IAEA
International Atomic Energy Agency
*Atoms for Peace*

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Setting the Scene for the Next Decade
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# Radiation protection in radionuclide therapy in the next decade

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## Many names:
## Radionuclide therapy - Targeted radionuclide therapy - Radiopharmaceutical therapy - Therapeutic nuclear medicine - Nuclear medicine therapy

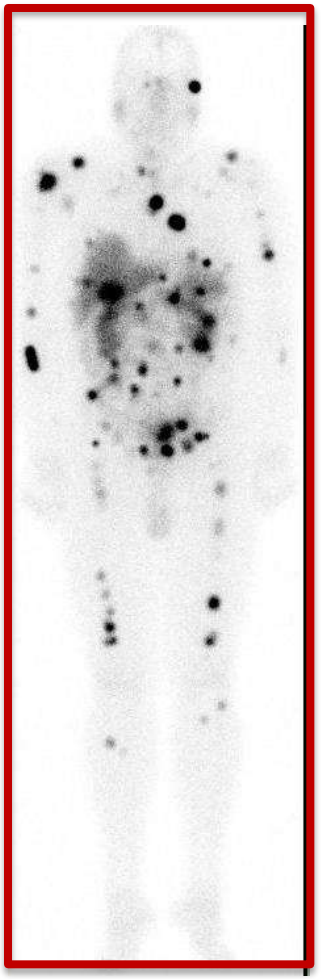
- The biological effects are deliberately sought
- The upper limits of activity are set by the need to avoid damage of healthy tissues or organs (tolerance level, often badly known)
- The lower limits of activity are dictated by the need to exceed the threshold for a beneficial biological effect (either curative or palliative)

Historically, the amount of administered activity was set by clinical experience and protocol and was not patient specific (other than, perhaps, by scaling the activity with body weight)

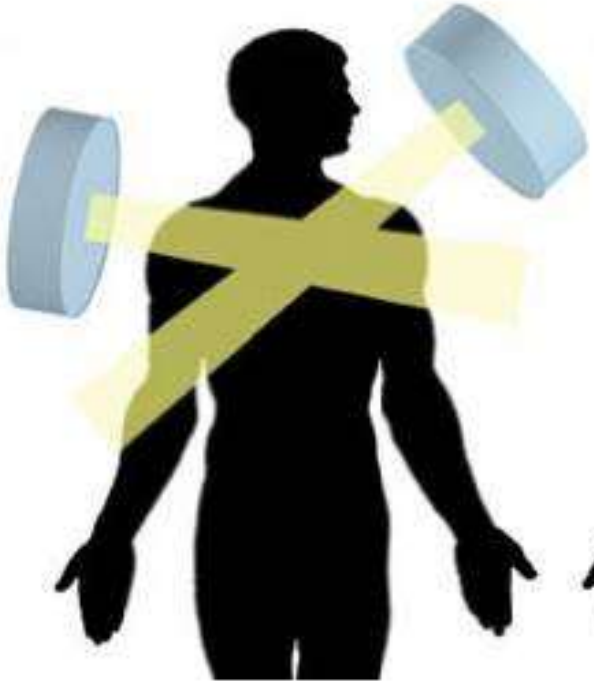
# Targeted therapy (with radiopharmaceuticals)

- Paul Ehrlich postulated the idea of a "magic bullet": if a compound could be made that selectively targeted against a disease-causing organism, then a toxin for that organism could be delivered along with the agent of selectivity (1908 Nobel Prize)

- Potential to cure patients with spread tumour disease (not possible to cure with surgery and/or external radiation therapy and/or brachytherapy)

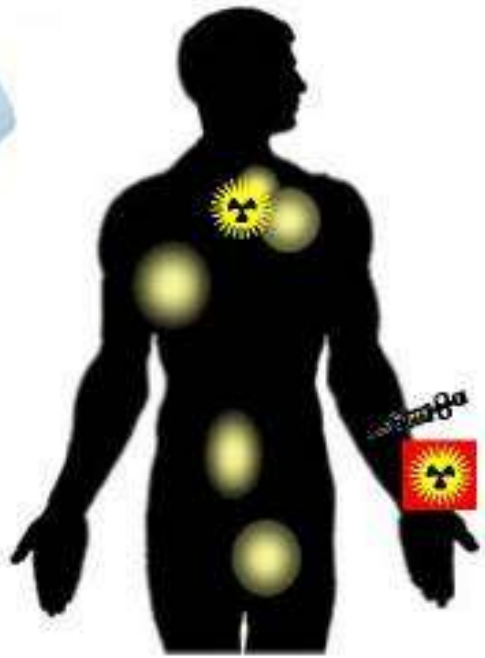


External Beam



Requires knowledge of tumor location

Targeted Radionuclide



Requires knowledge of tumor biology

- Brain Tumor Targeted Radiotherapy:
  - Less toxic effects to normal brain
  - Can be designed for treating small deposits of tumor cells infiltrating normal brain

External beam therapy and targeted radionuclide therapy

Michael Zalutsky, Duke University

# Tumour therapy with radiopharmaceuticals

???

2010

$^{177}$Lu-octreotate, $^{90}$Y-octrotide

2000

$^{131}$I-MAb , $^{90}$Y-MAb

$^{111}$In-octreotide

1990

1980

$^{131}$I-MIBG

1970

1960

1950

$^{131}$I-iodide, $^{32}$P-phosphate

1940

Relatively slow development
Still not the anticipated success

# Nuclear medicine for therapy

**Small (Sweden 2010: 2.8%) in relation to nuclear medicine diagnostic procedures**

**Therapeutic nuclear medicine**

| | |
|---|---|
| • *Hyperthyroidism and thyroid cancer* | *$^{131}$I-iodide* |
| • *Polycytemia* | *$^{32}$P-orthophosphate* |
| • ***Severe pain in metastatic bone disease*** | ***$^{89}$Sr-chloride*** |
| | ***$^{153}$Sm- or $^{177}$Lu-EDTMP*** |
| | ***$^{186}$Re-EHDP*** |
| | ***$^{223}$Ra-chloride*** |
| • ***Tumours (monoclonal antibodies and peptides, receptor specific substances)*** | *$^{90}$Y-Zevalin, $^{131}$I-Bexxar* ***$^{90}$Y-,$^{131}$I-, $^{177}$Lu-, $^{211}$At-MAb*** |
| • *Neuroendocrine tumours* | *$^{131}$I-MIBG* |
| | *$^{90}$Y-, $^{177}$Lu-octreotate* |
| • ***Liver tumours*** | ***$^{90}$Y-microspheres (SIRT)*** |
| • ***Rheumatoid arthritis*** | ***$^{90}$Y-colloide, -silicate*** |

## Mechanisms for targeting

### Normal metabolism

- $^{131}$I-iodide
- $^{32}$P-phosphate
- $^{90}$Sr-chloride
- $^{223}$Ra-chloride

### Tumour seeking molecules

- $^{90}$Y-MAb, -peptide
- $^{131}$I-MAb, -peptide
- $^{177}$Lu-peptide
- $^{211}$At-MAb
- $^{123,\ 131}$I-MIBG

### Particles

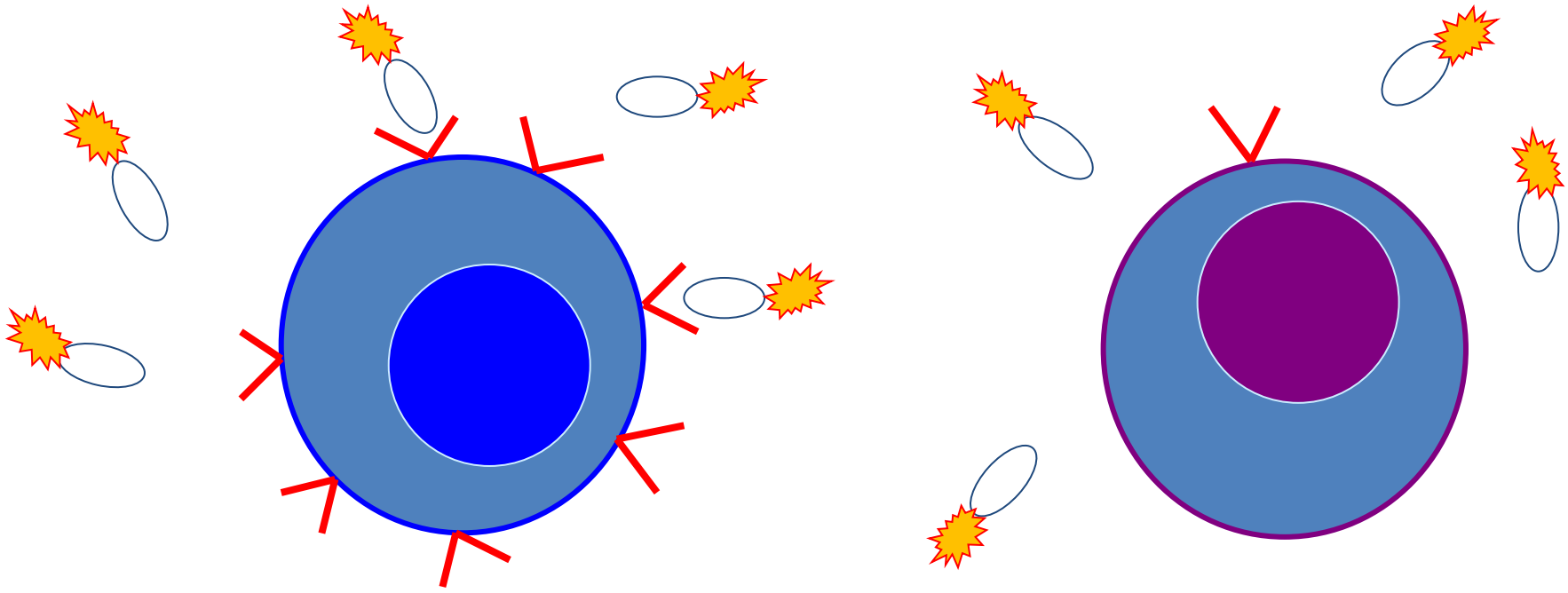
- $^{32}$P-colloid
- $^{90}$Y-colloide, -silicate,
  -microspheres

*MAb 150 000 Da*
*Somatostatin (polypeptide) 2 000 Da*
*MIBG 100 Da*

# Therapy with radiopharmaceuticals

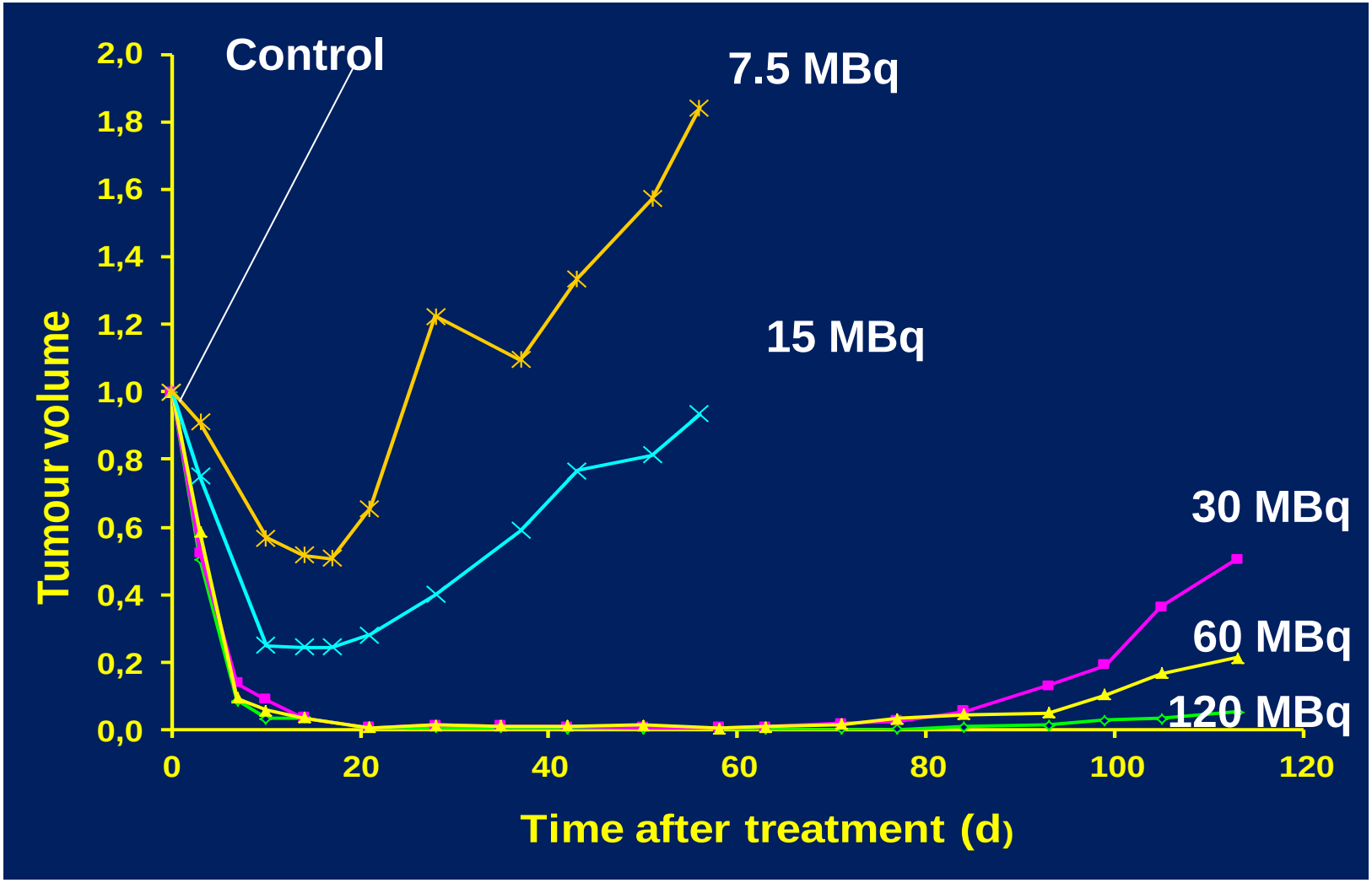
## Tumour cell

## Normal cell



= target (antigen, receptor, transporter, …) more frequently expressed on the surfaces of tumour cells than on normal cells

# Therapeutic effects on carcinoid tumour GOT1 on nude mice using $^{177}$Lu-octreotate




Kölby et al. Br J Cancer 2005

# Clinical experience from therapy with $^{177}$Lu-DOTA-octreotate Problems

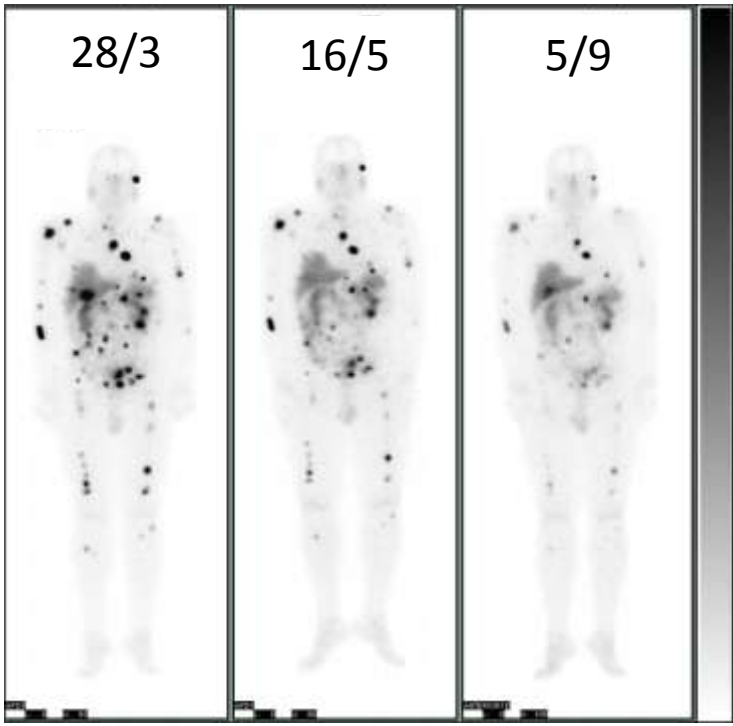
Low cure rate in patients treated with radiolabelled SS analogues

- Complete remission 0-2 %
- Partial remission ca 10-30 %

Usually very mild toxicity
Nephrotoxicity is dose-limiting
(Bone marrow toxicity)

Almost all studies use a standard protocol

- "Similar for all clinics"
- "Similar for all patients"




i.e., no individualized treatment

# Properties of some radionuclides used in radionuclide therapy

| Radio-nuclide | Half-life | Emission | $E_\alpha$ MeV | $E_{\beta max}$ MeV | $E_\gamma$ keV |
|---|---|---|---|---|---|
| $^{32}P$ | 14.3 d | β | | 1.71 | |
| $^{67}Cu$ | 2.58 d | βγ | | 0.58 | 185 |
| $^{89}Sr$ | 50.5 d | β | | 1.49 | |
| $^{90}Y$ | 2.67 d | β | | 2.28 | |
| $^{125}I$ | 60.0 d | Auger $e^-$ | | | (X:27) |
| $^{131}I$ | 8.04 d | βγ | | 0.61 | 364 |
| $^{153}Sm$ | 1.95 d | βγ | | 0.81 | 103 |
| $^{165}Dy$ | 2.33 d | βγ | | 1.29 | 95 |
| $^{169}Er$ | 9.5 d | β | | 0.34 | |
| $^{177}Lu$ | 6.71 d | βγ | | 0.50 | 208 |
| $^{186}Re$ | 3.77 d | βγ | | 1.08 | 137 |
| $^{188}Re$ | 20.0 h | βγ | | 2.1 | 155 |
| $^{198}Au$ | 2.7 d | βγ | | 0.96 | 411 |
| $^{211}At$ | 7.2 d | α | 6.8 | | |
| $^{212}Bi$ | 1.0 h | α | 7.8 | | |
| $^{223}Ra$ | 11.4 d | αβγ | 26 | | 82, 154, 270 |

# Back to patients

As quantitative imaging and dosimetry is seldom performed, many treatments are given blind

Imaging-based predictive and patient-specific dosimetry has slowly grown (mainly within research projects)

Achieved by pretherapy administration of a photon-emitting diagnostic radiopharmaceutical expected to have the same biodistribution as the particle-emitting therapeutic radiopharmaceutical

It the therapeutic radiopharmaceutical also emit photons in addition to particles, a diagnostic activity can be administered and imaged

# Typical activity and absorbed dose per administration

| Substance | Typical adm. activity [MBq] | Tumor dose [Gy] | Critical organ 1 [Gy] | Critical organ 2 [Gy] |
|---|---|---|---|---|
| $^{90}$Y-Zevalin® | 1000 | | Kidneys: 2.4 | Red marrow: 2.7 |
| $^{131}$I-Bexxar® | 3000 | | Thyroid: 8.1 | Kidneys: 5.9 |
| $^{153}$Sm- EDTMP | 2500 | | Bone surfaces: 17 | Red marrow: 3.8 |
| $^{89}$Sr - chloride | 150 | | Bone surfaces: 2.6 | Red marrow: 1.7 |
| $^{177}$Lu -octreotate | 7400 | 200 | Kidneys: 23 | |
| $^{32}$P- phosphate | 185 | | Red marrow: 2.0 | Bone surfaces: 2.0 |

# Need for action with regard to patients (I):

- Dose planning before therapy. No therapy without dose planning!
- Individual patient biokinetics
- Individual dose calculations
- Dose distributions within organs and tissues
- Same protocol for different hospitals and clinics for measurements of biokinetic data and for dosimetry
- A formalism for the addition of doses from nuclear medicine therapy, external radiation therapy and brachytherapy for patients receiving various treatments (Biologically Effective Dose, BED)

# Need for action with regard to patients (II): Women of fertile ages (15-55 years)

## 1. Careful check of pregnancy

## 2. Careful check of breast feeding


# Foetal thyroid

## Warning! Radioactive iodine. Especially therapy!

**Radioiodine administered to a woman, after 10-13 wk post-conception → the fetal thyroid concentrates the iodine which crosses the placenta.**

| Doses to the fetal thyroid per activity administered to the mother (mGy/MBq) Watson EE, 1992 | | | | |
|---|---|---|---|---|
| Gestational Age (mo) | I-123 | I-124 | I-125 | I-131 |
| 3 | 2.7 | 24 | 290 | 230 |
| 4 | 2.6 | 27 | 240 | 260 |
| 5 | 6.4 | 76 | 280 | 580 |
| 6 | 6.4 | 100 | 210 | 550 |
| 7 | 4.1 | 96 | 160 | 390 |
| 8 | 4.0 | 110 | 150 | 350 |
| 9 | 2.9 | 99 | 120 | 270 |

# Also diagnostics…

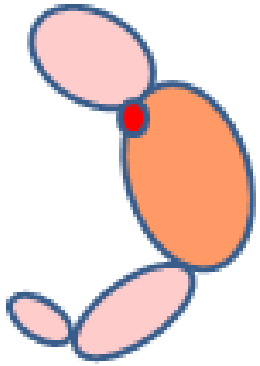
3 months - birth

*Example:*

*Dose to thyroid:*

150-300 mGy

300-600 mGy



*Mean dose to foetus:*

0,4-0,6 mGy

0,03-0,04 mGy

30 MBq $^{123}$I to mother

0.55 MBq $^{131}$I to mother

# Thyrotoxicosis-treatment

500 MBq $^{131}$I-iodide at18 weeks. Recognised after 10 days

Foetal mean whole body dose: 100 mGy

Thyroid dose: 600 Gy

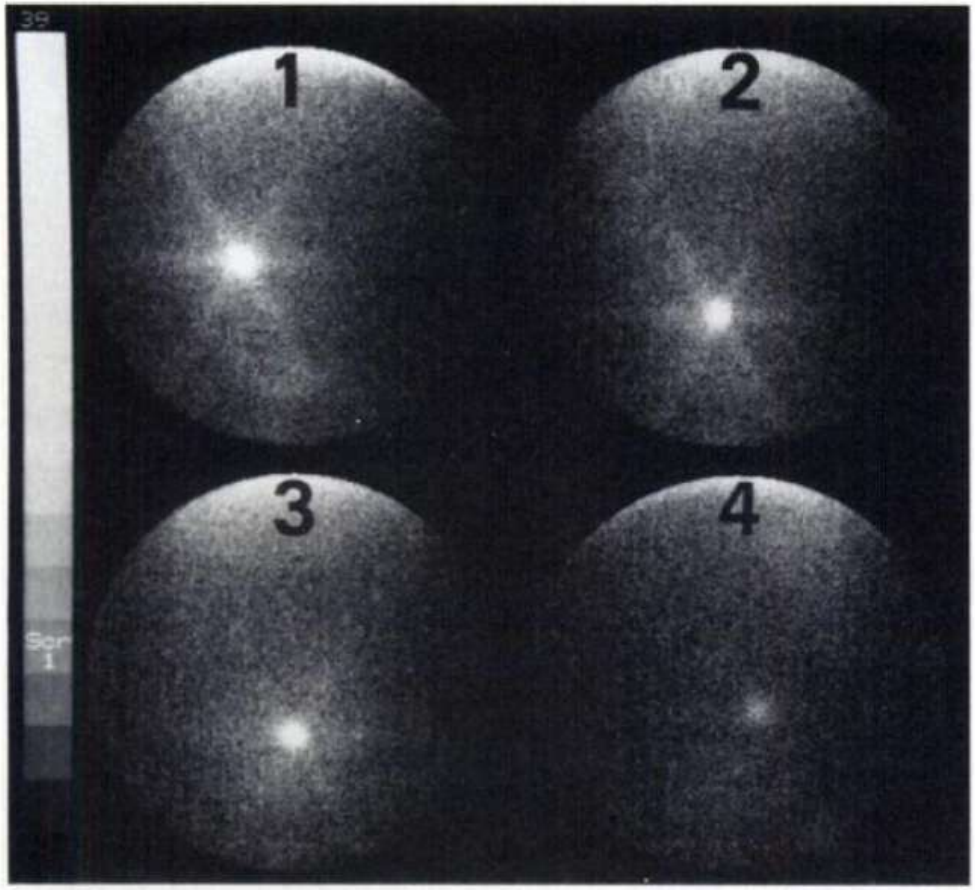



**FIGURE 1.** Gamma camera images of the abdomen of the woman 10 (panel 1), 11 (panel 2), 12 (panel 3) and 13 (panel 4) days after administration of radioiodine, showing the fetal thyroid.

Berg G et al., JNM 39, 357-361, 1998

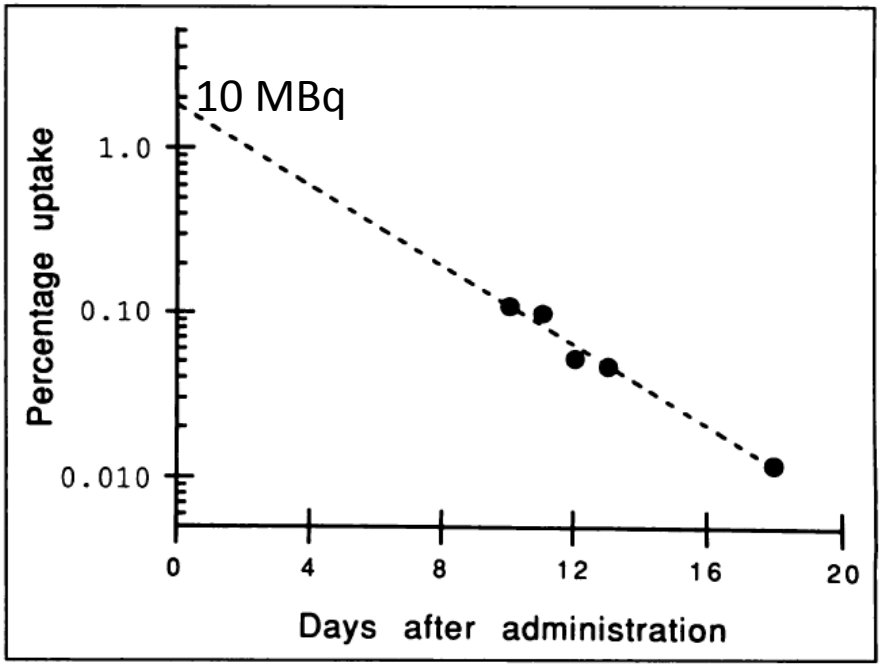



**FIGURE 2.** Uptake values in the fetal thyroid gland measured from the scintigraphic images 10, 11, 12, 13 and 18 days after radioiodine administration.

# Treatment of thyroid cancer

3700 MBq at18 weeks

Recognised after 25 days

Foetus: Whole body dose: 700 mGy

Thyroid dose: 300 Gy

**Berg G et al., Acta Oncol 47, 145-149, 2008**

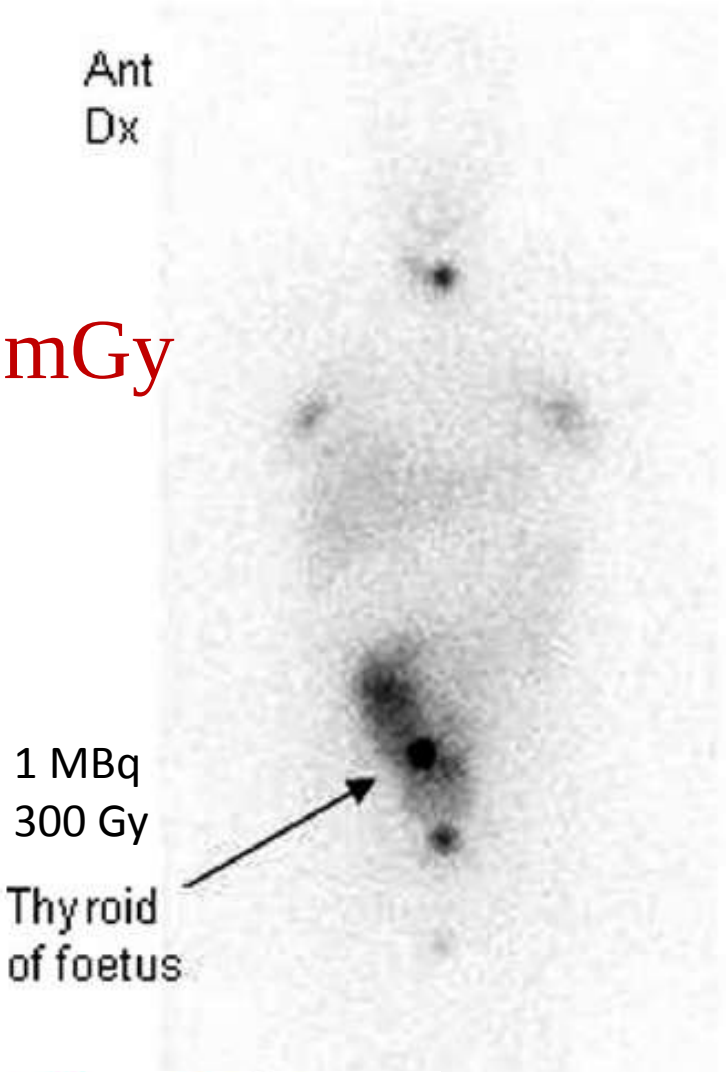



Figure 1. Gamma camera examination 6 days after administration of 3 700 MBq 131-I in Case 2. Note small uptake in the thyroid bed, uptake in mammary glands, and uptake in the fetal thyroid and fetal body/amniotic fluid.

A routine pregnancy test from urine can be used to confirm a suspected pregnancy, but can obviouly not be used to completely rule out a pregnancy

## How can we practically deal with this?

The possibility of pregnancy should be considered in all women of fertile ages before therapy with radionuclides or cytostatics, and a clinical investigation aimed at excluding a pregnancy undertaken on wide indications.
Make serum β-hCG (β-human chorionic gonadotropin) test + ultrasound examination.

**Need for action with regard to staff:**

Finger doses can be high > 500 mSv per year.

Monitoring needed.

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**Comforters and caregivers** (often family members)

**Members of public**

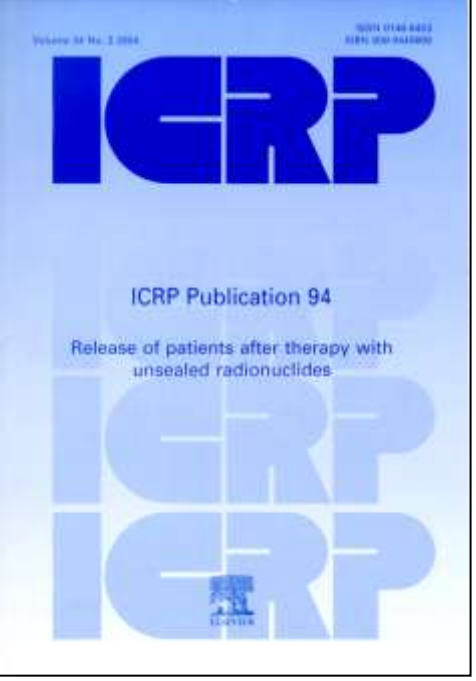
The main source of exposure is patients who have received radioiodine treatment for hyperthyroidism and thyroid cancer

# Release criteria
# Patients and excreta

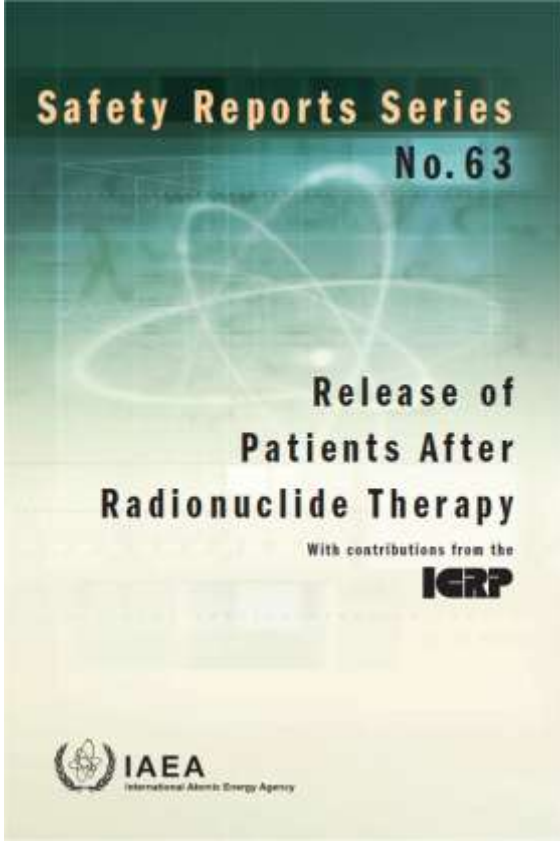
- To hospitalize the patient or not? Release criteria after radionuclide therapy
  - Number of days?
  - Amount of activity?
- Storage tanks for patient excreta or direct release?

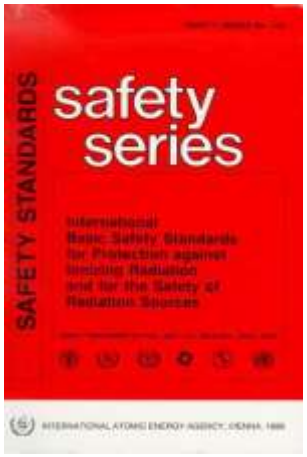
## The purpose is

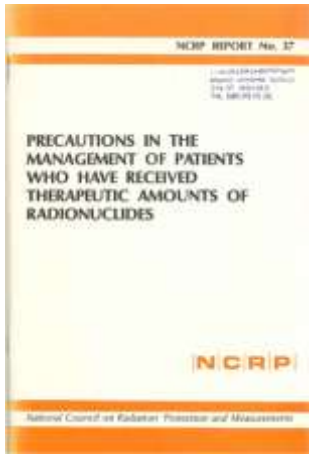
**Members of public**- should remain within dose limits
**Comforters and caregivers** (often family members) –
- dose constraints









**Release of patients after radionuclide therapy**

*The British Journal of Radiology*, 72 (1999), 121–125 © 1999 The British Institute of Radiology

## Patients leaving hospital after administration of radioactive substances

Working Party of the Radiation Protection Committee of the British Institute of Radiology, including representatives of the Health and Safety Executive, the Department of Health, the Environment Agency and the National Radiological Protection Board

*The British Institute of Radiology, 36 Portland Place, London W1N 4AT, UK*

TABLE 9. SOME NATIONAL MAXIMUM ACTIVITIES FOR PATIENT RELEASE

| Radionuclide | Retained activity (MBq) | | | | | |
|---|---|---|---|---|---|---|
| | USA | Germany | Sweden | Finland | Japan | Australia |
| | NRC [47], NUREG-1556 [68] | [64] | [65] | [71] | [67] | [45] |
| Phosphorus-32 | [a] | | 1200 | | | 1200 |
| Strontium-89 | [a] | | | | 200 | 300 |
| Yttrium-90 | [a] | | 1200 | | 1200 | 4000 |
| Iodine-131 | 1200[b] | 75 | 600 | 800 | 500 | 600 |
| Samarium-153 | 26 000 | | | | | 4000 |

[a] Value not given because of minimal exposure of the public.
[b] Historic value prior to change in approach to that based on 5 mSv. See Annex II.

IAEA, 2009

# ICRP Publication 94

Decision to hospitalize or release a patient should be determined on individual basis.

It should consider factors such as

- Residual activity in the patient
- Patient's wishes
- Occupational and public exposure
- Family considerations
- Cost
- Environmental aspects

# ICRP Publication 94/ IAEA 2009

- **Dose constraint of few mSv/episode for care givers**
- **Dose constraint of few mSv/episode should not apply to infants, young children and casual visitors. Instead they should be subjected to public dose limit of 1 mSv/yr**

TABLE 5. DOSE CONSTRAINTS PER EPISODE FOR DIFFERENT CATEGORIES

*(adapted from ICRP 94 [2] and based on a rationale developed in the EU [10])*

| Type of person/caregiver | Reason for dose constraint (e.g. risks or habits) | Dose constraint (mSv) |
|---|---|---|
| Third person (not carer) | A fraction of the dose limit for the public | 0.3/episode |
| *Family and close friends:* | | |
| Pregnant women | Protection of the unborn child | 1/a |
| Children up to two years old | Close physical contact with parents | 1/a |
| Children between three and ten years old | Same risk as that for unborn child | 1/episode |
| Children older than ten and adults up to 60 years old (average population) | Two to three times lower risk than that for younger children. Certain recommendations for partners not to be applied when comforting very ill hospitalized patients | 3/episode |
| Adults older than 60 years | Three to ten times lower risk than that for the average population | 15/episode |

IAEA, 2009

# Releases to the environment

***ICRP Publication 94:***
Radionuclides released into modern sewage systems are likely to result in doses to sewer workers and the public that are well below public dose limits

”Storing the urine of patients following radioiodine therapy appears to have minimal benefit”
ICRP recommendations do not require urine to be stored.

Holding tanks are not practical because of costs, exposure of hospital staff and because significant proportions of discharges occur after patient release (more and more patient treated as out-patients)

Information for
Health Professionals
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# Caregivers



## 1. What are the radiation risks for relatives and caregivers after discharge?

After discharge, the patient may be independent and able to carry on a normal life. In some cases however, the patient will need care and assistance with daily tasks such as mobility and feeding. It is the patient's family, or an external caregiver such as a community nurse, who would be providing this care.

International bodies such as the IAEA and ICRP provide guidance on radiation dose limits to both radiation workers and the general public. Within these limits, there are allowances for this situation.

The ICRP states that "medical exposure is confined to exposures incurred by individuals as part of their own medical diagnosis or treatment and to other exposures ... incurred knowingly and willingly by individuals in the support and comfort of patients undergoing diagnosis or treatment."

The IAEA further requires that the effective dose to any comforter or visitor (i.e. caregivers and family) should be unlikely to exceed 5 mSv during the period of the patient's treatment. For children, the level should be less than 1 mSv/yr.

The various national and international discharge guidelines are designed to provide compliance with these recommendations.

Page Top ↑

## 2. What if there are pregnant persons near, or living with, the patient?

If the patient has been treated with a gamma-emitting radionuclide, it may be advisable for pregnant women to either not visit the patient for a week following discharge, or to remain at a distance of at least one meter for this period of time.

In cases where this is an important consideration, it should be included in the specific therapy discharge guidelines.

Thank you for listening!

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