Chapter 19: Radionuclide Therapy

Slide set of 40 slides based on the chapter authored by G. Flux and Y. Du of the IAEA publication (ISBN 978–92–0–143810–2):

Nuclear Medicine Physics:
A Handbook for Teachers and Students

Objective:

To summarize the most used radionuclide therapies, the specific applications of dosimetry, the contributions of dosimetry and the issues concerning the physicists.

IAEA
International Atomic Energy Agency

Slide set prepared in 2015 by M. Cremonesi (IEO European Institute of Oncology, Milano, Italy)

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19.1 INTRODUCTION

Radionuclide therapy for cancer treatment exists since the 1940s.

Role of the physicist

Radiation protection

Important because high activities of unsealed sources are administered; **regulations** concerning acceptable levels of exposure (medical staff, comforters, public) **vary from country to country**.

Dosimetry

Accurate quantitative imaging after specific corrections allows to use the information about **absorbed dose distribution for clinical benefits**.

Imaging

If a gamma emitter is used → **qualitative or quantitative imaging**.

19.1 INTRODUCTION

- Historically: administration adopted for chemotherapy, with activities fixed / based on patient weight / body surface area.
- **Imaging is possible for many radiopharmaceuticals**; the principles of external beam radiation therapy apply equally to radionuclide therapies.

European Directive 97/43:

"For all medical exposure of individuals for radiotherapeutic purposes exposures of target volumes shall be individually planned; taking into account that doses of non-target volumes and tissues shall be as low as reasonably achievable and consistent with the intended radiotherapeutic purpose of the exposure"

19.1 INTRODUCTION

Internal dosimetry for optimized treatment protocols

Dosimetry studies have demonstrated for both target and normal tissues a wide range of absorbed doses for a same activity

individual variations in **uptake/retention** of a radiopharmaceutical + **individual** variations in **radiosensitivity** ⇨ **variable response** seen with radionuclide therapy

Advances in the quantification of SPECT and PET + patient specific rather than model based dosimetry ⇨ **Personalized patient treatments** according to individual biokinetics

19.2 THYROID THERAPIES

19.2.1 Benign thyroid disease

❑ **Benign thyroid disease** (hyperthyroidism or thyrotoxicosis) most commonly caused by Graves' disease (autoimmune disease causing the thyroid gland to swell). Thyroid toxic nodules are responsible for **overactive thyroid glands**.

❑ **Iodine-131 NaI** (radioiodine) has been used **successfully since the 1940s** and is widely accepted as a treatment for hyperthyroidism.

❑ Limited evidence to compare long term results from surgery, anti-thyroid drugs or radioiodine.

Guidelines

- ⇨ European Association of Nuclear Medicine (EANM)
- ⇨ American Thyroid Association
- ⇨ Individual countries (e.g. Germany, United Kingdom)

IAEA

19.2 THYROID THERAPIES

19.2.2. Thyroid cancer

Thyroid cancer: < 0.5%
of all cancers; 28 000 new cases/year in Europe and USA.

- ❑ Papillary and follicular thyroid cancer (80–90% of cases), anaplastic carcinomas, medullary carcinomas, lymphomas and rare tumours
- ❑ Increased risk: benign thyroid disease, radiation therapy to the neck and poor diet
- ❑ Treatement: **radioiodine** for over 60 years with thyroidectomy for initial ablation of residual thyroid tissue

Metastastatic disease: ≤ 20%

- ❑ Typically lungs, bones, but also liver, brain).
- ❑ Treatment for distant metastases: **further/higher** administrations of **radioiodine**.

Most common application of radionuclide therapy. Complete response rate: 80,90%

19.2 THYROID THERAPIES

19.2.2.1. Treatment specific issues

Standardized vs. personalized treatments: debated since the early 1960s

Fixed activities

- for ablation: **1100 to 4500 MBq**,
- for subsequent therapy: **up to 9000 MBq**.

Published guidelines report their variations but do not make recommendations.

- absorbed doses to remnant tissue, residual disease, normal organs that can vary by several orders of magnitude

Possible undertreatment

risk of dedifferentiation over time, so that tumours become less iodine avid.

Possible overtreatment

unnecessary toxicity: sialadenitis, pancytopenia, radiation pneumonitis/pulmonary fibrosis (patients with diffuse lung metastases), risk of leukaemia (patients receiving high cumulative activities).

19.2 THYROID THERAPIES

19.2.2.1. Treatment specific issues

Personalized activities

- First explored in the 1960s, to **deliver 2 Gy absorbed dose to the blood** and constraints of uptake levels at 48 h.
- Afterwards, approaches based on **whole body absorbed doses** - surrogate for absorbed doses to the red marrow.

Different challenges of dosimetry

- For **thyroid ablations**:
the small volume of remnant tissue can render **delineation inaccurate** → inaccuracy of dose calculation.
- Therapies of **metastatic disease**:
can involve larger volumes, often with **heterogeneous uptake**; lung metastases in particular require careful image **registration** and **attenuation correction**.

19.2 THYROID THERAPIES

19.2.2.1. Treatment specific issues

Stunning?

- ❑ A tracer level of activity may mitigate further uptake for an ablation or therapy: if so, consequences for individualized treatment planning
- ❑ Its extent and existence is being contested
- ❑ A lower extent of uptake may be seen from a **tracer** administration than from a larger **therapy** administration

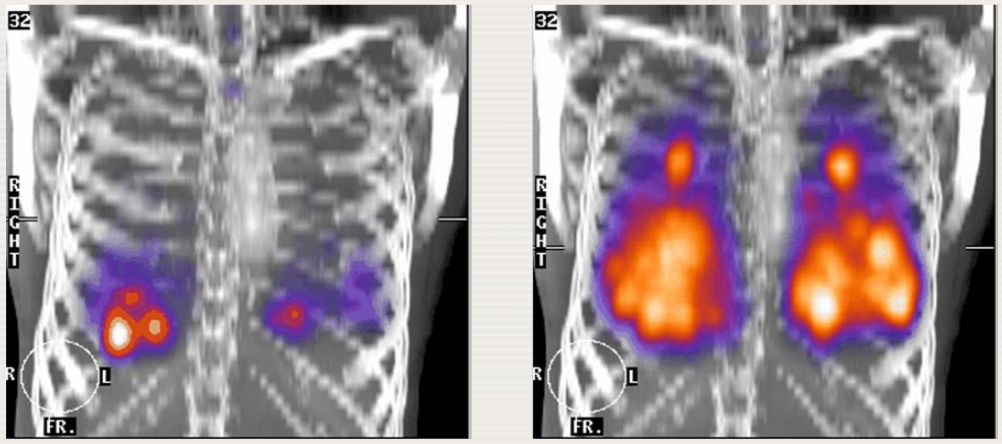


FIG. 19.1. Absorbed dose maps resulting from a tracer administration of 118 MBq ^{131}I NaI (left) and, subsequently, 8193 MBq ^{131}I NaI for therapy (maximum absorbed dose: 90 Gy). The absorbed doses were calculated using 3-D dosimetry on a voxel by voxel basis.

19.2 THYROID THERAPIES

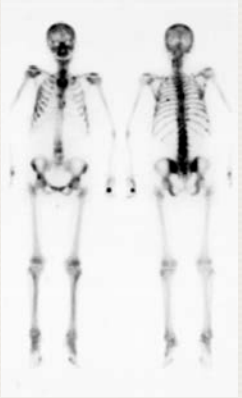
19.2.2.1. Treatment specific issues

Radiation protection

- ❑ Subject to national regulations
- ❑ Patients receiving radioiodine treatment frequently require in-patient monitoring until retention of activity falls to levels acceptable to allow contact with family members and the public.
- ❑ The physicist must give strict advice on radiation protection, taking into account the patient's home circumstances.

19.3 PALLIATION OF BONE PAIN

- Bony metastases arise predominantly from **prostate and breast cancer**.
- **Radiopharmaceuticals** have been established as an effective agent for bone pain palliation for almost **70 years** (^{89}Sr first used in 1942).



wide range of radio-pharmaceuticals

- **^{89}Sr chloride** (Metastron)
- **^{153}Sm lexidronam** (Quadramet)

} commercially available, FDA approval

- **^{32}P**
- **^{186}Re-HEDP**
- **^{188}Re-HEDP**
- **^{117m}Sn and ^{177}Lu-EDTMP**
- **^{223}Ra α emitter**, randomized Phase III clinical trials, FDA approval.

19.3 PALLIATION OF BONE PAIN

Administered activities

- For ^{89}**Sr** and ^{153}**Sm** tend to be **standardized** according to the manufacturer's guidelines.
- For **other agents vary widely** according to local protocols
- **Re-treatments** are generally considered to be **beneficial**, subject to recovery of haematological toxicity
- **Recommendations** for the timing of re-treatments have been made by **EANM** and **IAEA**, although no trials have been performed to assess the optimal timing or levels of administration

19.3 PALLIATION OF BONE PAIN

19.3.1. Treatment specific issues

Ideal treatment protocol

Optimal radionuclide ?

Standardized or based on patient characteristics?

In practice, local logistics and availability…

Radionuclides used

Vary widely in terms of beta emissions

longer range β emitters rationale: to target all of the disease

shorter range β emitters (and α emitters) rationale: to avoid unnecessary toxicity

Vary widely in terms of physical half-lives

there is some evidence suggesting that the longer lived ^{89}Sr can produce a response that takes longer to occur but that is longer lasting

19.3 PALLIATION OF BONE PAIN

19.3.1. Treatment specific issues

Dosimetry challenge

- To assess the **distribution of uptake** in newly formed **trabecular bone** and its geometrical relation to **red marrow** and to **disease**.
- Some models have been developed
- A statistically **significant correlation** has been demonstrated between **whole body absorbed doses** and **haematological toxicity**.

Dosimetry is highly dependent on the imaging properties of the radionuclides.
It could potentially be used to increase administered activities in individual patients.

19.4. HEPATIC CANCER

- Hepatocellular carcinoma is a major cause of cancer deaths.
- **Primary and secondary liver cancers** have been treated with various **radionuclides administered intra-arterially**, based on the fact that while the liver has a joint blood supply, tumours are supplied only by the hepatic artery.

⇒ treatments can be **highly selective**, minimizing absorbed doses to healthy liver and other normal organs.

- This procedure (named radioembolization or selective internal radiation therapy) requires interventional radiology

↪ multidisciplinary nature of radionuclide therapy

- Prior to administration, a diagnostic level of ^{99m}Tc macroaggregate of albumin (MAA) is given to semi-quantitatively estimate the activity shunting to the lung.

19.4. HEPATIC CANCER

Radio-pharmaceuticals / medical devices

- Two commercial products use **^{90}Y**:
- **Theraspheres** (^{90}Y incorporated into small silica beads); **SIR-Spheres** (^{90}Y incorporated into resin). Both received FDA approval.

- **Lipiodol** (mixture of iodized ethylesters of the fatty acids of poppy seed oil), has also been used for intra-arterial administration, radiolabelled with both **^{131}I** and **^{188}Re**, the latter having the benefit of superior imaging properties, a longer β path length and fewer concerns for radiation protection (shorter half-life).

19.4 HEPATIC CANCER

19.4.1. Treatment specific issues

Optimal activity ?

- Usually based on patient **weight** or **body surface area**, arteriovenous **shunting** and extent of **tumour involvement**.
- More rarely, based on estimated **absorbed doses** to non-tumoral liver

  → potential for individualized treatment planning to avoid toxicity
- **Radiobiological approaches** considering biologically effective doses have been used for tentative conclusions that **multiple treatments** may deliver higher absorbed doses to tumours while minimizing absorbed doses to normal liver.

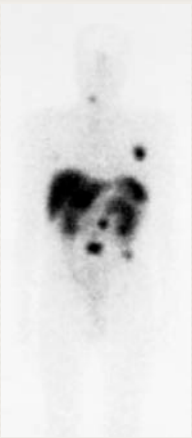
Imaging

- evaluation of lung shunting by ^{99m}Tc MAA scan
- bremsstrahlung imaging for estimate absorbed doses ?

19.5. NEUROENDOCRINE TUMOURS

Neuroendocrine tumours (NETs)

- Arise from cells that are of neural crest origin and usually produce hormones
- **Several types**: phaeochromocytoma, paraganglioma, carcinoid tumours (in appendix, small intestine, lung, kidney, pancreas), medullary thyroid cancer
- tend to be considered as one malignancy, frequently treated with radiopharmaceuticals
  → **similar radiopharmaceuticals**
- differences in radiosensitivity and proliferation
  → **response is variable among diseases**



19.5. NEUROENDOCRINE TUMOURS

Radio-pharmaceuticals

^{131}I-metaiodobenzylguanidine (MIBG)

over 20 years, high uptake and complete responses have been seen

^{90}Y-, ^{111}In- or ^{177}Lu- - peptides

analogues of somatostatin, more recently developed, offer a range of treatment options

Guidelines

EANM, European Neuroendocrine Tumour Society
focusing mainly on procedural aspects

19.5. NEUROENDOCRINE TUMOURS

Administered activities

Recommendations are not given

Can vary from

- **3700 to 30 000 MBq** of **^{131}I-MIBG**
- cumulated of **12 000–18 000 MBq** of **^{90}Y-DOTATOC**

Administrations are often repeated, but **no standardized protocols** for the intervals between therapies.

19.5. NEUROENDOCRINE TUMOURS

19.5.1. Treatment specific issues

No studies directly comparing the effects of the different radiopharmaceuticals

Different radio-pharmaceuticals

different path lengths, imaging properties, toxicity

Risks

^{111}In octreotide

relies on **internalization** and radiation delivered by **Auger emissions**

- **imaging** possible

myelosuppression
higher activities may require stem cell support

Kidney toxicity
another activity-limiting factor

^{90}Y-peptides

can cause irradiation over 1 cm

- images only with **bremsstrahlung**

19.5. NEUROENDOCRINE TUMOURS

19.5.1. Treatment specific issues

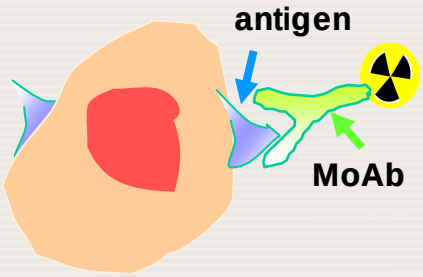
Ideal treatment protocol

- Standardized or personalized? Forefront of debate.
- In practice, **fixed** or modified activities according to patient weight; in some cases, **based on absorbed whole body doses**
- fixed activities → **wide range of absorbed doses** are delivered to tumours and to normal organs

Imaging for dosimetry

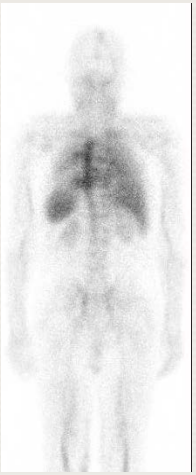
- **^{131}I-MIBG**: must deal with problems resulting from camera **dead time, photon scatter, attenuation.**
- **^{90}Y-peptides**: using low levels of **^{111}In** given either prior to therapy or with therapy administration.
  Bremsstrahlung imaging has been more recently developed

19.6. NON-HODGKIN'S LYMPHOMA



- Arise from haematological tissues
- Most commonly targeted with **radiopharmaceuticals**
- **Several types**: high grade or low grade (growth rate)
- Inherently **radiosensitive**
- Express antigens and can be successfully treated with radioimmunotherapy (RIT) using **monoclonal antibodies** (MoAbs) radiolabelled usually with **^{131}I or ^{90}Y**

^{90}Y Ibritumomab Tiuxitan (Zevalin) and **^{131}I-Tositumomab (Bexxar)** target the B-cell specific CD 20 antigen. Both received FDA approval. **Superior therapeutic efficacy to prior chemotherapies**



19.6. NON-HODGKIN'S LYMPHOMA

19.6.1. Treatment specific issues

Zevalin: internal dosimetry in the trial for FDA approval

- **Absorbed doses** to tumours and critical organs varied by at least tenfold and did **not correlate with toxicity or response**
- **Treatment safe** with the activity prescribed

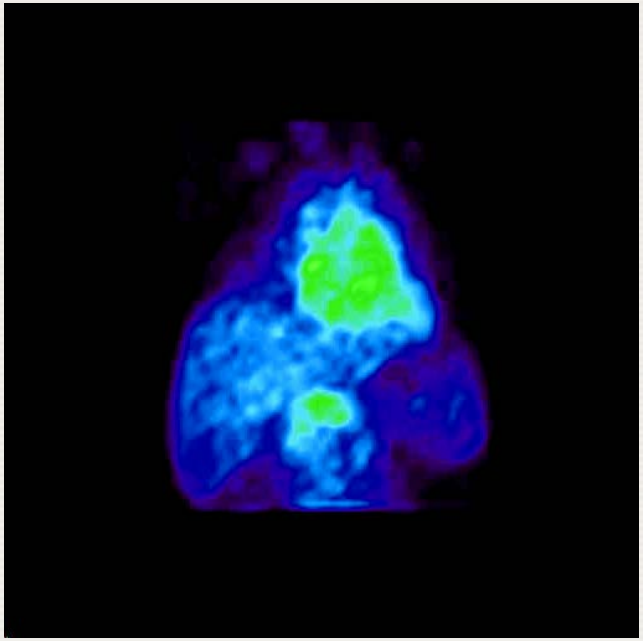
Individualized dose not considered essential. Activity based on patient weight.

But **need for biodistribution** (FDA) prior to therapy using **^{111}In-MoAb** as a surrogate for ^{90}Y-MoA b.

19.6. NON-HODGKIN'S LYMPHOMA

19.6.1. Treatment specific issues

Some studies assess biodistribution and dosimetry based on Bremsstrahlung imaging.



Absorbed dose map (maximum dose: 39 Gy) resulting from 3-D dosimetry of **Bremsstrahlung** data acquired from treatment of non-Hodgkin's lymphoma with **^{90}Y-Ibritumomab Tiuxitan** (Zevalin).

19.6. NON-HODGKIN'S LYMPHOMA

19.6.1. Treatment specific issues

Bexxar: internal dosimetry

bone marrow toxicity is significantly related to dosimetry

Therapy is based on individualizing absorbed doses to bone marrow

Activity determined according to a

whole body absorbed dose of 0.75 Gy,

calculated from three whole body scintigraphy scans.

19.7. PAEDIATRIC MALIGNANCIES

Cancer in children

is rare: **incidence < 130 / million**;
overall relative survival rate of 57

leukaemia and lymphoma: 50% of cases

Radionuclide therapy for children / young people

- **scientific and logistical challenges**, different from adult treatments
- **in-patient care**: increased nursing requirements
- **radiation protection**: role in decisions to allow children to leave hospital, as they frequently have siblings at home

19.7. PAEDIATRIC MALIGNANCIES

19.7.1. Thyroid cancer

Ablation and therapy of thyroid cancer

Performed with **radioiodine** for children, who are considered a high risk group.

There is commonly a **significantly higher incidence of metastatic disease in children than in adults**.

Fatalities can be as high as **25%**, after many years of repeated radioiodine treatments and **high cumulated activities**.
Thus, **potential late toxicity** in children from radionuclide therapy needs to be considered.

19.7. PAEDIATRIC MALIGNANCIES

19.7.2. Neuroblastoma

- malignancy of the neuroendocrine system
- specific to **children** and young people
- inherently **radiosensitive**

Neuro-blastoma

^{131}I-MIBG since the 1980s, particularly for primary refractory or relapsed patients.

Treatments generally palliative, but **complete responses** have been reported.

Recent interest in **radiolabelled peptides**, e.g. **^{177}Lu-DOTATATE**.

19.7. PAEDIATRIC MALIGNANCIES

19.7.2.1. Treatment specific issues

Neuro-blastoma

EANM guidelines: principle of individual treatment of thyroid cancer in children.

German procedure guidelines: administration based on the 24 h uptake of a tracer activity prior to ablation.

Wide variation in treatment protocols:

→ **fixed activities (3700-7400 MBq)**

→ development of quantitative imaging → higher degree of dosimetry **personalized** treatments based on **whole body absorbed doses**

whole body absorbed doses correlate with haematological toxicity

19.8. ROLE OF THE PHYSICIST

Physicist involved in radionuclide therapies: wide range of tasks.

Maintenance of **imaging equipment / computer systems.**

quality controls of the equipment.

Radiation protection and implementation of national legislation.

high activities of unsealed sources → higher responsibility than for diagnostic imaging

Staff are potentially exposed to high levels of radiation of **γ, β, α emissions**.
Careful monitoring must be performed, being aware of national regulations.

Increasing opportunity for development in accurate **quantitative imaging**.

predominantly focused on the radionuclide, with the inclusion of
scatter, attenuation, dead time corrections.

19.8. ROLE OF THE PHYSICIST

Pharmacokinetic analysis

derived from sequential scanning, which requires advice on image acquisition.
It evaluates the inter/intra-patient variations in uptake and retention for understanding and optimizing the use of radiopharmaceuticals (particularly new products).

Accurate **dosimetry calculations** for patient specific treatment planning.

to the tumour and critical organs from a given administration.
They are related to accurate quantitative imaging and analysis; are emerging as no standardized protocols or guidelines exist and are now becoming mandatory for new products.

In house software development to perform absorbed dose calculations.

as there is only limited software available for dosimetry calculations at present.

19.8. ROLE OF THE PHYSICIST

Interpretation and understanding of the **biological relevance of absorbed doses: radiobiology** for radionuclide therapy is not straightforward

It has not been developed as for external beam radiotherapy (EBRT) but is now considerably attracting attention.

Models explaining physiological phenomena of radionuclide therapy have **still to be constructed**, although may be adapted from EBRT models (predominantly based on the linear quadratic model).

There are some **confounding factors** (e.g. relatively low but continuous absorbed dose rates, evidences suggesting that DNA is not the only target causing cell death).

It is likely to become **more complicated** as radiopharmaceuticals are administered with **concomitant** chemotherapy or EBRT and new factors are discovered (e.g. bystander effect, hyper-radiosensitivity)

19.8. ROLE OF THE PHYSICIST

Radionuclide therapy is the only cancer treatment modality that allows imaging of the therapeutic drug in situ

It is the duty of the physicist to capitalize on this by providing the information necessary to enable optimal and cost effective treatment.

19.9. EMERGING TECHNOLOGY

New imaging technology with hybrid scanners

→ significant impact on accuracy of dosimetry from radionuclide therapies

New radiopharmaceuticals

→ growing interest in **α-emitters**, with therapies including **^{211}At** (direct infusion into resected gliomas), **^{213}Bi** or **^{225}Ac** radiolabelled MoAbs (leukaemia), **^{223}Ra** (bone metastases).

Dosimetry for α-emitters remains largely unexplored. Difficulty of localization; need to take into account the emissions of daughter products

more stringent regulatory

→ **more accurate internal dosimetry required**
FDA now requires dosimetric evaluation of new radiopharmaceuticals
Phase I/II clinical trials ascertain absorbed doses delivered to critical organs

19.9. EMERGING TECHNOLOGY

Longer lasting survival

→ critical organ dosimetry will become more important to ensure minimization of unnecessary late toxicity

More strict radiation protection procedures

→ necessary to assess exposure with greater accuracy for patients, families and staff

Options of combined therapies

chemotherapy or EBRT administered concomitantly with radiopharmaceuticals are explored
→ dosimetry based treatment planning will become essential for patient management

19.9. EMERGING TECHNOLOGY

The practice of **internal dosimetry** includes different approaches

- **image** based
- **whole body** based
- **blood** based
- **model** based

- Particular focus at present is on **red marrow dosimetry**, as this is the absorbed dose limiting organ for many therapies.

- **Multi-centre prospective data collection** is crucial to the development of this field, and international networks will be required to accrue a **sufficient number of patient statistics** to enable the formulation of agreed and standardized treatment protocols.

19.10. CONCLUSION

1. Nuclear medicine **physicists** play an increasingly important role in radionuclide therapies, with tasks that include:

   - maintenance of **imaging** and associated **equipment**
   - **radiation protection** and **national regulations**
   - patient specific **treatment planning**
   - internal **dosimetry** and **radiobiological** considerations

2. **Radionuclide therapy** requires a **multidisciplinary approach** involving diverse staff of clinical or medical oncology, endocrinology...

3. There is currently the **need** for **increased training** in this field; **multi-centre networks** will facilitate the exchange of expertise and the gathering of prospective data necessary to advance the field.

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