# PATIENT EXPOSURE AND ADVERSE RADIATION EFFECTS FROM DIAGNOSTIC & THERAPEUTIC NUCLEAR MEDICINE PROCEDURES

*International Experience*

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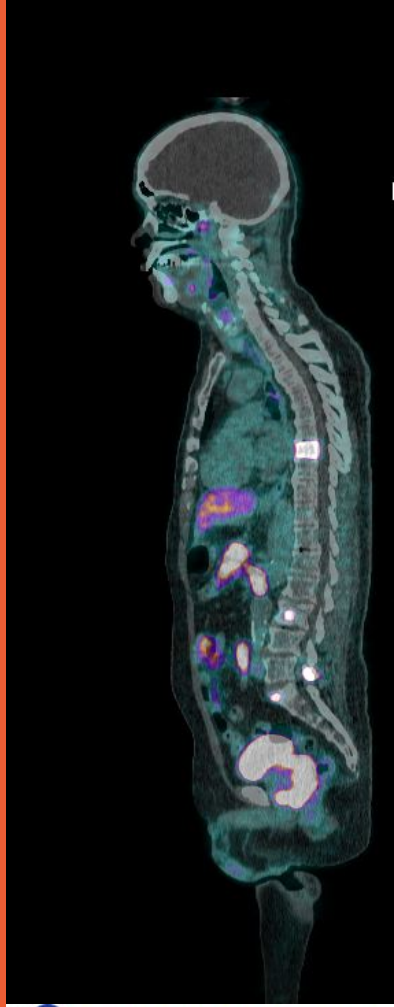
AUSTRALIA

THE UNIVERSITY OF SYDNEY



SYDNEY VITAL
TRANSLATIONAL CANCER RESEARCH

# An exciting time for Nuclear Medicine…

## Diagnostic Imaging

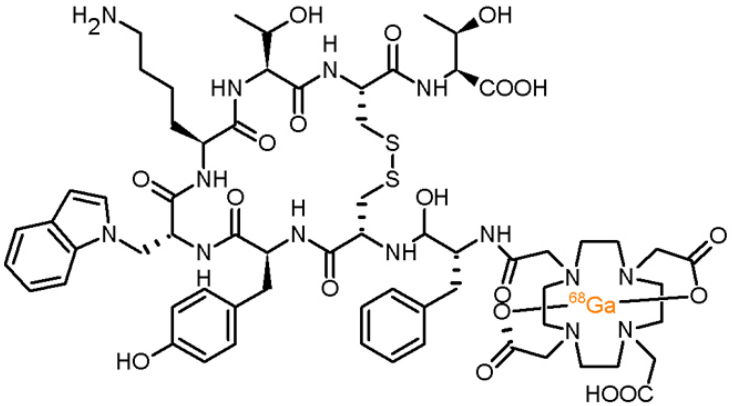
- Great advances in peptide radiochemistry with radiometals (e.g., $^{68}$Ga, $^{64}$Cu, $^{89}$Zr) for PET
- New devices: PET/MRI, solid state detectors, SiPMTs

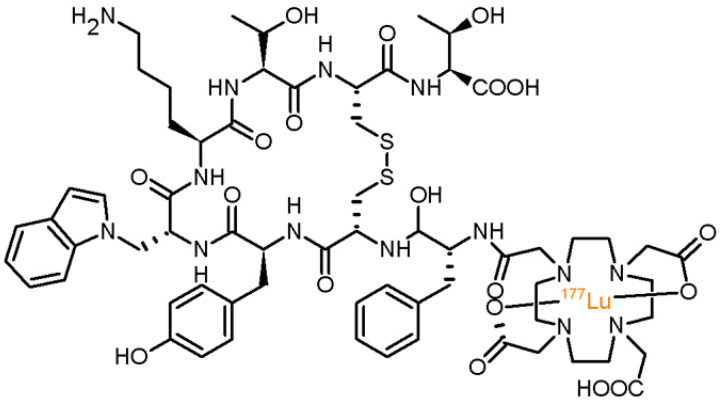
## Therapeutics

- Great advances in peptide radiochemistry with radiometals (e.g., $^{177}$Lu, $^{67}$Cu, $^{90}$Y) for therapy
- New therapies: Metastatic NETs, Metastatic Prostate Ca, Metastatic Pancreatic AdenoCa

**WE ARE ENTERING THE ERA OF THERANOSTICS**

# THERANOSTICS (THERApy & diagNOSTICS)




Diagnostic

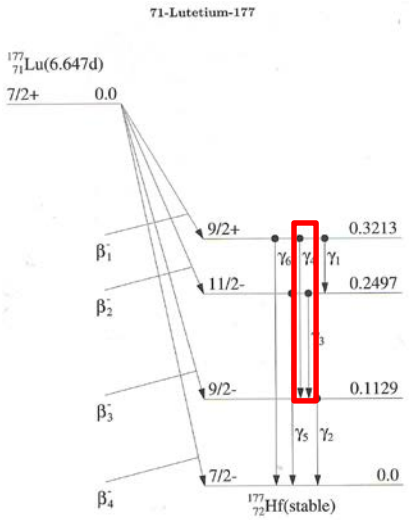
[$^{68}$Ga]DOTATATE

Therapy

[$^{177}$Lu]DOTATATE

# THERANOSTICS – Neuroendocrine Tumours (NETs)


| Time after injection (hrs) | 0.5 | 2.3 | 20.8 | 92.9 |
|---|---|---|---|---|
| Radioactivity retained (MBq) | 6378 | 2745 | 997 | 484 |



# 2018 *Society of Nuclear Medicine* Image of the Year

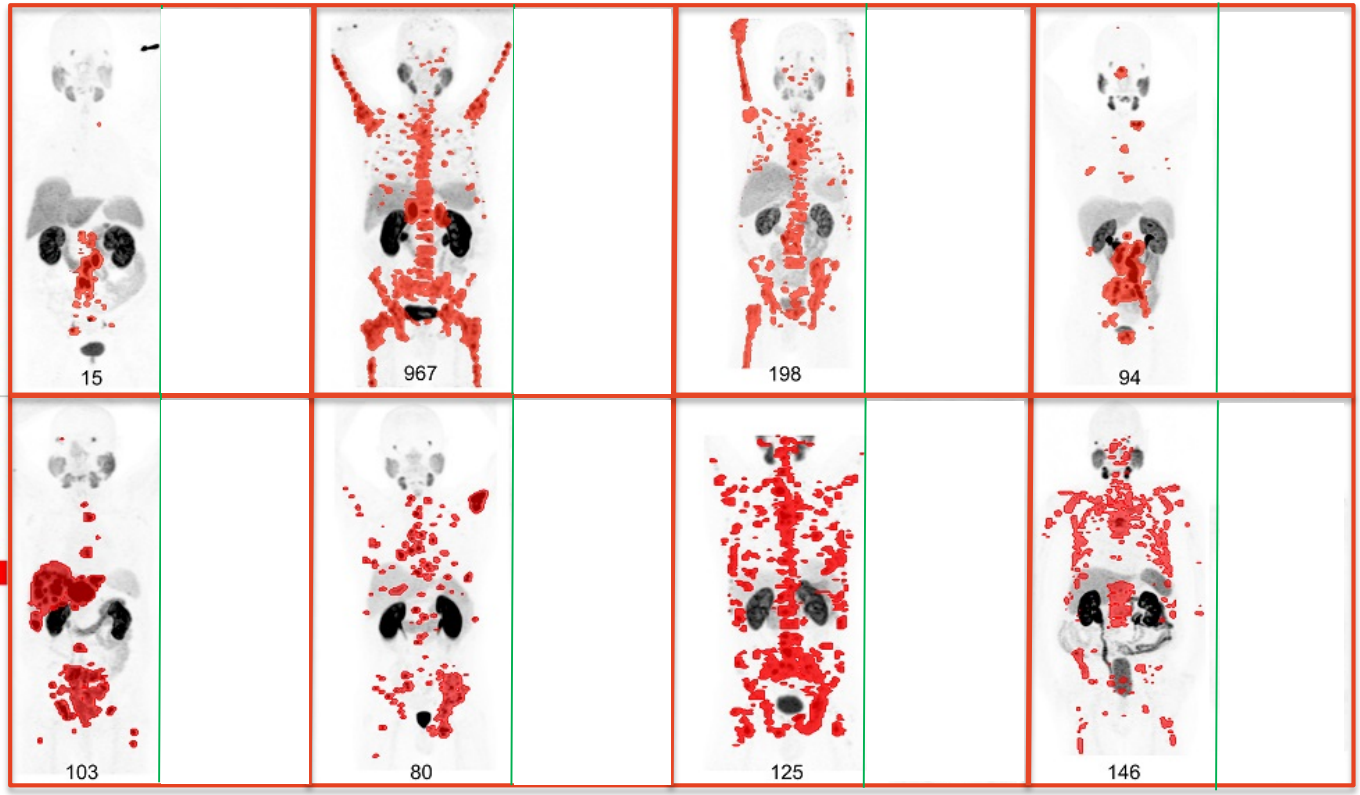



**IMAGE OF THE YEAR: PSMA PET before and after lutetium-177 PSMA617 theranostic in 8 patients with metastatic prostate cancer who exhausted standard therapeutic options.** $^{68}$Ga-PSMA11 PET maximum intensity projection (MIP) images at baseline and 3 months after $^{177}$Lu-PSMA617 in 8 patients with PSA decline ≥ 98 percent in a prospective phase II study. Any disease with SUV over 3 is in red. *Credit: Michael Hofman et al, Peter MacCallum Cancer Centre, Melbourne, Australia.*

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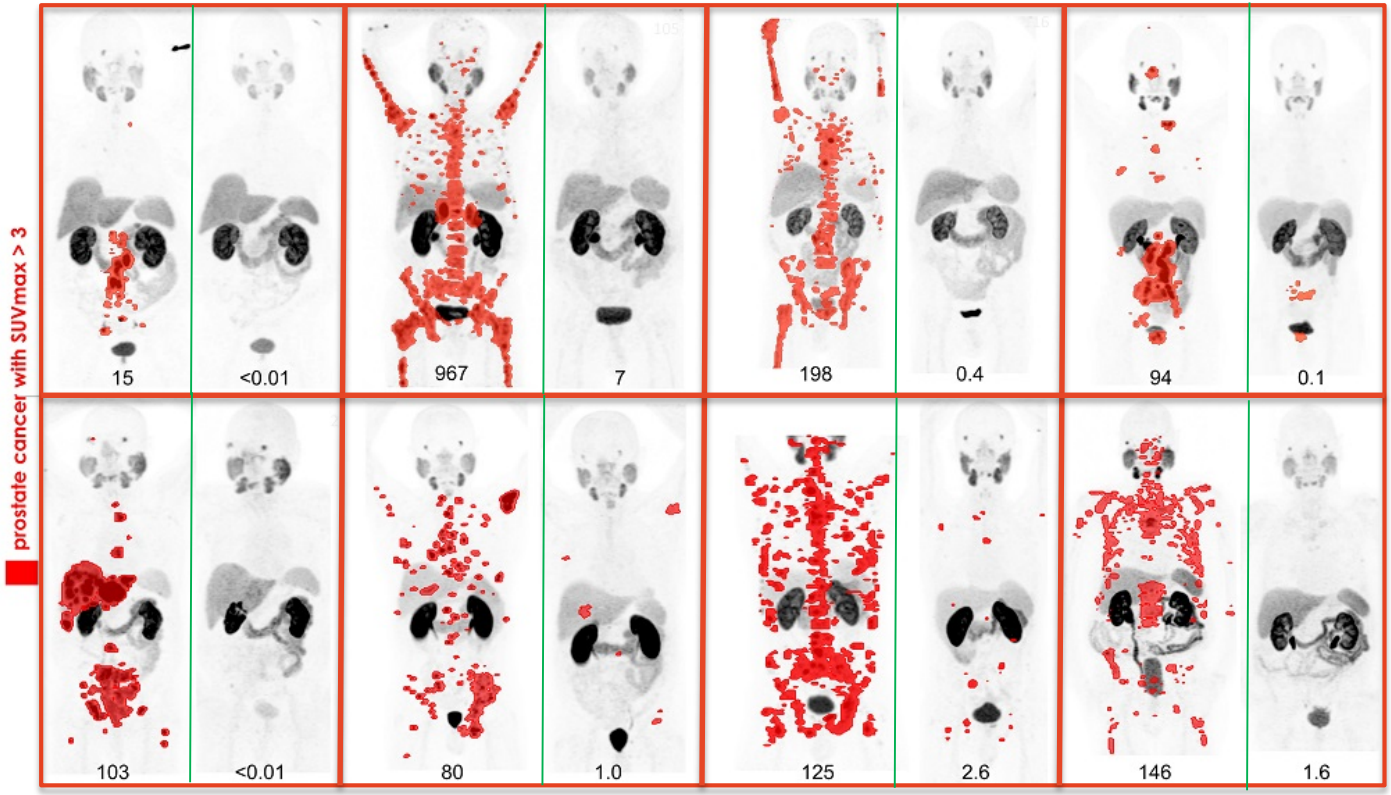



**IMAGE OF THE YEAR: PSMA PET before and after lutetium-177 PSMA617 theranostic in 8 patients with metastatic prostate cancer who exhausted standard therapeutic options.** $^{68}$Ga-PSMA11 PET maximum intensity projection (MIP) images at baseline and 3 months after $^{177}$Lu-PSMA617 in 8 patients with PSA decline ≥ 98 percent in a prospective phase II study. Any disease with SUV over 3 is in red. *Credit: Michael Hofman et al, Peter MacCallum Cancer Centre, Melbourne, Australia.*

# THERANOSTICS AVAILABLE – RNS Hospital, Sydney 2018

| Target | Examples | Mechanism | $D_x$ Radionuclide | Imaging | $R_x$ Radionuclide | Imaging |
|---|---|---|---|---|---|---|
| Thyroid | Thyroid Ca | Cellular uptake | $^{123}I$ or $^{131}I$ | SPECT | $^{131}I$ ($\beta^-$) | SPECT |
| Neural crest tumours | Neuroblastoma, phaeo, carcinoid | Cellular uptake | $^{123}I$-MIBG | SPECT | $^{131}I$ ($\beta^-$)-MIBG | SPECT |
| Neuroendocine tumours (NETs) | Pancreatic, gut NETs | Somatostatin receptor | $^{68}Ga$-DOTATATE | PET | $^{177}Lu$ ($\beta^-$)-DOTATATE | SPECT |
| Liver neoplasia | CRC, HCC, NETs, melanoma | Radio-embolisation | $^{99m}Tc$-Microsphere | SPECT | $^{90}Y$ ($\beta^-$)-SIR-Spheres | PET |
| Lymphoma | Diffuse large B cell non-Hodgkin's lymphoma | Antibody targeting | $^{131}I$-Rituximab | SPECT | $^{131}I$ ($\beta^-$)-Rituximab or **$^{177}Lu$ ($\beta^-$)-Rituximab | SPECT |
| Skeleton | Prostate Ca 2°s | Bone seeking ion | $^{99m}Tc$-MDP (Bone Scan) | SPECT | $^{223}Ra$ ($\alpha^{2+}$)-$RaCl_2$ | SPECT |
| Prostate | Prostate cancer | PSMA targeting | $^{68}Ga$-PSMA | PET | $^{177}Lu$ ($\beta^-$)-PSMA | SPECT |

** *Hopefully soon*

# RADIOPHARMACEUTICALS

## - *they are* RADIO*active* &

## *they are* PHARMACEUTICALS

| RADIOPHARMACEUTICAL | Mass of Radionuclide | Mass of Pharmaceutical |
|---|---|---|
| FDG PET/CT Whole Body ([$^{18}$F]FDG – 250 MBq) | 0.08 ng | 0.72 ng |
| Somatostatin Receptor (NET) PET/CT ([$^{68}$Ga]DOTATATE – 200 MBq) | 0.14 ng | 3 ng |
| Thyroid SPECT ([$^{123}$I]NaI – 160 MBq) | 2.2 ng | 2.7 ng |
| Bone scan for metastatic cancer ([$^{99m}$Tc]MDP – 800 MBq) | 4.1 ng | 12.9 ng |
| Thyroid Cancer Whole Body Surveillance Scan ([$^{131}$I]NaI – 160 MBq) | 35 ng | 41 ng |

# DIAGNOSTIC IMAGING – Radiation Doses

| Procedure/Radiopharmaceutical | ED from Radiopharmaceutical (mSv) | ED from CT (mGy) | Approx. Total ED (mSv) | Additional Risk of Fatal Cancer (0.05 deaths per Sv) |
|---|---|---|---|---|
| Myocardial Perfusion SPECT/CT ([$^{99m}$Tc]MIBI – 1000 MBq) (Stress + Rest) | 12.5 | 1.2 | ~14 | 0.07% |
| V/Q Lung scan ([$^{99m}$Tc]Technegas - 40 MBq (V) / [$^{99m}$Tc]MAA - 160 MBq (Q)) | 0.6(V) + 1.6(Q) | 2 | ~4 | 0.02% |
| Bone scan for metastatic cancer ([$^{99m}$Tc]MDP – 800 MBq) (Incl. 1 SPECT/CT) | 4.6 | 2 | ~7 | 0.035% |
| FDG PET/CT Whole Body ([$^{18}$F]FDG – 250 MBq) | 5 | 8-10 | 14 | 0.07% |
| Somatostatin Receptor (NET) PET/CT ([$^{68}$Ga]DOTATATE – 200 MBq) | 4.2 | 8-10 | 13 | 0.07% |
| Renal scan ([$^{99m}$Tc]MAG3 – 250 MBq) | 1.8 | 2 | ~4 | 0.02% |
| Prostate Cancer PET/CT ([$^{68}$Ga]PSMA – 200 MBq) | 3-4 | 8-10 | ~12 | 0.06% |
| Thyroid SPECT ([$^{123}$I]NaI – 200 MBq) | 2.5 | - | 2.5 | 0.013% |
| Thyroid Cancer Whole Body Surveillance Scan ([$^{131}$I]NaI – 400 MBq) (incl. 1 SPECT/CT) | 24 | 2 | ~25 | 0.13% |
| X-ray CTPA (240 mAs, 130 $kV_p$) | - | 4-20 | ~10 | 0.05% |
| X-ray CT: Thorax + Abdomen + Pelvis (240 mAs, 130 $kV_p$) | - | 21 (7+8+6) | ~20 | 0.11% |

# Reported AEs for Diagnostic Radiopharmaceuticals

BRIEF COMMUNICATION

## Evaluation of Radiopharmaceutical Adverse Reaction Reports to the British Nuclear Medicine Society from 2007 to 2016

Tracia-Gay Kennedy-Dixon[1], Maxine Gossell-Williams[2], Margaret Cooper[1], Moez Trabelsi[1], and Sobhan Vinjamuri[3]

*[1]Radiopharmacy, Royal Liverpool and Broadgreen University Hospitals Trust, Liverpool, United Kingdom; [2]Pharmacology Section, Department of Basic Medical Sciences, University of the West Indies, Mona Campus, Kingston, Jamaica; and [3]Royal Liverpool and Broadgreen University Hospitals Trust (consultant), Liverpool, United Kingdom*

**Results:** During the study period, there were 204 reports of radiopharmaceutical adverse reactions, of which 13 were considered invalid, primarily because of incomplete entries or because a causal relationship between the radiopharmaceutical and the adverse reaction could not be determined. Tetrofosmin (34 reports) and oxidronate (32 reports) had the highest prevalence, followed by medronate (21 reports) and then sestamibi and nanocolloid (14 reports each). Rash (84 reports), itching (46 reports), and vomiting (30 reports) were the 3 most frequently occurring adverse reactions. Most reports (96.8%) were for diagnostic radiopharmaceuticals. **Conclusion:** The prevalence of adverse reactions to radiopharmaceuticals reported in the BNMS database remains low, with a frequency of 3.1 reports per 100,000 administrations in 2013 and 2.5 per 100,000 administrations in 2015. In our review spanning 10 years, we did not find any particular concern about the use of radiopharmaceuticals.

**Key Words:** radiopharmaceuticals; adverse reactions; BNMS; pharmacovigilance

**J Nucl Med 2017; 58:2010–2012**
DOI: 10.2967/jnumed.117.194092

**Summary ($D_x$ Radiopharmaceuticals):**

- 2.5 - 3.1 reports per 100,000 (0.0025% - 0.0031%)
- Most common symptoms: rash, itching, vomiting

**Comparison*:**

- Iodinated contrast: 1-12%
- Non-iodinated contrast: 3%

* Katayama H et al. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. *Radiology*. 1990;175(3):621-628

# DIAGNOSTIC RADIOPHARMACEUTICALS – Adverse Reactions

- In the published literature concerning safety of PET drugs, in 1996 Silberstein, Ryan and the Pharmacopeia Committee of the Society of Nuclear Medicine published in the *Journal of Nuclear Medicine* reporting a five year prospective study of 18 collaborating institutions using a questionnaire which enumerated monthly the number of procedures used and the adverse reactions noted for radiopharmaceuticals and non-radioactive drugs used in nuclear medicine[†];

- The study utilized operational definitions for adverse reactions and significant adverse reactions and devised an algorithm to categorize probability of causation. The published study included a copy of the actual questionnaire, which required itemization of any and all radiopharmaceuticals administered, adverse reactions to radiopharmaceuticals, dose, route, reaction, *etc.*, as well as total non-radiopharmaceuticals (such as adenosine or dipyridamole) administered and adverse reactions to these agents;

- No reactions are reported for FDG PET. The study also performed a reference check of listed adverse reactions by references and no adverse reactions were listed by the U.S. Pharmacopeial Convention's Drug Information for the Health Care Professional, 1995;

- Silberstein and the Pharmacopeia Committee of the Society of Nuclear Medicine also conducted a retrospective and prospective study of the prevalence of adverse reactions to PET radiopharmaceuticals published in 1998 in the *Journal of Nuclear Medicine*[‡]. Dr. Silberstein reported 22 PET centres provided monthly adverse reaction data from 1994 to 1997 related to PET drug administration in 47,876 dosages. In addition, retrospective data was collected from the opening of these centres on 33,925 radiopharmaceutical dosages;

- **In no case were there any adverse reactions.**

[†]Silberstein EB, Ryan J. Prevalence of adverse reactions in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. *J Nucl Med.* 1996 Jan;37(1):185-192.

[‡]Silberstein EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. *J Nucl Med*. 1998 Dec;39(12):2190-2192.

# SPECTRUM OF TREATMENT OPTIONS

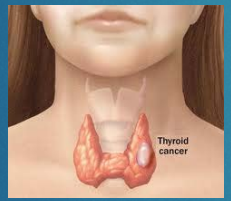
**Little or no patient-specific info**

| PROs | Little prep - routine | | |
|---|---|---|---|
| **CONs** | "One size fits all" approach may not always work;<br>Wide spectrum of responses: Over-treatment in some, under-treatment in others? | | |

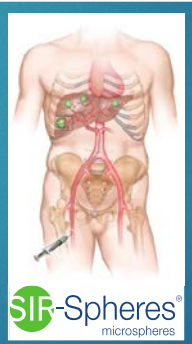

# SPECTRUM OF TREATMENT OPTIONS

**Little or no patient-specific info** | **Minimal patient-specific info (*e.g.*, height & weight)**

| PROs | Little prep - routine | Only minor adjustments to dosing regime required – can be done on day of treatment | |
|---|---|---|---|
| **CONs** | "One size fits all" approach may not always work;<br>Wide spectrum of responses: Over-treatment in some, under-treatment in others? | Insufficient data to make an informed decision on dose;<br>Information used may not be relevant to disease burden | |







# SPECTRUM OF TREATMENT OPTIONS

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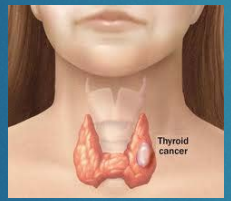



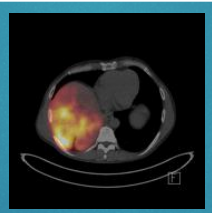

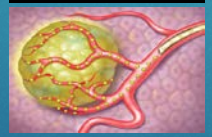

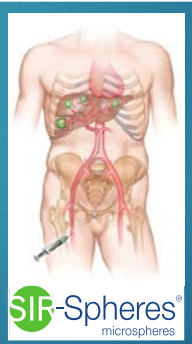


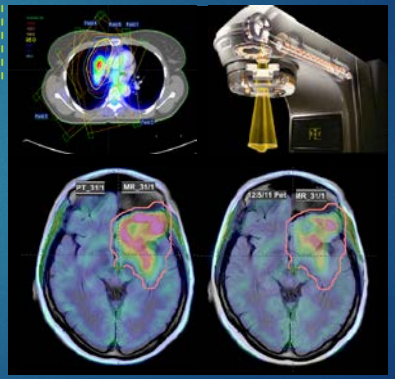

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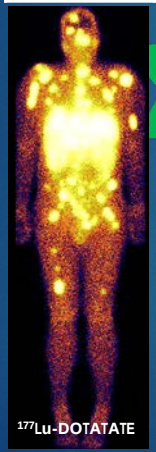
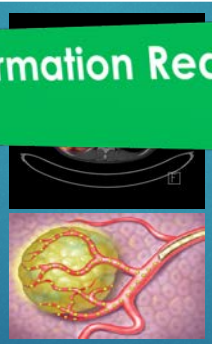
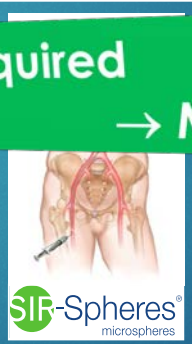
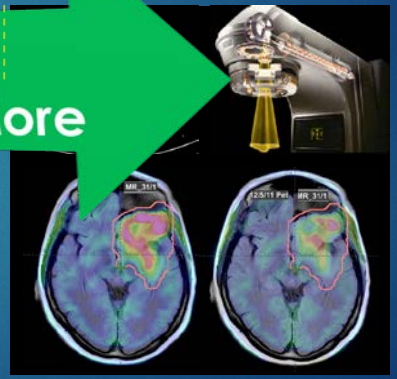






Less ← Information Required → More

# THERAPEUTIC RADIOPHARMACEUTICALS

| RADIOPHARMACEUTICAL | Particle | Mass of Radionuclide | Mass of Pharmaceutical |
|---|---|---|---|
| Somatostatin Receptor (NET) PRRT ([$^{177}$Lu]DOTATATE – 8000 MBq) | $\beta^-$ | 1.97 μg | 200 μg |
| Xofigo ([$^{223}$Ra]$RaCl_2$ – 4 MBq) | $\alpha^{2+}$ | 7.6 ng | 11.2 ng |
| Thyroid Cancer Ablation ([$^{131}$I]NaI – 4000 MBq) | $\beta^-$ | 0.87 μg | 1.0 ng |
| SIR-Spheres ([$^{90}$Y]resin microspheres – 1500 MBq) | $\beta^-$ | 75 ng | (Resin microspheres) |

# THERAPEUTIC RADIONUCLIDES – Radiation Doses

| Procedure/Radiopharmaceutical | ED from Radiopharmaceutical (Gy) |
|---|---|
| Somatostatin Receptor (NET) PRRT ([$^{177}$Lu]DOTATATE – 8000 MBq) | 0.4 |
| Bony metastases from Prostate Ca: Xofigo™ ([$^{223}$Ra]$RaCl_2$ – 4 MBq) | (mGy) |
| Thyroid Cancer Ablation ([$^{131}$I]NaI – 4000 MBq) | 0.2 - 0.3 |
| SIRT: SIR-Spheres ([$^{90}$Y]resin microspheres – 1500 MBq) | 2 (~40 Gy to liver) |

# RADIOIODINE FOR THYROID CANCER
# THE 1st THERANOSTIC IN NUCLEAR MEDICINE

**The Harvard Crimson**

May 24, 1949

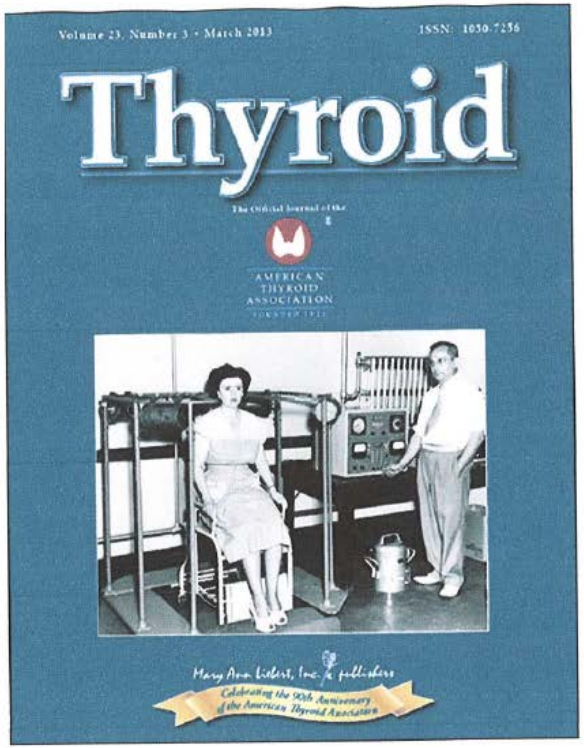
## Hertz to Use Nuclear Fission in Cure for Cancer

By Donald G. Vincent

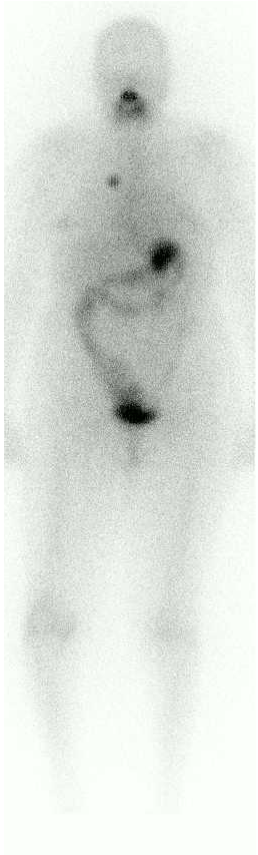
Dr. Saul Hertz, instructor in Medicine in the Medical School, has announced that he has founded an institution, The Radioactive Isotope Research Institute, whose purpose is to apply radioactive fission products to the treatment of the thyroid cancer, goiter, and other malignant growths.

Dr. Hertz is connected with both the Medical School and Beth Israel Hospital as medical associate and research associate. In the past, he has been in charge of the Thyroid Clinic of the Massachusetts General Hospital and Research Associate at the Massachusetts Institute of Technology.

The research conducted by Dr. Hertz and others which led to the Radioactive Isotope Research Institute, was financed by a grant from the John and Mary Markle Fund in New York City and the Milton N. Proctor Fund here. Most of the work was done at the Massachusetts General Hospital and at M.I.T.



# ADVERSE EVENTS – RADIOIODINE $^{131}$I (THYROID CANCER)



| Adverse Event | Reported Incidence | Transient/Chronic |
|---|---|---|
| Gastritis/Nausea | 30% | Transient |
| Radiation thyroiditis | 10%-20% | Transient |
| Sialadenitis | ≤ 30% | Transient |
| Xerostomia | 4%-20% | Chronic |
| Bone marrow suppression | 20% | Transient |
| Amenorrhea | 20%-27% | Transient |
| Dry eye | Rare | Transient |
| Leukaemia (Cum. Doses > 20 GBq) | Slight | Chronic |
| Second Primary Malignancy | No significant risk | - |



Fard-Esfahani A et al. Adverse effects of radioactive iodine-131 treatment for differentiated thyroid carcinoma. *Nucl Med Commun*. 2014;35(8):808-817

# ADVERSE EVENTS – [$^{223}$Ra]Xofigo (PROSTATE CANCER)

The University of Sydney

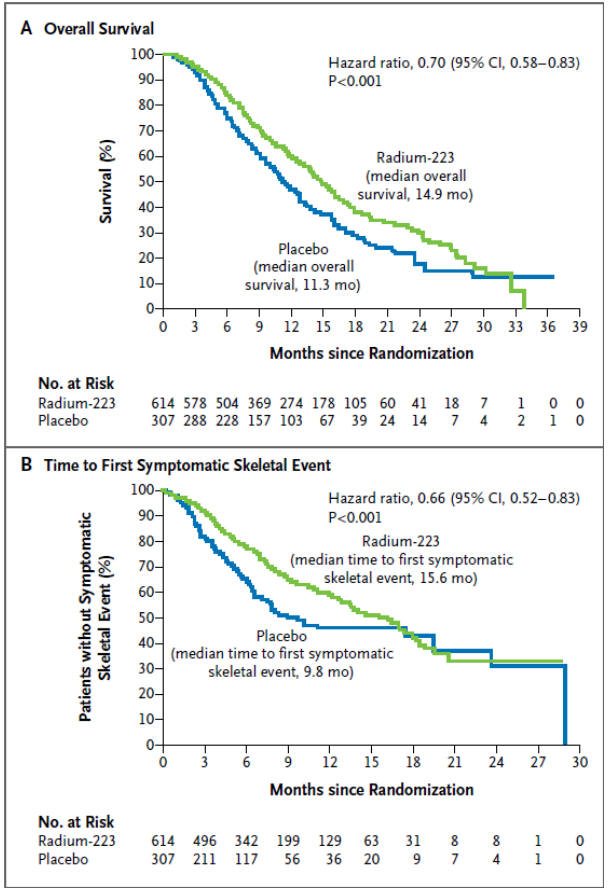
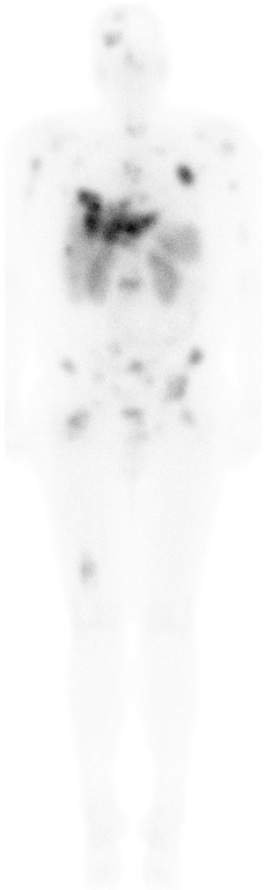



**Table 3.** Adverse Events That Occurred in at Least 5% of Patients in Either Study Group in the Safety Population.

| Adverse Event | Radium-223 (N=600) | | | | Placebo (N=301) | | | |
|---|---|---|---|---|---|---|---|---|
| | All Grades | Grade 3 | Grade 4 | Grade 5* | All Grades | Grade 3 | Grade 4 | Grade 5* |
| | *number of patients (percent)* | | | | | | | |
| **Hematologic** | | | | | | | | |
| Anemia | 187 (31) | 65 (11) | 11 (2) | 0 | 92 (31) | 37 (12) | 2 (1) | 1 (<1) |
| Thrombocytopenia | 69 (12) | 20 (3) | 18 (3) | 1 (<1) | 17 (6) | 5 (2) | 1 (<1) | 0 |
| Neutropenia | 30 (5) | 9 (2) | 4 (1) | 0 | 3 (1) | 2 (1) | 0 | 0 |
| **Nonhematologic** | | | | | | | | |
| Constipation | 108 (18) | 6 (1) | 0 | 0 | 64 (21) | 4 (1) | 0 | 0 |
| Diarrhea | 151 (25) | 9 (2) | 0 | 0 | 45 (15) | 5 (2) | 0 | 0 |
| Nausea | 213 (36) | 10 (2) | 0 | 0 | 104 (35) | 5 (2) | 0 | 0 |
| Vomiting | 111 (18) | 10 (2) | 0 | 0 | 41 (14) | 7 (2) | 0 | 0 |
| Asthenia | 35 (6) | 5 (1) | 0 | 0 | 18 (6) | 4 (1) | 0 | 0 |
| Fatigue | 154 (26) | 21 (4) | 3 (1) | 0 | 77 (26) | 16 (5) | 2 (1) | 0 |
| Deterioration in general physical health | 27 (4) | 9 (2) | 2 (<1) | 5 (1) | 21 (7) | 8 (3) | 2 (1) | 2 (1) |
| Peripheral edema | 76 (13) | 10 (2) | 0 | 0 | 30 (10) | 3 (1) | 1 (<1) | 0 |
| Pyrexia | 38 (6) | 3 (1) | 0 | 0 | 19 (6) | 3 (1) | 0 | 0 |
| Pneumonia | 18 (3) | 9 (2) | 0 | 4 (1) | 16 (5) | 5 (2) | 2 (1) | 0 |
| Urinary tract infection | 47 (8) | 7 (1) | 0 | 0 | 28 (9) | 4 (1) | 1 (<1) | 1 (<1) |
| Weight loss | 69 (12) | 4 (1) | 0 | 0 | 44 (15) | 5 (2) | 0 | 0 |
| Anorexia | 102 (17) | 9 (2) | 0 | 0 | 55 (18) | 2 (1) | 0 | 0 |
| Decreased appetite | 35 (6) | 2 (<1) | 0 | 0 | 13 (4) | 0 | 0 | 0 |
| Bone pain | 300 (50) | 120 (20) | 5 (1) | 0 | 187 (62) | 74 (25) | 3 (1) | 0 |
| Muscular weakness | 9 (2) | 2 (<1) | 1 (<1) | 0 | 17 (6) | 6 (2) | 0 | 0 |
| Pathologic fracture | 22 (4) | 13 (2) | 0 | 0 | 15 (5) | 8 (3) | 1 (<1) | 0 |
| Progression of malignant neoplasm | 77 (13) | 9 (2) | 4 (1) | 55 (9) | 44 (15) | 4 (1) | 1 (<1) | 33 (11) |
| Dizziness | 43 (7) | 2 (<1) | 0 | 0 | 26 (9) | 2 (1) | 0 | 0 |
| Spinal cord compression | 25 (4) | 14 (2) | 6 (1) | 1 (<1) | 23 (8) | 16 (5) | 1 (<1) | 0 |
| Insomnia | 27 (4) | 0 | 0 | 0 | 21 (7) | 1 (<1) | 0 | 0 |
| Hematuria | 30 (5) | 7 (1) | 0 | 0 | 15 (5) | 3 (1) | 0 | 0 |
| Urinary retention | 25 (4) | 9 (2) | 0 | 0 | 18 (6) | 6 (2) | 0 | 0 |
| Dyspnea | 49 (8) | 10 (2) | 1 (<1) | 1 (<1) | 26 (9) | 7 (2) | 0 | 3 (1) |

Parker C, Nilsson S, Heinrich D, Helle SI, O'Sullivan JM, Fossa SD, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med*. 2013;369(3):213-23

# ADVERSE EVENTS – [$^{177}$Lu]DOTATATE (NETs)



The University of Sydney

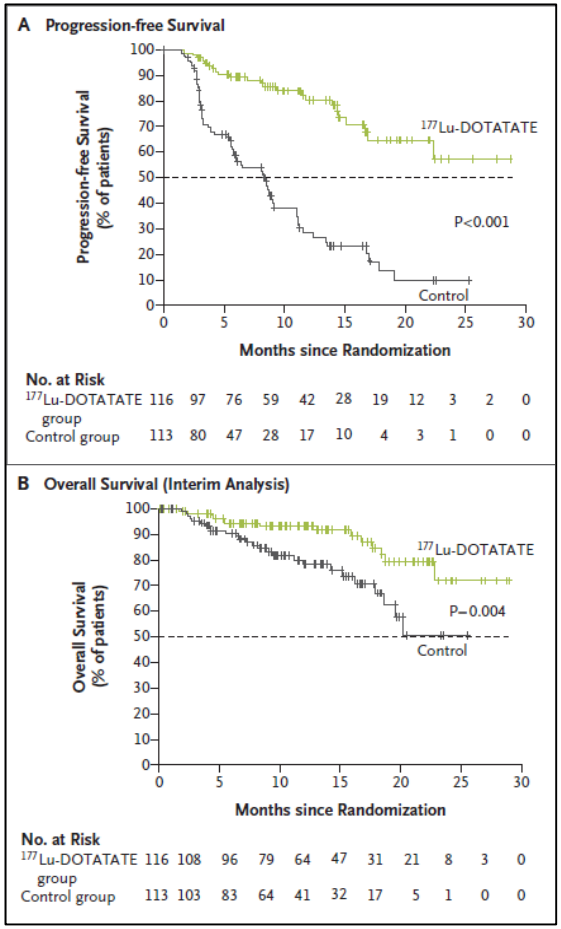
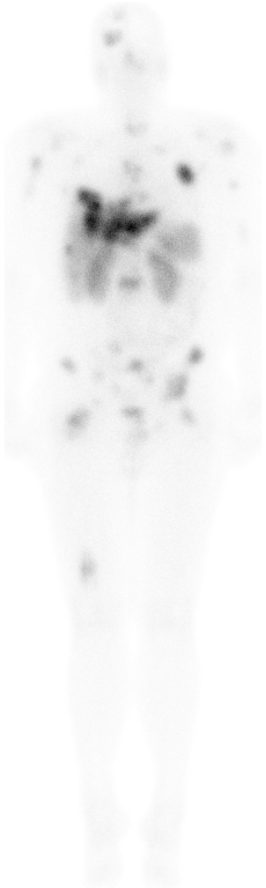



**Table 4. Adverse Events (Safety Population).***

| Event | $^{177}$Lu-Dotatate Group (N=111) | | Control Group (N=110) | | P Value† |
|---|---|---|---|---|---|
| | Any Grade | Grade 3 or 4 | Any Grade | Grade 3 or 4 | Any Grade |
| | *number of patients (percent)* | | | | |
| **Any adverse event** | 105 (95) | 46 (41) | 92 (84) | 36 (33) | 0.01 |
| **Gastrointestinal disorders** | | | | | |
| Nausea | 65 (59) | 4 (4) | 13 (12) | 2 (2) | <0.001 |
| Vomiting | 52 (47) | 8 (7) | 11 (10) | 1 (1) | <0.001 |
| Abdominal pain | 29 (26) | 3 (3) | 29 (26) | 6 (5) | 1.00 |
| Diarrhea | 32 (29) | 3 (3) | 21 (19) | 2 (2) | 0.11 |
| Distension | 14 (13) | 0 | 15 (14) | 0 | 0.84 |
| **General disorders** | | | | | |
| Fatigue or asthenia | 44 (40) | 2 (2) | 28 (25) | 2 (2) | 0.03 |
| Edema peripheral | 16 (14) | 0 | 8 (7) | 0 | 0.13 |
| **Blood disorders** | | | | | |
| Thrombocytopenia | 28 (25) | 2 (2) | 1 (1) | 0 | <0.001 |
| Anemia | 16 (14) | 0 | 6 (5) | 0 | 0.04 |
| Lymphopenia | 20 (18) | 10 (9) | 2 (2) | 0 | <0.001 |
| Leukopenia | 11 (10) | 1 (1) | 1 (1) | 0 | 0.005 |
| Neutropenia | 6 (5) | 1 (1) | 1 (1) | 0 | 0.12 |
| **Musculoskeletal disorders** | | | | | |
| Musculoskeletal pain | 32 (29) | 2 (2) | 22 (20) | 1 (1) | 0.16 |
| **Nutrition disorders** | | | | | |
| Decreased appetite | 20 (18) | 0 | 9 (8) | 3 (3) | 0.04 |
| **Nervous system disorders** | | | | | |
| Headache | 18 (16) | 0 | 5 (5) | 0 | 0.007 |
| Dizziness | 12 (11) | 0 | 6 (5) | 0 | 0.22 |
| **Vascular disorders** | | | | | |
| Flushing | 14 (13) | 1 (1) | 10 (9) | 0 | 0.52 |
| **Skin disorders** | | | | | |
| Alopecia | 12 (11) | 0 | 2 (2) | 0 | 0.01 |
| **Respiratory disorders** | | | | | |
| Cough | 12 (11) | 0 | 6 (5) | 0 | 0.22 |

Strosberg J et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*. 2017;376(2):125-35

# LONG-TERM ADVERSE EVENTS – [$^{177}$Lu]DOTATATE (NETs)



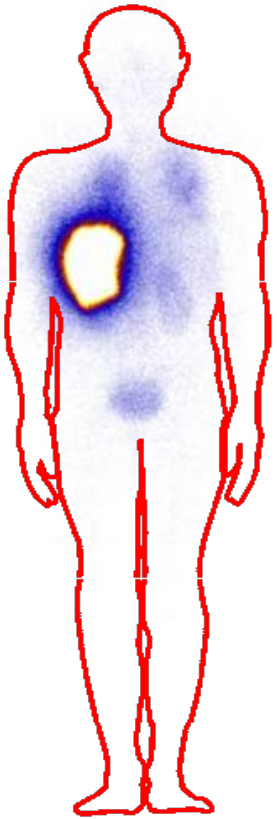
| Long-term Adverse Event | Reported Incidence |
|---|---|
| Acute Leukaemia | 0.7% |
| Myelodysplastic Syndrome | 1.5% |
| Renal Failure attributable to PRRT | None |
| Liver Failure | None |

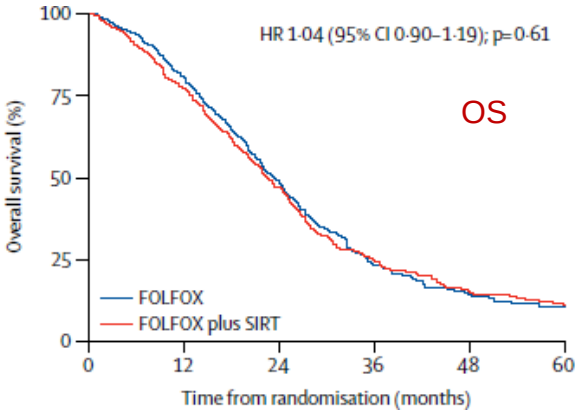
1214 patients treated with 4 cycles [$^{177}$Lu]Lutate 2000-2015
610 were evaluable with follow-up

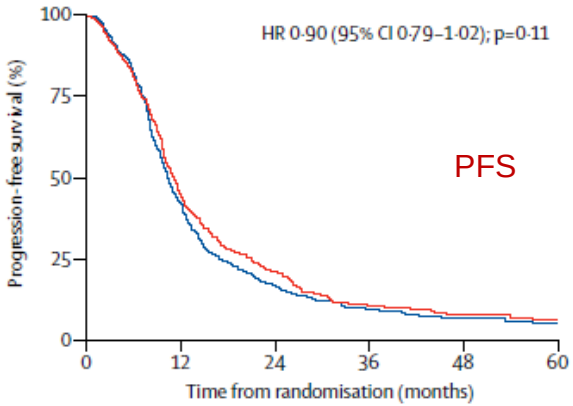


Report from ENETS 2017 – Erasmus Medical Centre (NED): Long-term Safety Data in 1214 Treated Subjects

# ADVERSE EVENTS – [$^{90}$Y]SIR-SPHERES (SIRT)






| | FOLFOX alone (n=571) | | | | FOLFOX plus SIRT (n=507) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
| Overall | 189 (33%) | 266 (47%) | 103 (18%) | 11 (2%) | 131 (26%) | 239 (47%) | 126 (25%) | 10 (2%) |
| Haematological | 102 (18%) | 108 (19%) | 56 (10%) | 1 (<1%) | 109 (21%) | 144 (28%) | 86 (17%) | 1 (<1%) |
| Neutropenia | 50 (9%) | 89 (16%) | 48 (8%) | 1 (<1%) | 55 (11%) | 115 (23%) | 71 (14%) | 0 |
| Febrile neutropenia | 0 | 11 (2%) | 5 (1%) | 0 | 0 | 25 (5%) | 7 (1%) | 1 (<1%) |
| Thrombocytopenia | 77 (13%) | 6 (1%) | 1 (<1%) | 0 | 153 (30%) | 37 (7%) | 2 (<1%) | 0 |
| Leucopenia | 28 (5%) | 10 (2%) | 3 (1%) | 0 | 41 (8%) | 20 (4%) | 10 (2%) | 0 |
| Non-haematological | 265 (46%) | 232 (41%) | 61 (11%) | 10 (2%) | 219 (43%) | 218 (43%) | 59 (12%) | 9 (2%) |
| Fatigue | 275 (48%) | 28 (5%) | 0 | 0 | 261 (51%) | 43 (8%) | 0 | 0 |
| Diarrhoea | 256 (45%) | 35 (6%) | 2 (<1%) | 0 | 189 (37%) | 33 (7%) | 1 (<1%) | 0 |
| Pulmonary embolism | 1 (<1%) | 7 (1%) | 19 (3%) | 0 | 2 (<1%) | 4 (1%) | 24 (5%) | 0 |
| Neuropathy peripheral | 307 (54%) | 32 (6%) | 1 (<1%) | 0 | 273 (54%) | 18 (4%) | 0 | 0 |
| Abdominal pain | 95 (17%) | 13 (2%) | 0 | 0 | 151 (30%) | 30 (6%) | 1 (<1%) | 0 |
| SIRT-associated | 13 (2%) | 9 (2%) | 1 (<1%) | 0 | 52 (10%) | 24 (5%) | 3 (1%) | 3 (1%) |
| Ascites | 2 (<1%) | 4 (1%) | 0 | 0 | 23 (5%) | 6 (1%) | 0 | 0 |
| Blood bilirubin increased | 3 (1%) | 2 (<1%) | 0 | 0 | 6 (1%) | 3 (1%) | 0 | 0 |
| Gastric ulcer | 0 | 0 | 0 | 0 | 8 (2%) | 3 (1%) | 1 (<1%) | 0 |
| Hyperbilirubinaemia | 1 (<1%) | 1 (<1%) | 0 | 0 | 2 (<1%) | 3 (1%) | 0 | 0 |
| Gastrointestinal haemorrhage | 0 | 0 | 1 (<1%) | 0 | 2 (<1%) | 1 (<1%) | 2 (<1%) | 0 |
| Radiation hepatitis | 0 | 0 | 0 | 0 | 2 (<1%) | 2 (<1%) | 0 | 2 (<1%) |
| Duodenal ulcer | 1 (<1%) | 0 | 0 | 0 | 4 (1%) | 3 (1%) | 0 | 0 |
| Pancreatitis | 0 | 0 | 0 | 0 | 1 (<1%) | 2 (<1%) | 0 | 0 |
| Hepatic failure | 0 | 0 | 0 | 0 | 0 | 1 (<1%) | 0 | 1 (<1%) |
| Jaundice | 0 | 2 (<1%) | 0 | 0 | 0 | 0 | 0 | 0 |
| Jaundice cholestatic | 0 | 0 | 0 | 0 | 0 | 2 (<1%) | 0 | 0 |
| Hepatic encephalopathy | 0 | 0 | 0 | 0 | 0 | 2 (<1%) | 0 | 0 |
| Duodenitis | 0 | 0 | 0 | 0 | 4 (1%) | 1 (<1%) | 0 | 0 |
| Portal hypertension | 1 (<1%) | 0 | 0 | 0 | 0 | 1 (<1%) | 0 | 0 |
| Duodenal ulcer haemorrhage | 0 | 0 | 1 (<1%) | 0 | 0 | 0 | 0 | 0 |
| Cholecystitis acute | 0 | 0 | 0 | 0 | 0 | 1 (<1%) | 0 | 0 |
| Perihepatic abscess | 0 | 0 | 0 | 0 | 0 | 1 (<1%) | 0 | 0 |
| Gastritis | 4 (1%) | 0 | 0 | 0 | 18 (4%) | 0 | 0 | 0 |
| Oesophagitis | 3 (1%) | 0 | 0 | 0 | 2 (<1%) | 0 | 0 | 0 |
| Splenomegaly | 1 (<1%) | 0 | 0 | 0 | 2 (<1%) | 0 | 0 | 0 |
| Oesophageal ulcer | 0 | 0 | 0 | 0 | 1 (<1%) | 0 | 0 | 0 |

Data are n (%). Table shows grade 3 or worse haematological events occurring in at least 5% of patients, grade 3 or worse non-haematological events occurring in at least 5% of patients, and all SIRT-associated adverse events. Worst grade reported per patient per category, sorted by prevalence of grade 3 or worse. SIRT=selective internal radiotherapy.

***Table 2*: Adverse events reported in each treatment group**

# Extravasated Injection – [$^{177}$Lu]Lutate Therapy

# CONCLUSIONS

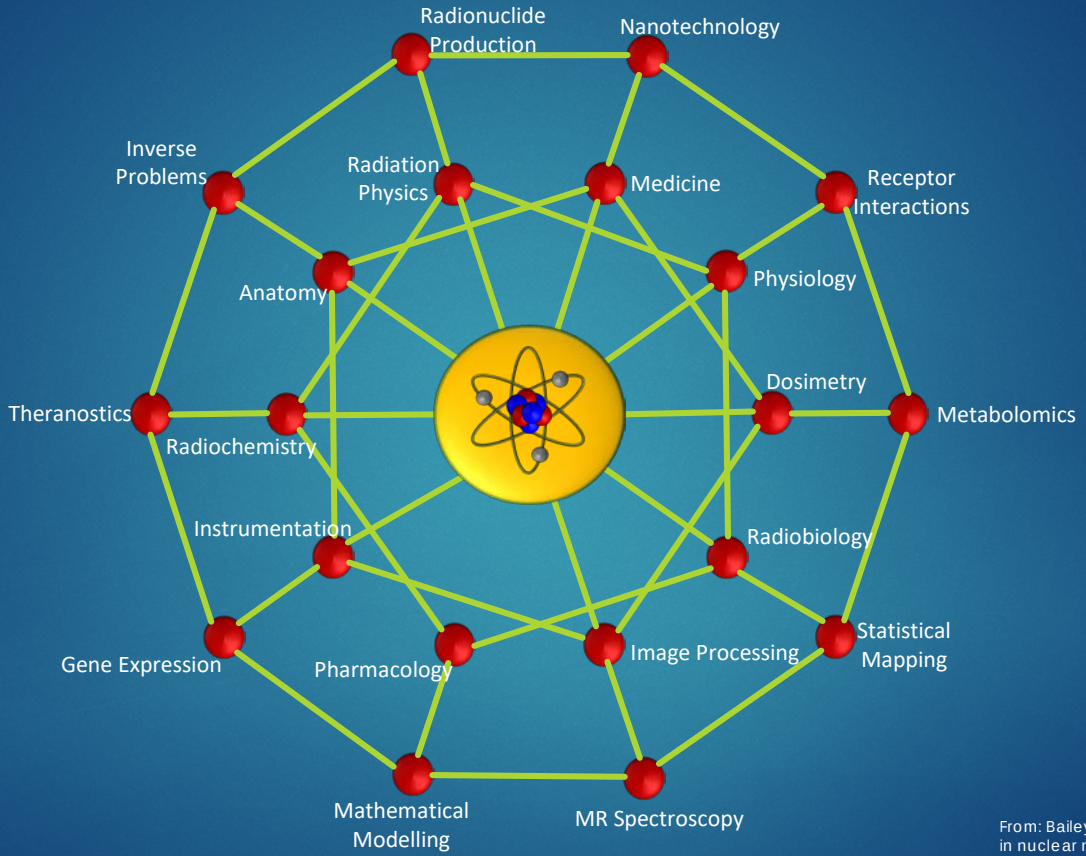
Diagnostic radiopharmaceuticals are extremely safe:

- Homeopathic amount of active compound involved
- Low levels of exposure to ionising radiation
- Addition of CT to SPECT & PET has roughly doubled the radiation dose

Radionuclide therapies are well tolerated in most subjects:

- Low levels of active compound
- Most reported AEs are usually transient
- Bone marrow is usually considered the organ at risk
- Very low levels of long-term or late effects such as secondary malignancy

# Radionuclide-Based Molecular Imaging 2014-2018




From: Bailey DL. Thirty years from now: future physics contributions in nuclear medicine. *Eur J Nucl Med Mol Imag Physics*. 2014;1(4).