Chapter 19: Radionuclide Therapy


*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.
19.1. Introduction
19.2. Thyroid therapies
19.3. Palliation of bone pain
19.4. Hepatic cancer
19.5. Neuroendocrine tumours
19.7. Paedriatic malignances
19.8. Role of the physicist
19.9. Emerging technology
19.10. Conclusion
Radionuclide therapy for cancer treatment exists since the 1940s.

**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.

**Role of the physicist**

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”
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
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)
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.

Metastatic disease: ≤ 20%

- 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
- Treatment: radioiodine for over 60 years with thyroidectomy for initial ablation of residual thyroid tissue

- 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

- 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.

**Stunning?**

**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.
Radiation protection

- Subject to national regulations
- Patients receiving radiiodine 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.
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 radiopharmaceuticals:

- $^{89}$Sr chloride (Metastron)
- $^{153}$Sm lexidronam (Quadramet)
- $^{32}$P
- $^{186}$Re-HEDP
- $^{188}$Re-HEDP
- $^{117m}$Sn and $^{177}$Lu-EDTMP
- $^{223}$Ra $\alpha$ emitter, randomized Phase III clinical trials, FDA approval.
19.3 PALLIATION OF BONE PAIN

- 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 $\beta$ emitters
  - rationale: to target all of the disease
- shorter range $\beta$ emitters (and $\alpha$ 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.
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.

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.
Two commercial products use $^{90}\text{Y}$:
- **Theraspheres** ($^{90}\text{Y}$ incorporated into small silica beads);
- **SIR-Spheres** ($^{90}\text{Y}$ 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 $^{131}\text{I}$ and $^{188}\text{Re}$, the latter having the benefit of superior imaging properties, a longer $\beta$ 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?
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
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 radiopharmaceuticals**
- different path lengths, imaging properties, toxicity

**Risks**
- myelosuppression
  - higher activities may require stem cell support
- Kidney toxicity
  - another activity-limiting factor

**111In octreotide**
- relies on internalization and radiation delivered by Auger emissions
- imaging possible

**90Y-peptides**
- can cause irradiation over 1 cm
- images only with bremsstrahlung

IAEA

Nuclear Medicine Physics: A Handbook for Teachers and Students – Chapter 19 – Slide 22/40
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

- **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 $^{111}\text{In-MoAb}$ as a surrogate for $^{90}\text{Y-MoAb}$. 
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 $^{90}\text{Y}$-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

<table>
<thead>
<tr>
<th>Ablation and therapy of thyroid cancer</th>
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<tr>
<td>Performed with <em>radioiodine</em> for children, who are considered a high risk group.</td>
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<td>There is commonly a <strong>significantly higher incidence of metastatic disease in children than in adults</strong>.</td>
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<td><strong>Fatalities</strong> can be as high as <strong>25%</strong>, after many years of repeated radioiodine treatments and <strong>high cumulated activities</strong>.</td>
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<td>Thus, <strong>potential late toxicity</strong> in children from radionuclide therapy needs to be considered.</td>
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19.7.2. Neuroblastoma

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

**Neuroblastoma**

- \(^{131}\text{I-MIBG}\) 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. \(^{177}\text{Lu-DOTATATE}\).
19.7. PAEDIATRIC MALIGNANCIES

19.7.2.1. Treatment specific issues

**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**
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 $\gamma$, $\beta$, $\alpha$ 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.
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)
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.
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
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
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.


