MEDICAL PHYSICS IN THE BALTIC STATES 2019
14TH INTERNATIONAL CONFERENCE "MEDICAL PHYSICS IN THE BALTIC STATES 2019", 7-9TH OF NOVEMBER

Radiation safety in high-dose radiopharmaceutical therapy

[1,2]Sören Mattsson and [1]Martin Andersson

[1]Medical Radiation Physics, Lund University/Skåne University Hospital, Sweden and [2]Department of Physics, Kaunas University of Technology, Lithuania

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Radiopharmaceutical therapy

Neuroendocrine tumors

^{131}I-mIBG

^{90}Y-, ^{177}Lu-peptides

^{68}Ga- for imaging

Hepatic tumors

Selective internal radiotherapy (SIRT)

^{90}Y-microspheres

Lymphomas (NHL)

^{90}Y-ibritumomab tiuxetan (Zevalin)

^{111}In- for imaging

Intraperitoneal therapy (ovarian ca)

^{211}At-labeled mAbs

Prostate cancer

^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer.

^{225}Ac-PSMA-617

^{68}Ga- for imaging

Thyroid diseases

^{131}I-iodide

Polycythaemia vera and essential thrombocythaemia

^{32}P-phosphate

Skeletal metastases - Bone pain

$^{223}RaCl_2$, ^{89}SrCl and ^{153}Sm-EDTMP (^{186}Re-HEDP, ^{188}Re-HEDP, ^{117m}Sn-DTPA, ^{177}Lu-EDTMP)

Joints

Treatment of arthritis (radionuclide synovectomy)

The ultimate goal is
Dosimetry guided personalized therapy

This can be done by combining diagnosis and therapy to enhance the efficacy and safety of procedures to an individual patient. **Thera**peutic + diag**nostic** = Theranostic

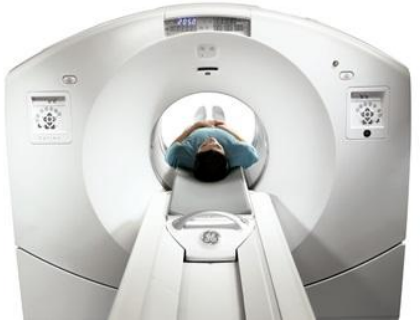
Imaging
Tumour uptake? (Yes/No)
Tumour and normal tissue uptake and retention
Dose planning

↓

Radiopharmaceutical therapy

↓

Imaging
Tumour and normal tissue uptake and retention
Dosimetry



PET/CT

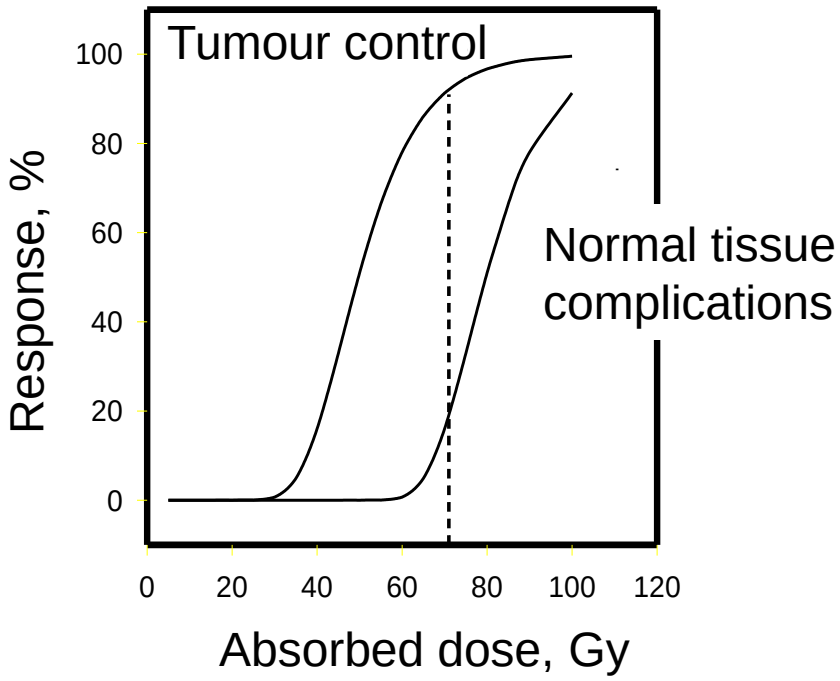
SPECT/CT

Examples from current clinical practise

Treatment of	Imaging with γ- or β^+-emitters	Treatment with β^-- or α- emitters
Thyrotoxicosis and thyroid cancer	^{123}I- (^{124}I-), ^{131}I-iodide	^{131}I-iodide
Non-Hodgkin's lymphoma	^{111}In-ibritumomab tiuxetan (Zevalin)	^{90}Y-ibritumomab tiuxetan
Neuroendocrine tumors	^{68}Ga-dotatate ^{68}Ga-(^{64}Cu-, ^{18}F-) peptides	^{177}Lu-dotatate ^{90}Y- or ^{177}Lu-peptides ^{213}Bi-peptides
Metastatic or treatment-resistant prostate cancer	^{68}Ga-PSMA	^{177}Lu-, ^{225}Ac- or ^{213}Bi-PSMA

Tumour control/Normal tissue complications

- The use of radiopharmaceuticals for therapy of various tumours is increasing (new radionuclides, tracer molecules and application techniques)
- The goal of all radiation therapy is to optimize the relation between the probability for tumour control and normal tissue complications



Radiation safety aspects specific for radiopharmaceutical therapy

- The exposure situation in nuclear medicine diagnostics and therapy is more complex than in x-ray imaging and external beam radiation therapy
- The radiation source exposes individuals before as well as after the diagnostic or therapeutic procedure
- Reported occupational exposure levels suggests great variability between work tasks and facilities
- The group of individuals influencing the exposure and being exposed is wide

ANNALS OF THE ICRP

PUBLICATION 140

Radiological Protection in Therapy with Radiopharmaceuticals

VOLUME 48 NO. 1, 2019 ISSN 0146-6453 • ISBN 9791526434982

New!

Authors on behalf of ICRP
Y. Yonekura, S. Mattsson, G. Flux, W.E. Bolch, L.T. Dauer, D.R. Fisher, M. Lassmann, S. Palm, M. Hosono, M. Doruff, C. Divgi, P. Zanzonico

First published September 30, 2019
https://doi.org/10.1177/0146645319838665

Contents

Key issues

- Improve dosimetry in the individual patient
  - Radiation absorbed dose to target (tumor) and normal healthy tissues
  - Should be estimated prior to therapy using a trace-labelled diagnostic administration or post-therapy on the basis of a retrospective assessment of the administration

- Improve quality of therapy with radiopharmaceuticals
  - Learn from external RT
  - Need systematic approach for treatment planning, monitoring the effect, and archiving the data

Dosimetry is a key issue

Individual absorbed dose estimates should be performed
for treatment planning and for post administration verification of doses to tumours and normal tissues.

Need to improve dosimetry (To reach the same standard as in external radiotherapy and brachytherapy)

To foresee the effects on the tumour

To estimate risk to "organs at risk, OAR"

Red bone marrow for most therapies
Kidneys for peptide therapy
Liver for mIBG
Lung for metastatic thyroid ca therapy

To estimate long term effects

Is it sufficient to calculate mean doses to OAR with basic assumptions and 'population' dosimetry? (Standard phantoms, mean doses etc.)?

Yes, if looking for rough estimate of dose for protection
No, if considering short or long term toxicity

Population-based medicine

- I-131 NaI for thyroid remnant ablation (fixed activities):

  O'Connell *et al* (Radiother Oncol 1993) 7 – 3500 Gy

  Sgouros *et al* (J Nucl Med 2004) 1.2 – 540 Gy

  Flux et al (EJNM 2010) 6 – 570 Gy

- Y-90 Zevalin for NHL (15 mCi / kg)

  Wiseman *et al* (Cancer 2002)

  Red marrow 0.3 – 1.2 Gy

  Absorbed tumour dose 0.6 – 243 Gy

- I-131 mIBG for neuroblastoma (555 MBq / kg):
  Matthay *et al* (JNM 2002)

  Tumour absorbed doses: 3-305 Gy

- Y-90 DOTATOC for neuroendocrine tumours

  Bodei *et al* (EJNM 2004)

  Kidneys 6 - 46 Gy

  Marrow 0.2 – 1.9 Gy

Courtesy of dr Glenn Flux,
Joint Department of Physics,
Royal Marsden Hospital &
Institute of Cancer Research,
Sutton, Surrey, UK

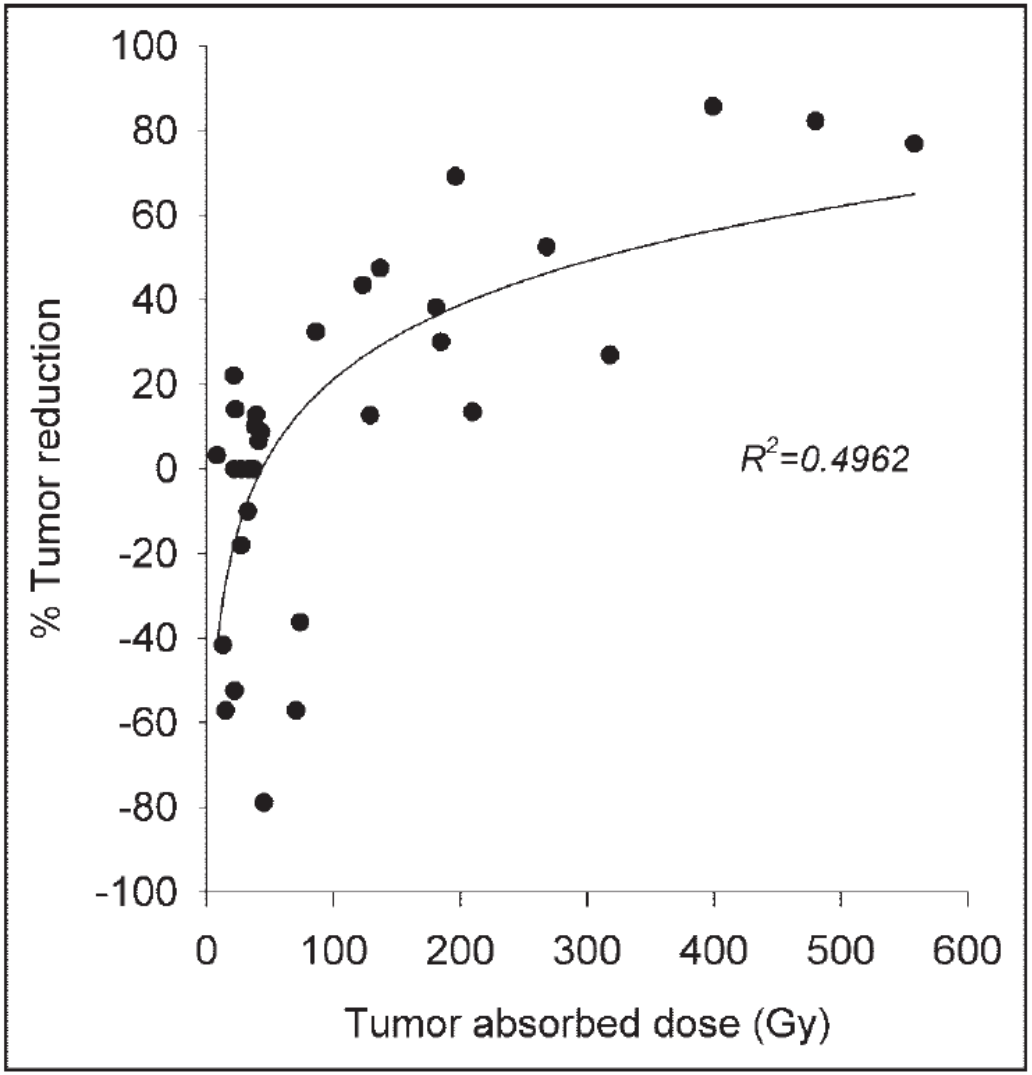
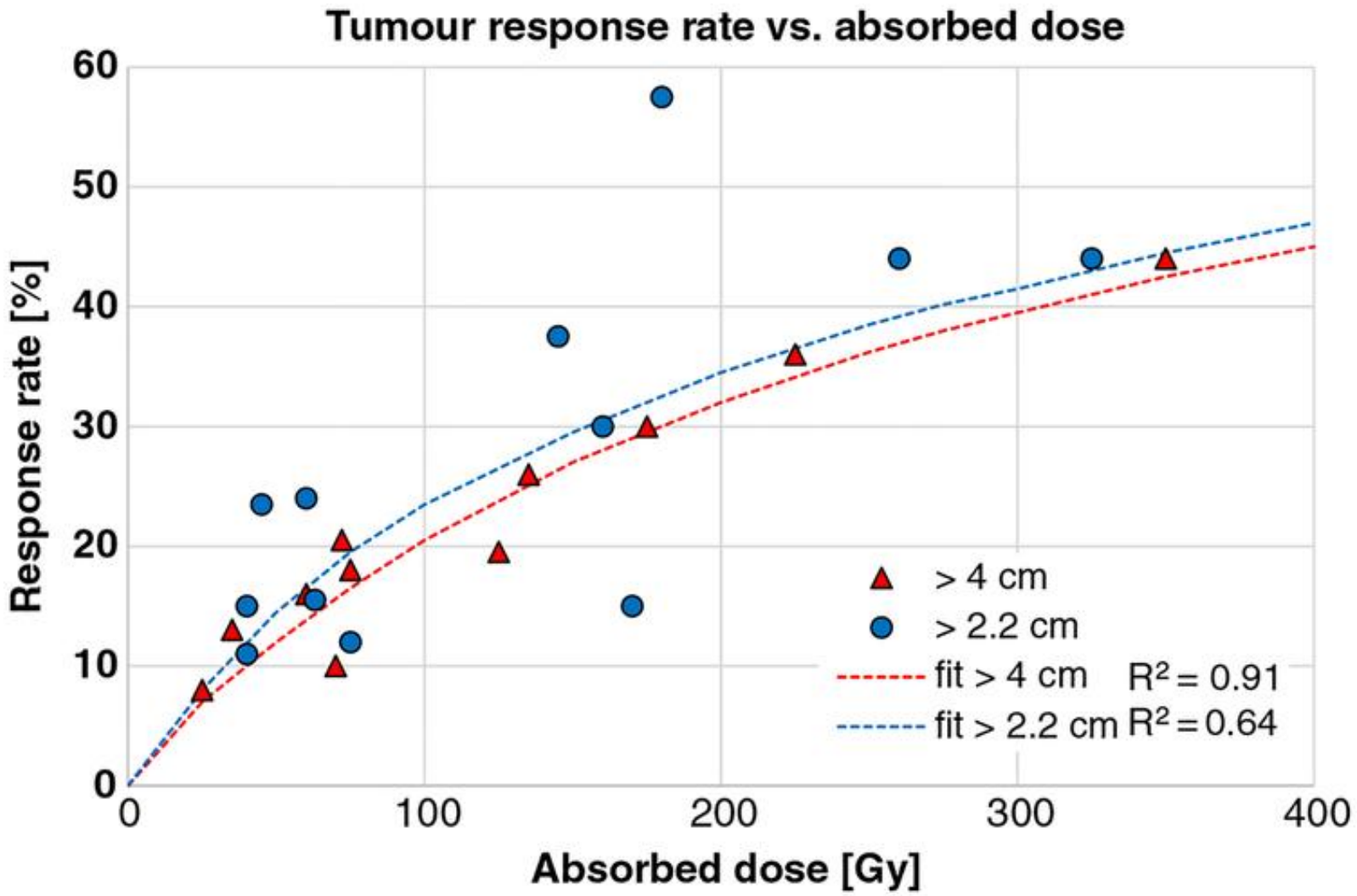


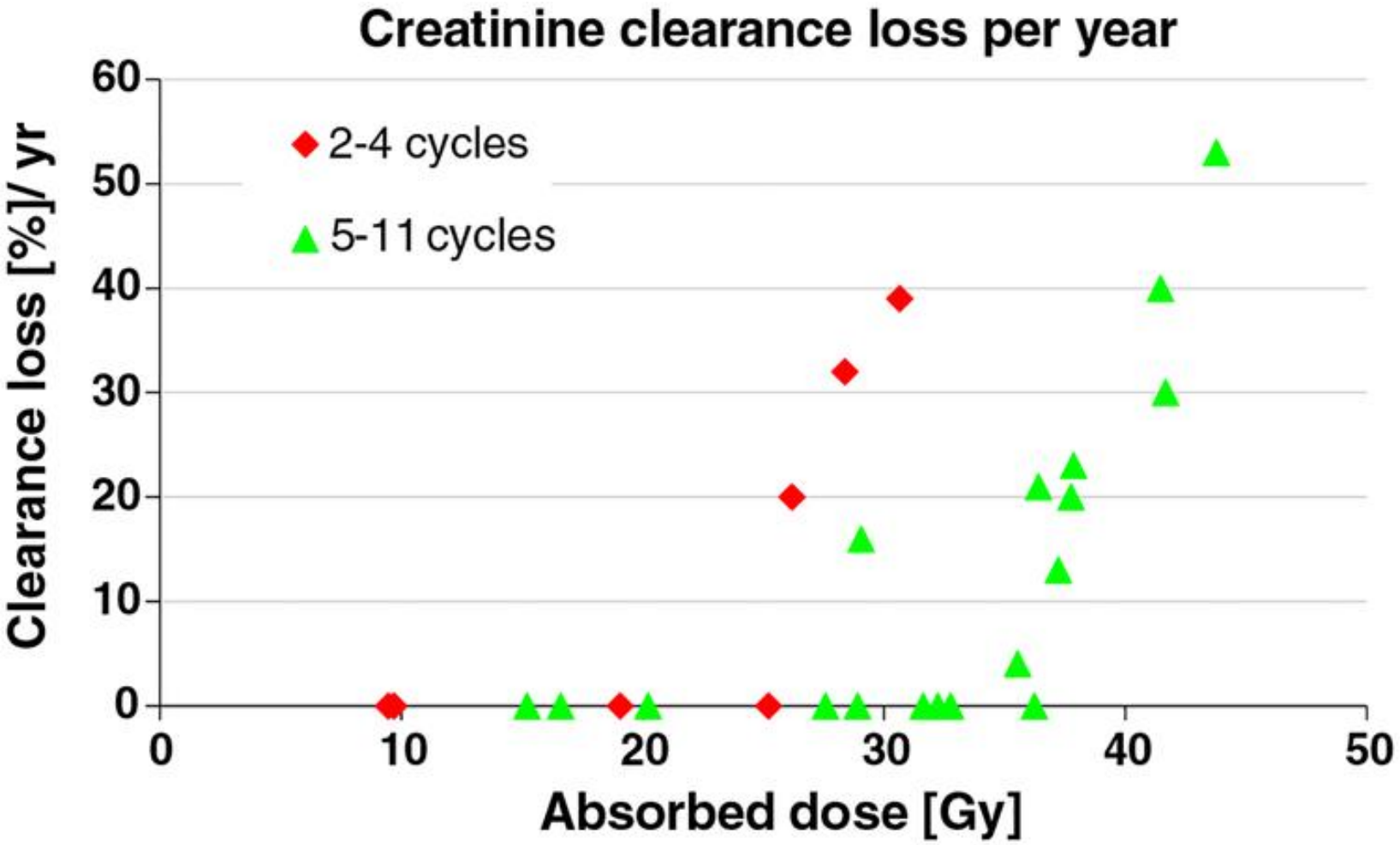
FIGURE 3. Tumor dose–response relationship in 13 patients treated with ^{90}Y-DOTATOC. Tumor volumes were assessed by CT before and after treatment. Tumor dose estimates were derived from CT scan volume measurements and quantitative ^{86}Y-DOTATOC imaging performed before treatment. Data were further computed using the MIRDOSE spheric model.

Pauwels et al.,
J Nucl Med 46, 92–98, 2005



Tumour response in relation to tumour absorbed dose for all lesions evaluated with a diameter >2.2 cm (*blue circles*) and for lesions with a diameter >4.0 cm (red triangles). Adapted from Ilan et al. J Nucl Med 56, 177–182, 2015

From Cremonesi et al., EJNMMI 45(13), 2426–2441, 2018



Creatinine clearance loss as a function of cumulative absorbed dose to the kidneys for 2 to 4 cycles (*diamonds*) and 5 to 11 cycles (*triangles*). Patients receiving therapy in a higher number of cycles experienced creatinine clearance loss at higher absorbed doses. Data derived from the study by Bodei et al. EJNMMI 35, 1847–1856, 2008

From Cremonesi et al., EJNMMI 45(13), 2426–2441, 2018

When absorbed dose estimates can´t be performed

In radiopharmaceutical therapy there are patients or situations where the absorbed dose to the target volume cannot be calculated or reliably predicted for technical or practical reasons

- Metastatic lesions may not be measurable
- There may be too many lesions with different uptake
- The molecule used in the tumour pre-treatment dosimetry may have limited power to predict the absorbed dose of the therapeutic agent during treatment

The next best alternative is to base therapy planning on the maximum tolerable absorbed dose to nontarget organs or tissues

Pregnancy and breast-feeding

Special consideration should be given to pregnant women and children exposed to ionizing radiation. Pregnancy is contraindicated in radiopharmaceutical therapy, unless the therapy is life-saving.

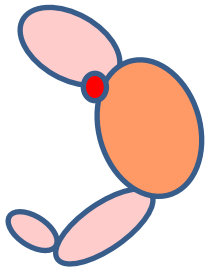
Breast feeding should be discontinued in patients receiving radiopharmaceutical therapy.

Warning! Pregnancy and radioactive iodine

- Radioiodine administered to a woman, after 8-10 weeks post-conception ➡ the foetal thyroid concentrates iodide which crosses the placenta

Examples:	*Mean dose to the foetus:*	*Dose to the foetal thyroid:*
Administration:		
a) 30 MBq $^{123}I^-$ to the mother	a) 0.3 mGy	a) 300 mGy
b) 0.4 MBq $^{131}I^-$ to the mother	b) 0.1 mGy	b) 300 mGy
c) 500 MBq $^{131}I^-$ to the mother	c) 100 mGy	c) 600 Gy (!)

- High foetal thyroid doses from radioiodide can result in permanent hypothyroidism that without treatment results in severe intellectual deficit and short stature



Thyrotoxicosis-treatment 500 MBq at 18 weeks

Detected 10 days after administration

Foetus: Mean absorbed dose: 100 mGy. Foetal thyroid dose: ≈ 600 Gy.

Risk for severe physical and mental retardation due to deficiency of thyroid hormones

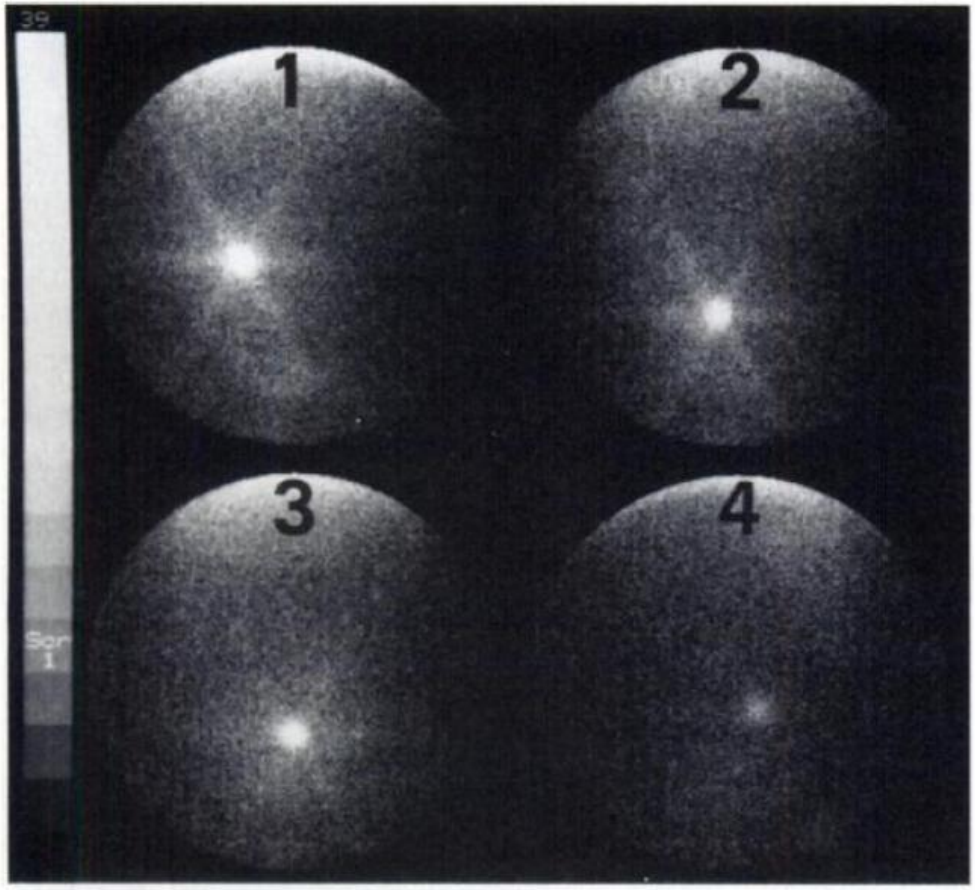


FIGURE 1. Gamma camera images of the abdomen of the woman 10 (panel 1), 11 (panel 2), 12 (panel 3) and 13 (panel 4) days after administration of radioiodine, showing the fetal thyroid.

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

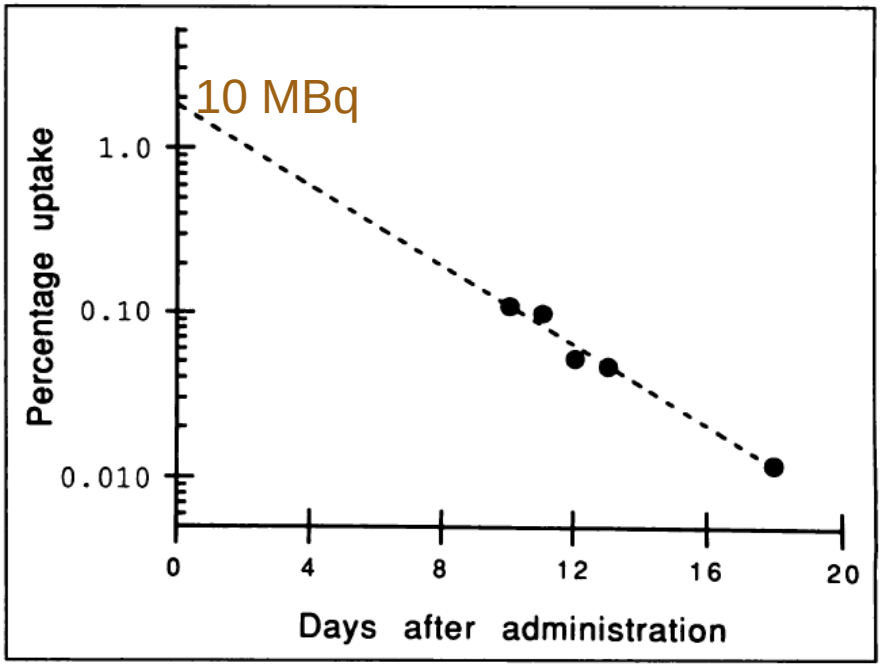


FIGURE 2. Uptake values in the fetal thyroid gland measured from the scintigraphic images 10, 11, 12, 13 and 18 days after radioiodine administration.

Treatment of thyroid cancer

3700 MBq at 18 weeks.
Foetus: Whole body dose: 700 mGy
Foetal thyroid dose: 300 (260-2 000) Gy
Foetus didn´t survive.

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

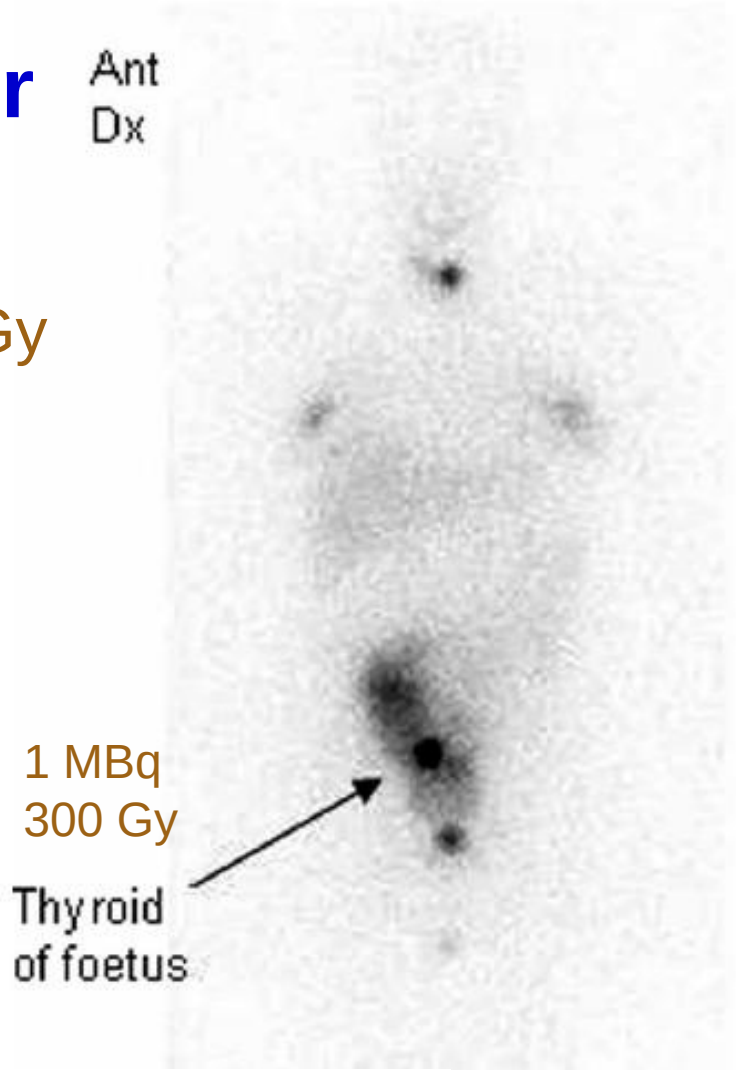


Figure 1. Gamma camera examination 6 days after administration of 3 700 MBq 131-I in Case 2. Note small uptake in the thyroid bed, uptake in mammary glands, and uptake in the fetal thyroid and fetal body/amniotic fluid.

How should we handle this in the clinic?

- Despite investigation of possible pregnancy, it still happens that pregnant women are treated, either because of incorrect information or because the pregnancy is at such an early or late stage that a conventional pregnancy test (urine β-hCG) is not positive. Instead, serum β-hCG should be analyzed, in addition to an abdominal/vaginal ultrasound examination
- Perhaps, it would be best to administer therapies on the basis of the 10-day rule, modified as required after detailed questions about the patient´s menstrual history

If a pregnant woman is treated …?

If pregnancy is discovered within 12 h of radioiodide administration, prompt oral administration of stable potassium iodide (60-130 mg) to the mother can reduce foetal thyroid dose This may need to be repeated several times

Foetal dose can be reduced through maternal hydration and encouraging voiding of urine

Termination of pregnancy?

- Termination of pregnancy at foetal doses of less than 100 mGy is **NOT** justified based upon radiation risk
- At foetal doses in excess of 500 mGy, there can be significant foetal damage, the magnitude and type of which is a function of dose and stage of pregnancy
- At foetal doses between 100 and 500 mGy, decisions should be based upon individual circumstances after information about
  - » - Risk of serious harm to the foetus
  - » - Increased risk of cancer later in life

Good dosimetry also gives a possibility to estimate long term risks

- The goal is to cure patients and the population of cancer survivors continues to grow
- There is a need to understand the long-term health of this population (cancer, non-cancer effects, hereditary effects)
- “Second primary malignancies” are a leading cause of morbidity and mortality among cancer survivors

Risk for secondary cancer

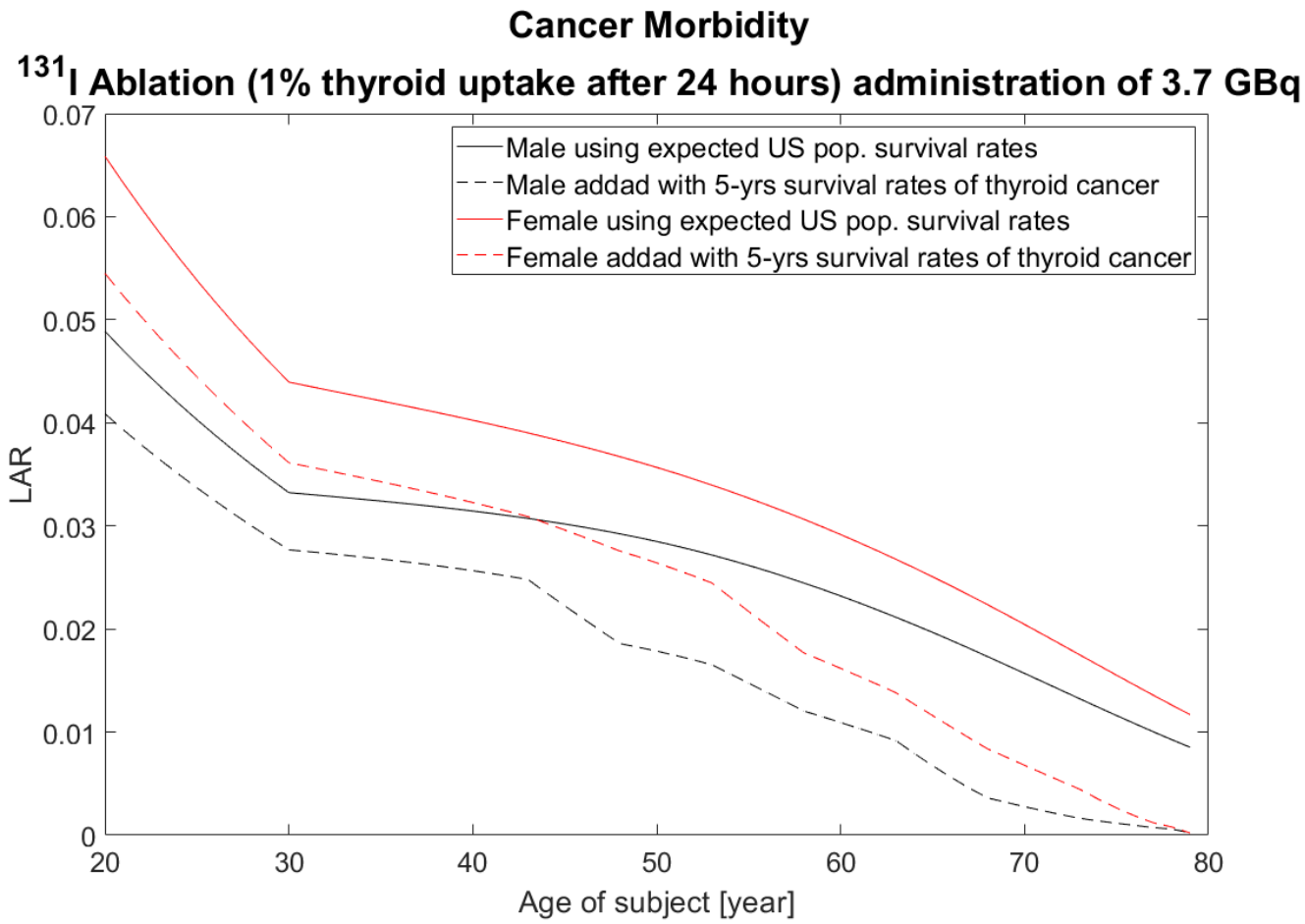
- The risk for secondary cancer development from external radiotherapy is investigated extensively
- Less is known about the radiation-induced cancer risk from radiopharmaceutical therapy
- Absorbed dose, dose distribution and dose rate differs between external and molecular radiotherapy

Methods to evaluate secondary cancer risk

- **Epidemiological observations**
  - Cohort studies.
  - Case-control studies

- **Estimations using risk coefficients from radiation epidemiological data in general**
  - (Effective dose)
  - Lifetime attributable risk (LAR) for allowing explicit accounting of the age, gender, diagnosis and organs at risk regarding secondary cancer

Treatment of thyroid cancer using 3.7 GBq ^{131}I-iodide



Organ/ Tissue (adult male)	Absorbed dose for 3.7 GBq, mGy
Brain	70
Kidneys	740
Liver	190
Lung	180
Red bone marrow	170
Salivary glands	990
Stomac wall	2 400
Urinary bladder wall	540

Risk estimates for patients undergoing radionuclide therapy, have to take into account both the age of the patient at exposure, and his/her life-expectancy post therapy. These may be used to inform Practitioners so that they can be considered as part of the Justification and Consenting processes.

Andersson et al. , Phys Med Biol, 2017

Thank you for listening!

soren.mattsson@med.lu.se

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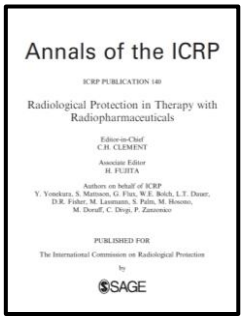

Summary and recommendations

- The increasing use of radiopharmaceuticals for cancer therapy promises new treatment options for patients.
- The challenge for all radiation therapy is to optimize the ability to treat cancer successfully (tumor control probability) against potential adverse effects and normal tissue complications. Radiopharmaceutical therapy provides opportunities to maximize the therapeutic index, a measure of both efficacy and safety.
- In radiopharmaceutical therapy, the absorbed dose to an organ or tissue is governed by the individual patient biokinetics (uptake, retention, and clearance), which may vary widely from one patient to another. Measurements of radiopharmaceutical biokinetics provide essential information needed for internal dose assessment.
- Due to biokinetic differences, personalized dosimetry must be performed for each patient. In principle, a fully personalized approach based on patient-specific measurements can ensure treatment with an appropriate activity level without exceeding normal organ and tissue toxicity thresholds.

Red marrow dosimetry

Possibly the most difficult dosimetry to perform accurately. Can be obtained from

- Direct sampling.
- Imaging.
- Evaluation from blood doses.
- Whole-body dosimetry?

Courtesy of dr Glenn Flux

Whole-body dosimetry

- Set up: counter above patient bed.
- Easy to perform
- Ward staff, carers can take measurements
- Many sample points are possible

Courtesy of dr Glenn Flux

Excess absolute cancer risk

Y-90 DOTATATE to a 47-yrs male patient (adm 3400 MBq)