pressure and heart rate, consciousness surveillance, prevention of complications, maintenance of appropriate climate and environmental conditions, teaching the patient to ensure appropriate hydration, administration of medications and evaluation of their effects, preparing the patient (physically and psychologically) and the materials for investigations (e.g. ECG, SPECT-CT, PET-CT), and helping in mobilisation and transport.

Inadequate nutrition

Example: some gastrointestinal tumours or advanced stages of disease. Potential nursing interventions include help/support in feeding, assuring balanced nutrition, improvement of nutritional status, maintenance of an appropriate nutritional status, hydroelectrolytic equilibrium, administration of medications and evaluation of their effects, dietary assessment, and patient training in relation to diet, encompassing the purpose

of the diet, the type and quantity of food, food to be avoided, how to replace forbidden nutriments and what substances to use to improve taste [5].

Inadequate intestinal evacuation

Example: serotonin-induced diarrhoea in patients with secreting neuroendocrine tumours. Potential nursing interventions include monitoring of vital and vegetative signs, evaluation of hydro-electrolytic equilibrium, hydro-electrolytic equilibration via intravenous infusion of solutions, assessment of signs of dehydration, maintenance of hygiene, administration of medications and evaluation of their effects, prevention of complications, maintenance of an appropriate climate and environmental conditions, prevention of infection, and helping in mobilisation and transport [6].

Alteration of body temperature; fever with or without rigors

Example: radionuclide metabolic therapy of lymphomas [7]. Potential nursing interventions include monitoring of body temperature, prevention of complications, maintenance of an appropriate position, maintenance of an appropriate climate and environmental conditions, maintenance of hygiene, and preparation of the patient for investigations or specific procedures.

Alteration of physical and psychological comfort

Potential nursing interventions include providing psychological support for the patient and his/her family, maintaining a supportive attitude in all phases through which the patient passes in relation to the illness (denial, confusion, resignation and acceptance), helping the patient to accept the illness according to his/her beliefs and traditions, improving self-esteem, maintaining a safe environment, and maintaining psychological comfort. In addition, the patient must be informed about the radionuclide metabolic therapeutic procedure and its potential side-effects [8].

Alteration of health status related to anxiety

Examples: the anxiety due to lack of knowledge regarding disease prognosis or the treatment, and anxiety due to alteration of self-image. Potential nursing interventions include efficient communication with the patient and his/her family and training relating to the prescribed treatment, e.g. names of medicines, doses, schedule of administration and path of administration. The patient should be encouraged to communicate feelings and thoughts, which will assist in acceptance of the disease [9].

Alteration of the need for movement

Example: due to increasing bone pain in the first days after bone pain palliation therapy or due to the restrictions on movement after radiosynovectomy). Potential nursing interventions include maintenance of an appropriate climate and environmental conditions, helping the patient to adopt an adequate position, and helping in mobilisation [10].

Alteration of self-image/self-esteem

Example: due to degradation of life, the main causes being the symptoms specific to each disease, especially in advanced stages. Potential nursing interventions include teaching the patient to accept his or her condition, helping the patient to improve self-perception and helping the patient to accept the conditions associated with being ill.

Alteration of the need for communication

Example: due to the restrictions required by radionuclide therapy regarding contact with others, such as in the case of radioiodine therapy for differentiated thyroid carcinoma. Potential nursing interventions include helping patients to stimulate and exploit their personal psychological resources, teaching patients how to gain confidence, teaching patients to express their feelings and concerns about their condition, helping patients to accept their situation and educating patients to respect the restrictions.

These are the patient's needs that are most frequently altered in the pathologies in which radionuclide therapy may be applied. Almost all nursing care needs arise due to the pathology itself, but some also appear as a consequence of therapy, as collateral effects. The nurse has an extremely important role in the multidisciplinary team, being directly responsible for identifying the nursing care required, establishing the nursing plan and applying the plan in accordance with established nursing principles, thereby contributing to recovery or improvement of the patient's health status.

References Section II, Chapter 8

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Section III

1. Future Perspectives in Radionuclide Therapy

Cathy S. Cutler

Introduction

Radiotherapy has progressed significantly since the days in which X-rays or radioactive sources were used to ablate cells. Today technology has advanced to methods that selectively deliver radiation to the tumour, thereby sparing normal tissue, leading to effective ablative doses. Advances in imaging and therapy have led to more effective approaches to treatment with fewer side-effects. This chapter presents methods still in the early stages of development that have the potential to change the way clinical practice in radiotherapy is performed.

Molecular imaging has shown its potential to non-invasively image both normal and abnormal biochemical pathways in individual patients. Molecular targets such as hypoxia, angiogenesis, receptor expression and metabolism are just a few of the biochemical pathways of interest to evaluate as end points in clinical trials. Preclinical imaging is becoming a key translational tool for proof of mechanism and concept studies. Agents currently being designed utilise radionuclides that emit photons that can be imaged as well as particles that can be used for treatment. Besides the obvious advantages, more exact patient assessment and dosage, there are significant savings of time and other resources when developing one drug that can serve two purposes rather than two separate drugs. Theranostics for [dual] imaging and therapy hold out promise for accelerated drug development and translation into the clinic. The aim of this chapter is to review some recent advances in the development of radiotherapeutic agents.

The fundamental challenge for therapy is to deliver toxic doses selectively to cancer cells while sparing all normal tissues. A variety of platforms have been used to design radiotherapy agents, from radiolabelling small molecules, tracers that mimic the *in vivo* behaviour of the natural substance, to the use of much more complex molecules such as antibodies and nanoparticles. Conventional agents have had low therapeutic indices due to suboptimal biodistribution — large doses are delivered to normal tissues while only a minute portion of the intravenously administered drug actually reaches the target. Targeted delivery techniques are being developed to circumvent such problems by resulting in selective localisation of drugs to cancer cells [1–6].

Radionuclide	Half-life (h)	Decay mode	E_{max} b- In, MeV (%)	Gamma energy in keV (%)	Mean tissue range (mm)
^{198}Au	64.7	β^-, γ	0.96 (99%)	412 (95.6)	0.38
^{199}Au	75.4	β^-, γ	0.45	208 (9.1) 158 (40)	0.14
^{177}Lu	161.0	β^-, γ	0.50	208 (11) 113 (6.6)	0.16
^{153}Sm	46.3	β^-, γ	0.81	103 (28.3)	0.30
^{186}Re	89.2	β^-, γ	1.10	137 (9)	0.43
^{212}Pb	10.6	β^-, γ	0.57	238.6 (43.1)	0.19
^{212}Bi	1.0	α, β^-	2.25 (55.5)	727 (11.8)	
^{225}Ac	240	α	5.94	99 (5.8)	

Table 1: Properties of selected radioisotopes for radiotherapy [34,35]

Palliative treatment

It has been estimated that 60-75% of patients diagnosed with breast and prostate cancer will eventually develop bone metastases. Among patients with metastatic, castrate-resistant prostate cancer, 90% have radiographic evidence of bone metastases [7]. These metastases are extremely painful and result in low quality of life. Radionuclides that mimic calcium/calcium metabolism or those that are bound to bone-seeking phosphorous chelators have been developed and used to palliate the pain associated with metastatic bone disease. Several radioisotopes such as samarium-153 (^{153}Sm)-EDTMP (Quadramet®) and strontium-89 chloride are approved for palliation of bone pain in some countries. Radionuclides chosen for bone pain palliation need to have particle emissions that are relatively low to minimise bone marrow ablation. Lutetium-177 (^{177}Lu) is a promising radionuclide for bone pain palliation due to its low-energy beta emission, long half-life and ability to be produced in large quantities at most medium flux reactors. ^{177}Lu complexed to both ethylene diamine tetramethylene phosphonate (EDTMP) and 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonate (DOTMP) is being evaluated for bone pain palliation [8]. A study comparing ^{177}Lu-DOTMP with ^{153}Sm-EDTMP showed that little to no toxicity was observed for

the ^{177}Lu agent when administered to give the same skeletal dose as the ^{153}Sm agent, indicating larger ^{177}Lu doses could be given that may result in longer remission times [8]. Clinical trials are ongoing through the International Atomic Energy Authority (IAEA) coordination evaluating ^{177}Lu-EDTMP. A scan showing the bone uptake observed for ^{177}Lu-EDTMP giving a dose of 37 MBq/kg and imaged at 7 days is shown in Figure 1.

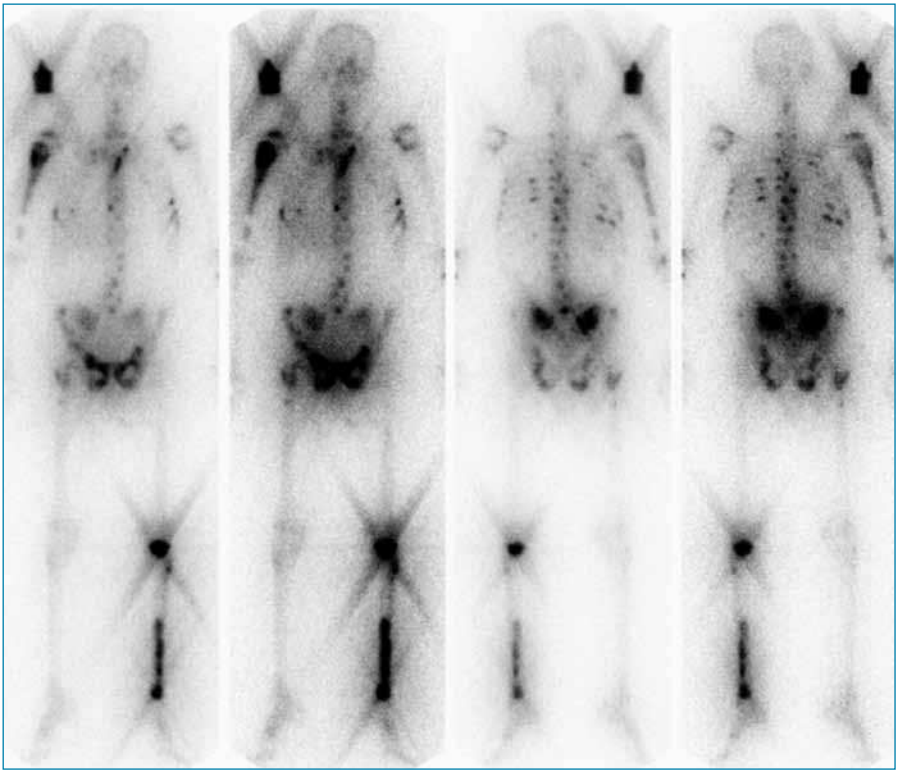

Figure 1: Planar image of a patient 7 days after receiving 37 MBq/kg of ^{177}Lu-EDTMP for palliation of pain due to metastatic bone cancer [35,37,38]

Radium-223 (^{223}Ra; $RaCl_2$) is an alpha-emitting radioisotope that has been shown to target areas of osteoblastic metastases. Unlike the agents described above, which are excreted very quickly (normally within 4 h) via the kidneys, ^{223}Ra is cleared primarily via

the intestines [9]. This may be advantageous in patients who have genitourinary cancers or reduced kidney function. ^{223}Ra, as an alpha emitter, delivers a very high dose to a very small area. This may lead to a reduction in some of the toxic side-effects observed with the beta-minus emitters such as leukopenia, thrombocytopenia and bone marrow suppression. In a large randomised phase III trial, ^{223}Ra has demonstrated improvements in overall survival, a delay of skeletal-related events (pathological fractures, spine cord compression and requirements for surgery or radiation to the bone) and biochemical parameters, with a remarkably tolerant adverse event profile in men with castration-resistant prostate cancer [9]. This has been the first agent to demonstrate improvement in overall survival, although it should be pointed out this was never evaluated for the other agents. Expanded trials are planned with this agent.

Peptides

The use of peptides and proteins such as monoclonal antibodies to deliver cytotoxic drugs has resulted in more selective treatments and in huge advancements in treating metastatic disease. CD20-targeted Bexxar® labelled with iodine-131 (^{131}I) and Zevalin® labelled with yttrium-90 (^{90}Y), routinely used to treat follicular non-Hodgkin's lymphoma, have demonstrated the effectiveness of the targeted approach. Large proteins such as monoclonal antibodies demonstrate high affinity, but due to their large sizes, suffer from long residence times in the blood, slow tumour penetration, dose-limiting toxicity to the liver and bone and, in some patients, adverse haematological effects and resistance. It can take up to 7 days for these large proteins to reach maximum uptake at the target site, limiting the radionuclides that can be used. A concerted focus has turned to evaluating peptides for their smaller size and rapid receptor targeting and blood clearance, ability to be easily synthesised and rapidly modified through solid phase and solution phase peptide synthesis, and increased tumour penetration and distribution; in addition, they do not elicit immune responses. Thus peptides are being developed as diagnostic tools and biomarkers for cancer prognosis and tumour targeting agents carrying radionuclides to cancer cells. Many are being used for theranostic applications in which they can be used both as an imaging characterisation tool and as a delivery device for radiotherapy radionuclides.

Peptide receptor radionuclide therapy (PRRT) combines peptides with radionuclides to target receptors overexpressed on cancer cells. Somatostatin analogues, the first developed, have been the most widely investigated. Octreoscan was the first radiolabelled peptide approved for imaging neuroendocrine tumours and is considered the gold standard for diagnosis of somatostatin receptor positive tumours [10, 11]. Upon injection, the radiolabelled octreotide attaches to somatostatin receptors overexpressed on cancer cells, thereby allowing an external SPECT

camera to image the location of the tumours in the body. A number of somatostatin analogues have been developed for imaging and have been expanded to bind radionuclides for PRRT. These agents are composed of a peptide conjugated to a bifunctional chelator through a linker. The peptide acts as the guiding system for selective delivery, the bifunctional chelator serves to stably complex the radioisotope, normally a metal, and the linker serves not only for stable conjugation but also as a pharmacodynamic modifier. Changes to the linker can be made to fine tune the uptake and clearance of the agent, such as increasing the hydrophobicity if the overall molecule proves to be too hydrophilic and clears too quickly. The most commonly used chelator has been DOTA (1,4,7,10-tetraazacyclotetradecane-*N*,*N*′,*N*″,*N*‴-tetra-acetic acid) which forms kinetically and thermodynamically stable complexes with a variety of metals but suffers from having to be heated at high temperatures for long periods of time and promiscuous binding with all metals, which can result in lowered specific activity. Other chelators have been developed that are more metal specific and that can be labelled at room temperature in high yields and often negate the need for a terminal purification. The technetium-99m (^{99m}Tc) somatostatin analogue, NeoTect®, approved in the United States, is used for the differentiation of malignant versus benign masses in the lungs, often after initial disclosure with CT or MRI. It differs from octreotide in that the disulphide bond between the two Cys is removed, enabling a bond between the Phe and Cys of the cyclic hexapeptide targeting vector. Hydrophobicity was added by substituting a Tyr for a Val and linking to a linear tetrapeptide chelator motif, which serves to coordinate the Tc at the Dap-Lys-Cys sequence (Dap= β-diaminopropionic acid) shown in Fig. 2 [12, 13]. The chelation involves three nitrogens (two amide nitrogen atoms of Lys and Cys and one amine nitrogen of Dap) and one sulphur of Cys. ^{99m}Tc offers better imaging quality than indium-111 (^{111}In) and is more widely available. NeoTect® itself has demonstrated higher affinity than Octreoscan® for receptor subtypes 2 and 5 and slower clearance from normal tissues via the kidneys, where it is excreted intact.

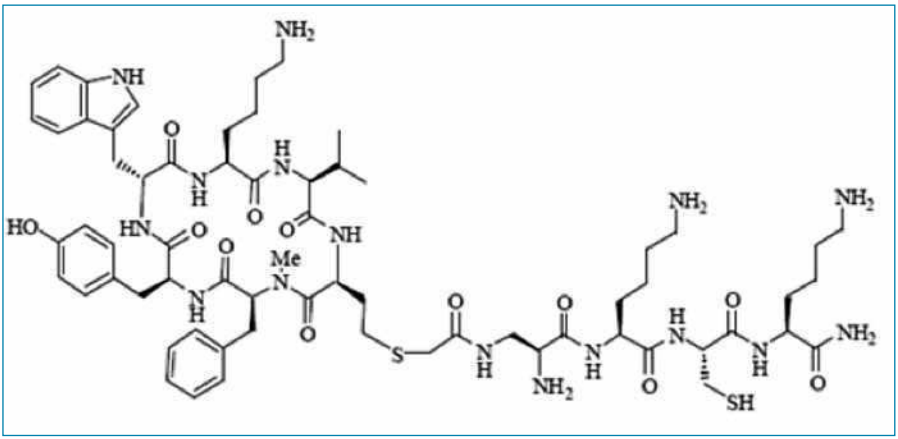

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Figure 2: Structure of the somatotastatin analogue for the drug NeoTect®

Significant work has gone into developing analogues that could deliver therapeutic doses. It was determined that replacement of tyrosine with phenylalanine enhanced affinity for the subtype 2 receptor, and that changing the chelate from DTPA to DOTA resulted in a more stable complex that could be used with ^{90}Y, i.e. ^{90}Y-DOTA-Tyr^{3}-octreotide [14]. The DOTA chelator is able to coordinate most +2 and +3 radiometals and remain stable *in vivo*. This version is termed DOTATOC and, labelled with ^{90}Y, it has been used to treat hundreds of patients. Toxicity in the kidneys led to the development of DOTATATE, which has been predominantly used with ^{177}Lu. ^{177}Lu has lower b^{-} than ^{90}Y and an imageable gamma emission at 208 keV that can be utilised to assess post-therapy uptake and dosimetry. ^{177}Lu has also been used in a large number of patients in Europe and is expected to enter clinical trials in the United States within the next year. Further studies have shown that using the two radionuclides in combination results in a more efficacious treatment than using either alone. A small study in 50 patients in which combined ^{90}Y/^{177}Lu-DOTATATE therapy was evaluated in comparison to ^{90}Y-DOTATATE alone, applying ^{90}Y/^{177}Lu-DOTATATE in a ratio of 1:1, demonstrated higher progression-free survival in the tandem therapy group: 29.4 months vs 21.4 months [15]. Treatment has also been enhanced by the use of PET imaging with gallium-68 (^{68}Ga) labelled to DOTATOC, DOTATATE or the new analogues NODAGATOC (DOTA has been replaced with the NOTA chelator) and DOTANOC (NOC = Nal^{3}-octreotide, an sst2, sst3 and sst5 binding peptide), in which the peptide has been further modified. PET imaging with ^{68}Ga allows for the determination of the receptor

density through the standardised uptake value (SUV). Novel derivatives such as NODAGATOC made with the NOTA chelator have allowed for room temperature synthesis in high yields that have been converted to easy kit formulations similar to those routinely used for ^{99m}Tc.

PRRT and imaging have been extended to looking at other peptides, such as bombesin, that target the gastrin-releasing peptide receptor known to be over-expressed in breast, prostate and lung tissues [16, 17]. A phase 1 clinical trial of ^{177}Lu-DOTA- [4-aminobenzyl]-BB (6–14) was undertaken [18]. Newer bombesin versions have been developed, such as the antagonists that demonstrate less non-specific uptake and higher receptor affinity [19, 20]. Other peptides being evaluated include those that target cholecystokinin (CCK) receptors [21]. In addition to new analogues, new radiometals have been evaluated, including scandium-44 (^{44}Sc) for imaging and bismuth-213 (^{213}Bi) for therapy. The longer half-life of ^{44}Sc (4.4 h) allows for imaging at later time points. ^{213}Bi-DOTATOC was evaluated and demonstrated higher therapeutic efficacy when compared to ^{177}Lu-DOTATOC in human adenocarcinoma cells.

Monoclonal antibodies

Targeted radioisotope therapy involves the administration of radiolabelled compounds to selectively damage and/or destroy diseased tissue (e.g. cancer). The design of a successful radiotherapeutic agent must therefore involve selection of a compatible combination of a *targeting molecule*, to deliver the radiolabelled compound with high selectivity to site(s) of disease, and a *radioisotope*, to cause damage/destruction to its local environment through its energetic decay properties. Radioimmunotherapy treatment of cancer uses a class of compounds that combine monoclonal antibodies (mAbs) and particle-emitting radioisotopes. mAbs target receptors either uniquely expressed on cancer cells or expressed in significantly higher numbers on cancer cells than on cells of healthy tissue; this difference in receptor expression allows for selective targeting of diseased cells. Particle-emitting radioisotopes (i.e. Auger electron, beta and alpha emitters) deposit their energy over short distances, thereby localising tissue damage. For example, lymphomas have been successfully treated with the RIT compounds Zevalin® and Bexxar®, CD20 receptor-targeting mAbs radiolabelled with beta-emitting radioisotopes. ^{90}Y and ^{131}I, respectively. Zevalin® and Bexxar® exploit the long blood circulation time of mAbs (large proteins) for targeting of these blood-based cancers; however, the residence time in blood (~7 days after injection) limits the efficacy of RIT using mAbs for solid tumour treatment. Prior to selective binding of their receptor targets, the blood circulation of conventional RIT compounds contributes to whole-body irradiation and results in substantial radiation dose to the radiosensitive bone marrow. Protecting the bone marrow from excessive radiation exposure limits

the amount of radioactivity that can be safely injected into a patient, consequently lowering tumour doses and reducing therapeutic efficacy.

To administer the highest possible radiation dose to target tissue and the lowest possible dose to non-target tissue, most of the decay process should occur after the radiolabelled compound has been delivered to the target site and cleared from the blood and normal tissues. Thus, RIT pretargeting methods have been developed which decouple delivery of the radioactivity from that of the mAb. In brief, the mAb is conjugated with a tag or artificial receptor designed to bind with high affinity to a small molecular probe. The tagged mAb is injected and allowed sufficient time to reach maximum uptake at the tumour and clearance from the blood. Then, a small radiolabelled probe is injected that binds rapidly and with high affinity to the "receptor" on the pre-localised mAb, with the remaining unbound fraction excreted rapidly via the kidneys. The outcomes of pretargeting methods are higher radiation dose delivery to the tumour (typically tenfold improvement), increased therapeutic efficacy and minimal dose and toxicity to normal tissues, such as the bone marrow.

Most pretargeting strategies are based on high-affinity biological recognition systems (e.g. mAb/hapten and biotin/avidin), which suffer from immunogenicity-inducing responses as they are recognised by the body's defence system. Such an immune response precludes repeat or dose fractionation treatments of solid tumours, which have demonstrated maximum efficacy for some cancer treatments, such as external beam therapy and chemotherapy. A new pretargeting method has been proposed that uses an unusually rapid organic chemical reaction, instead of biological components, to bind the small radiolabelled probe to the tumour-bound mAb with high affinity. Bertozzi and others have developed biorthogonal reactions using ring-strained cyclo-octene derivatives for biological labelling. The approach is based on the inverse electron demand Diels-Alder reaction between a DOTA-tetrazine analogue (Fig. 3), which demonstrates high thermodynamic and chemical stability with most metals, and a *trans*-cyclo-octene (TCO) (Fig. 3) conjugated to the murine mAb CC49 [22]. This reaction was chosen based on its exceptionally high second-order rate constant of 13,090 ± 80 $M^{1}s^{-1}$ at 37°C in phosphate-buffered saline [22]. CC49 has high affinity to TAG-72, an antigen with limited internalisation and shedding that is over-expressed in a wide range of solid tumours, such as colon cancer [23, 24]. It is hypothesised that, by moving away from biological pretargeting components and instead using an orthogonal chemical reaction, it may be possible to avoid an immune response to allow repeat and/or fractionated treatments and thereby improve therapeutic efficacy.

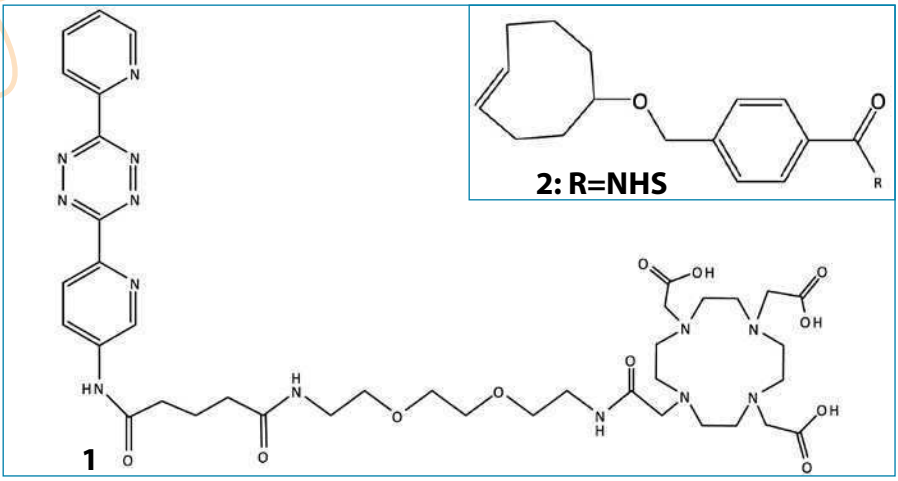

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Figure 3: Structures of bio-orthogonal pretargeting molecules tetrazine DOTA (1) and *trans*-cyclo-octene TCONHS (2)[36]

Initial *in vivo* proof-of-principle imaging studies were performed in mice bearing colon cancer xenografts that were administered 100 µg of TCO-CC49 followed one day later with 3.4 equivalents of ^{111}In-DOTA-tetrazine (40.7 MBq) [22] . The animals were imaged 3 h later, and the tumour was shown to have a 4.2% ID/gram uptake and a 13:1 tumour to muscle ratio. Besides the tumour, the bulk of the activity was found in the bladder, a small amount in the kidneys and some residual in the liver and blood that was attributed to circulating TCO-CC49. Control studies with unmodified CC49 and TCO-modified rituximab, a mAb with no TAG-72 affinity, showed no tumour uptake and supported the antigen-specific binding of TCO-CC49 with ^{111}In-DOTA-tetrazine. Following such promising results, the TCO-CC49/DOTA-tetrazine pretargeting method was further improved (e.g. for dosing and timing of radiolabelled probe) and evaluated against conventionally labelled DOTA-CC49 with the therapeutic radioisotope ^{177}Lu [25]. Using the biodistribution data obtained, the estimated maximum deliverable dose to the tumour without being lethal to bone marrow was nearly five times higher with the pretargeting method at 80 Gy than the sub-therapeutic dose of 17 Gy for the conventional labelling method. If such an approach works out, it could change the way we currently use antibodies and also give greater efficacy.

Nanoparticles

A disadvantage of the conventional bifunctional chelating system is that, at most, only one radioactive molecule per targeting moiety is delivered. This is highly dependent on the specific activity of the radioisotope and on any metal contaminants, as many chelators are not selective but will bind to a number of common metals. A low specific activity and/or high presence of unwanted metal impurities can result in low labelling yields for the desired radioisotope and saturation of the receptor sites if they are present in low quantities. This has been recently demonstrated by Asti et al. [26], who performed a systematic study evaluating the effect of specific activity and incorporation of a variety of metals on a typical DOTATOC clinical formulation. Furthermore, it is often not possible to design a chelator that can stably complex a metal such as an alpha emitter and its daughters upon decay. The release of the daughter can result in unwanted radiation dose to normal tissues and further decrease the effectiveness of the administered dose. For example, DOTA is known to form strong complexes with ^{213}Bi and lead-212 (^{212}Pb); however, decay of ^{212}Pb results in more than a 35% release of ^{213}Bi. Rosenow was the first to investigate using liposomes to stably encapsulate ^{212}Pb and its daughters [26]. It has been demonstrated that 10-nm liposomes result in the retention of ^{213}Bi after the decay of ^{212}Pb [27].

Liposomes have been radiolabelled either by incubating the liposome with the radionuclide of interest, allowing it to incorporate into the lipid bilayer, or by attachment of chelators to the surface, such as DTPA analogues and other familiar chelators. Both of these methods suffer from significant loss of the radionuclides and modification to the surface, adversely impacting targeting vectors. To overcome this, another method has been developed in which the radiometal is first chelated to a lipophilic chelator, which then crosses the bilayer, resulting in entrapment of the radiometal in the aqueous core. Examples include the use of oxime to label ^{111}In and hexamethylpropylene oxime to incorporate ^{99m}Tc. Rhenium-186 (^{186}Re) has been incorporated using the chelator *N*,*N*-bis(2-mercaptoethyl-*N*,*N*-diethylenediamine, which reacts with encapsulated cysteine to secure the ^{186}Re within the core [28]. Fullerenes have been evaluated both in the spherical configuration commonly referred to as Bucky balls and as carbon nanotubes. Their surface allows for the conjugation of targeting vectors, while the inside serves to safeguard the radioisotope from interacting with the biological milieu, thus offering the potential of stably retaining and delivering the radionuclide, something that has not been possible through standard chelation. Ultra-short single-walled carbon nanotubes (SWNT) were first tested filled with iodine-125 (^{125}I). The ^{125}I was loaded and then oxidised to $^{125}I_2$, which demonstrated long retention. The carbon nanotubes were directed

to the lung and no uptake was observed in the thyroid, which is where free iodine in the body is known to collect. This method was also shown to deliver a 10 times higher dose per gram of tissue than is obtainable with other methods.

There is considerable interest in using alpha emitters for treating micrometastases or single cell leukaemias because the path length of the typically used beta-minus particle emitters is hundreds of cell diameters, resulting in damage to healthy normal tissue. With their high LET, alpha emitters are more lethal over a shorter range — it is estimated that only one to three alpha emissions are required to kill a cell versus thousands for beta emitters. Astatine-211 (^{211}At) is a prospective radionuclide for therapy owing to its 7.2-h half-life and its ability to be imaged by SPECT for post-therapy distribution and dosimetry; furthermore, it can be produced on a cyclotron. Astatine, however, has proven to be difficult to complex as carbon–astatine bonds are weak and result in dehalogenation *in vivo*. Consequently, carboranes and nanoparticles have been evaluated [9,10]. Two different types of nanoparticle have been assessed: silver nanoparticles covalently coated with poly(ethylene oxide) and SWNT. Reducing conditions with silver nanoparticles resulted in high labelling yields. SWNT nanoparticles were labelled with $^{211}At^-$ in the same manner as the $^{125}I^-$; initially the anion was loaded and, as with the I, significant leakage was reported; however, upon oxidation with chloramine-T or *N*-chlorosuccinimide, the AtCl molecules were more highly retained, showing labelling yields of 78–93%; these yields are much higher than those previously reported for corborane derivatives, which have demonstrated the highest incorporation, 40–60%. Incubation in water showed retention of 72–85% of the At in the SWNT and 85–93% retention in serum, indicating that these may well serve as stable delivery systems for At.

The alpha emitter actinium-225 (^{225}Ac) holds much promise for targeted alpha therapies as an *in vivo* generator. The nuclear decay of ^{225}Ac (10-day half-life with the emission of four alpha particles) holds the potential to become an ideal radiotherapy system. The 10-day half-life provides sufficient time for complex syntheses and attachment to targeting biomolecules, while the rapid decay and high LET of the daughters' alpha emissions ensure that the therapeutic payload is delivered in the vicinity of the target tissue. Despite the clear benefits of delivering multiple alpha particles from the decay of ^{225}Ac directly to tumour sites, the difficulty of sequestering the alpha-emitting daughters in traditional bifunctional-conjugated targeting modalities leads to release of the daughters and non-specific uptake in non-target organs. This non-target dose negates the advantages of targeted alpha therapy, namely high tumour dose with minimal collateral damage to healthy tissue. In order to harness the potential of multiple alpha particles from

^{225}Ac, nanoparticles are being studied as a way to retain the decay products for delivery to the target site. Initially a multivesicular liposomal carrier was evaluated. The nanoparticles were further tagged with a vector for anti-HER2/*neu* and evaluated in an ovarian cell line. While internalisation was at a high rate, however, retention of the ^{225}Ac was not as high as needed. A lanthanum phosphate nanoparticle ($LaPO_4$ NP) evaluated *in vivo* showed higher retention, and upon complexation with an antibody to lung endothelium, high retention in mouse lung tissue [29]. This design has been further modified to include a gold coating and incorporation of gadolinium into the lanthanum gadolinium phosphate nanoparticles (NPs) for the purpose of retaining both ^{225}Ac and its daughters in an attempt to increase retention. The magnetic gadolinium simplified the separation and purification chemistry. Transmission electron microscopy analysis of $LaGdPO_4$-AuNPs particles showed monodisperse particles with average diameters of 4–5 nm. Radiochemical analysis indicated that $LaGdPO_4$-AuNPs without additional layers sequestered 60.2±3.0% of the first decay daughter of ^{225}Ac, francium-221 (^{221}Fr). The addition of two shells of $LaGdPO_4$ and one shell of Au increased ^{221}Fr retention to 69.2±1.7%, while the addition of four shells of $GdPO_4$ and one shell of Au increased retention to 92±1.0%. Retention of the first decay daughter is essential to minimising normal tissue toxicity. *In vivo* distribution of the nanoparticles conjugated to a monoclonal antibody that targets lung endothelium showed that the nanoparticles exhibited high lung uptake (151%ID/g) [30]. Additionally, the uptake could be blocked by administering cold unlabelled antibody: uptake dropped to 16.8%ID/g. After 24 h the activity was transferred to the liver and spleen due to the reticuloendothelium system. This can be overcome by using clodronate liposomes to reduce reticuloendothelial functioning. The properties of low toxicity and favourable biodistributions make the $LaGdPO_4$-AuNP system a promising platform for targeted alpha therapy with ^{225}Ac.

A major challenge in cancer therapy has been delivery and retention. Due to their size and ability to circumvent some of the hurdles encountered with traditional agents, nanoparticles are promising alternatives. They have unique properties that can be optimised to allow for higher penetration and retention in tumour cells. Unlike traditional medicine, the field of nanomedicine utilises particulate matter with sizes that are the same or smaller than those of cellular components, allowing nanoparticles to cross multiple biological barriers to enhance delivery and retention for optimal treatment. The size similarity to cellular components makes nanoparticles attractive candidates for curing functional abnormalities that instigate disease at the cellular level. Current approaches result in serious adverse side-effects that significantly limit the number of therapeutic molecules that can be delivered to the tumour site, resulting in low efficacy. Effective tumour treatment

requires a high-impact therapeutic payload to destroy cancer cells. Due to the enhanced permeability of tumour cells, nanoparticles can be sized such that they are selectively taken up and retained in cancer cells, this being called the enhanced permeability and retention (EPR) effect [31]. Control over the supply of therapeutic payload enables oncologists to deliver an optimised effective treatment for cancer patients. In this regard, it is important to note that nanoparticulates containing radioactive isotopes provide an opportunity to tune the radioactive therapeutic dose delivered to tumour cells.

The conventional method for delivering radioisotopes has been either to complex them to a targeting molecule for selective delivery, or to form a chemical complex with *in vivo* properties that will effect uptake at the tumour site. Although the conventional method has produced successful treatments, not all metals can be stably complexed by simple ligands. Some, such as gold and silver, have no stable chelation methods; *in vivo* injection results in their release. Others, such as many of the alpha emitters, are released from the compound upon decay and therefore cause significant toxicity, limiting their usefulness. The first nanoparticles developed and translated to the clinic were liposomes. Comprising various platforms, they basically consist of a lipid outer sphere and an aqueous core, which allows the trapping of hydrophobic drugs in the lipid layer and of hydrophilic drugs in the aqueous inner core. Targeting vectors can be attached to the surface to aid in localisation and recognition, as well as ligands for complexing diagnostic radionuclides.

Radioisotopes of gold and other coinage metals have nuclear properties that make them ideal for use in imaging and therapeutic applications. However, their biologically active redox chemistry and lack of stable chelating agents have to date limited their utilisation *in vivo*. They have had application in the area of brachytherapy with the bare metal being encapsulated, but otherwise have been used sparingly, the major concern being the inherent toxicities observed for the free metals *in vivo*. A novel approach is the development of metal nanoparticles that can be derivatised on their surface, allowing for optimisation of biodistribution *in vivo*.

Once a metal nanoparticle is fabricated, its *in vivo* properties can be evaluated and altered by varying such properties as its size, charge, hydrodynamic size, organic surface layer and shape. These can be optimised to enable more favourable uptake and clearance *in vivo*. Furthermore, owing to their high surface area, they can be conjugated with a plethora of agents that can be used for selective targeting, such as peptides and small molecules, to enhance retention in the bloodstream or to enhance clearance. These properties can be optimised through *in vivo* studies to develop lead compounds for imaging and therapy. A major advantage of nanoparticles over the commonly used bifunctional chelator approach is that

the nanoparticle platform allows for a much higher payload delivery, as more than one radioisotope can be incorporated into the nanoparticle, producing a much higher dose delivery even with a low specific activity radionuclide.

Radioisotopes of gold (Au) as shown in Table 1 have attractive nuclear properties that make them ideal for imaging and therapy. Two radioisotopes of gold stand out. ^{198}Au has a moderate enegry beta particle (0.96 keV β^- max), making it a good candidate for therapy, and more than 90% emission of a 412-keV gamma emission that allows for *in vivo* tracking and dosimetry calculation. These properties prompted its use as a brachytherapy agent for prostate cancer. ^{199}Au has a low-energy beta max (0.46 MeV) and emits a 158-keV gamma in 36% yield that is easily detected by SPECT cameras. Additionally, ^{199}Au can be produced carrier-free by neutron irradiation of platinum-198, which produces platinum-199, which decays in 3.2 min to ^{199}Au.

FGold nanoparticles (AuNPs) have been around for quite some time, but their harsh production methods with toxic chemicals have prevented them from being attached easily to biomolecules for evaluation *in vivo*. An improved synthesis has been developed that uses THPAL, a trimeric phosphino alanine, to reduce gold salts in water-containing organics, which coat the surface of the gold nanoparticles and form 12- to 15-nm-sized gold nanoaprticles with a hydrodynamic diameter of 60–85 nm [32]. These methods have been shown to be robust and non-toxic in the non-radioactive form. The methods have been altered to allow for formation of both ^{198}Au and ^{199}Au nanoparticles and also have been shown to permit formation of nanoparticles of other coin metals such as palladium and silver.

Gum arabic-coated gold nanoparticles (GA-^{198}AuNPs) have been the most studied to date [33]. This formulation was initially evaluated for therapeutic efficacy in SCID mice bearing induced human prostate tumours. Different modes of injection were tried, with the intratumoral injection resulting in the highest uptake and retention. The particles were then evaluated for their efficacy in tumour stabilisation in the same tumour models. Tumours received a 70 Gy dose by administering 15 MBq. An overall 82% reduction in tumour volume was noted between the mice receiving the GA-^{198}AuNP compared to controls receiving saline injections. Biodistributions at the end showed a reduction of gold nanoparticles in the tumour, from 70% at 24 h to 19.9%±4.2% ID at 30 days post injection. Clearance was predominantly through the urinary tract and minimum uptake was observed in other organs. Based on these results, these nanoparticles are now being evaluated for their therapeutic efficacy in dogs with spontaneous prostate cancer. Prostate cancer in dogs has been shown to mimic that observed in humans on the functional level as well as in metastatic rate and occurrence. A phase 1 study in dogs starting

at 50 Gy and increasing to 105 Gy has shown no toxicity issues in the dogs and up to a 60% reduction in tumour volume. Based on these results, these nanoparticles are being evaluated in other solid tumours and are being considered for a phase 1 human study.

Conclusion

An expanding role for radiotherapy is unfolding through the recent advances presented here. These novel delivery methods are giving rise to even higher doses to cancer cells while vastly minimising the dose to surrounding normal tissues. These methods are providing more flexibility in the use of radionuclides on the one hand and increasingly personalised treatments regimens on the other. These novel delivery systems are going to make radiotherapy a more exciting option for patients and their physicians.

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kreativ · Mag. Evelyne Sacher-Toporek
Linzer Strasse 358a/1/7, 1140 Vienna, Austria
Phone: +43-(0)1-416 52 27 | Fax: +43-(0)1-416 85 26
Email: office@kreativ-sacher.at | URL: www.kreativ-sacher.at

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Email: hubert.jaud@printandsmile.co.at

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