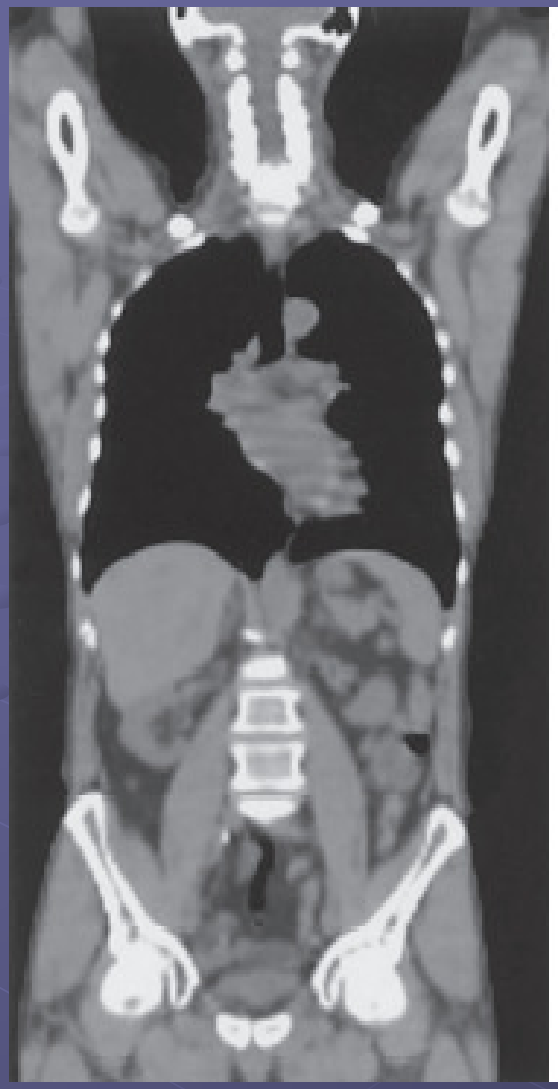
NUCLEAR MEDICINE IN NETS

David Farlow
Director
Dept of Nuclear Medicine, PET and Ultrasound
Westmead Hospital, Sydney, Australia

Unicorn Foundation Neuroendocrine Education/Support Group Meeting
North Shore Private Hospital, St Leonards
11 August 2010

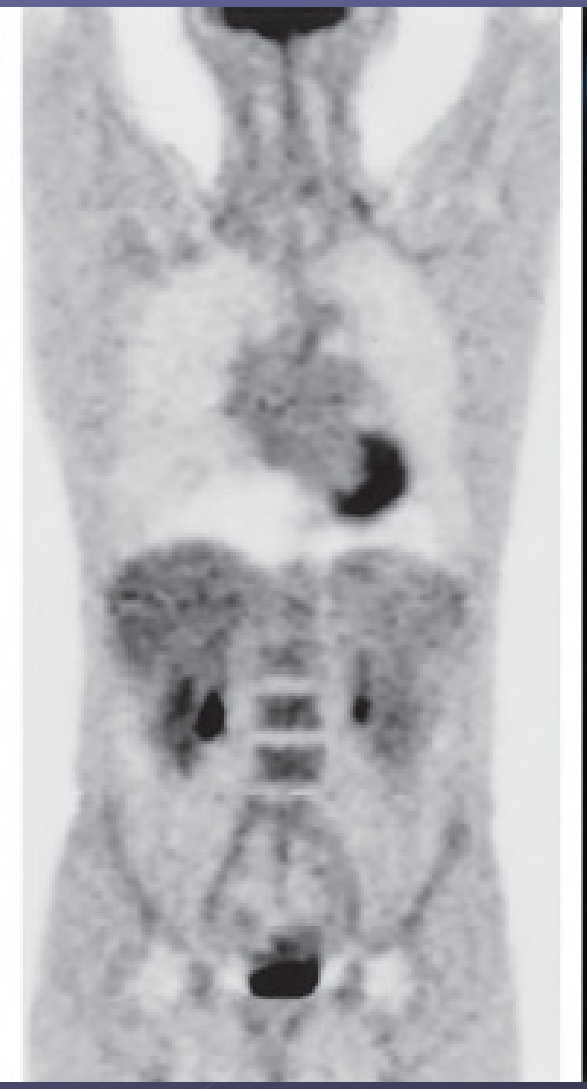
WHAT IS NUCLEAR MEDICINE ?

- uses medical isotopes to map physiology and pathophysiology in human body
- also known as functional or molecular imaging
- complements Radiology which displays anatomy
- 70 year history and recent rapid growth due to convergence technologies such as PET-CT.



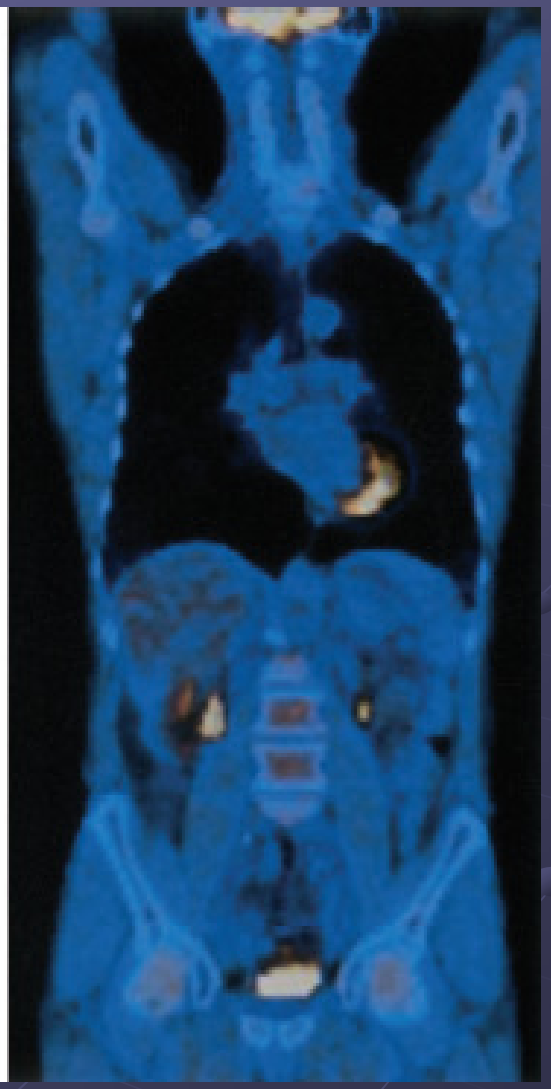
computed tomography

? dead or alive



FDG positron emission tomography

maps metabolism
but where is the finding?



PET-CT

RADIOPHARMACEUTICAL

radiopharmaceutical

= isotope + ligand

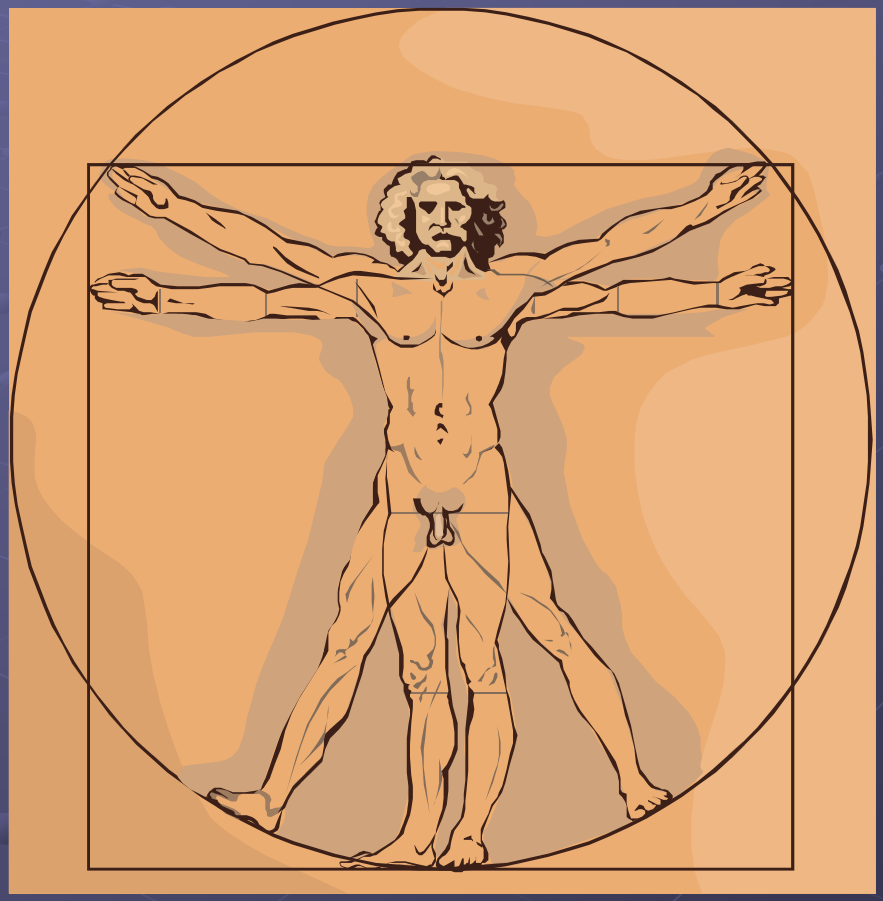
administered
intravenously, orally, etc

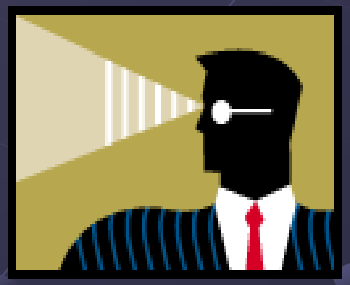
localises in target organ,
or target pathology

emits gamma rays

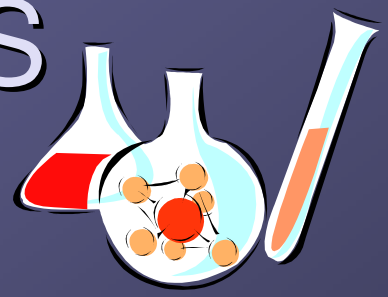
or beta rays

detected by gamma camera or
PET camera with or without CT

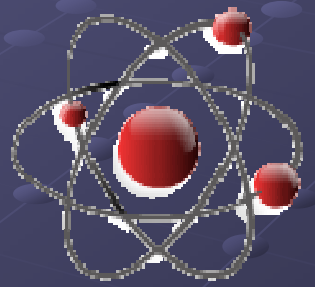


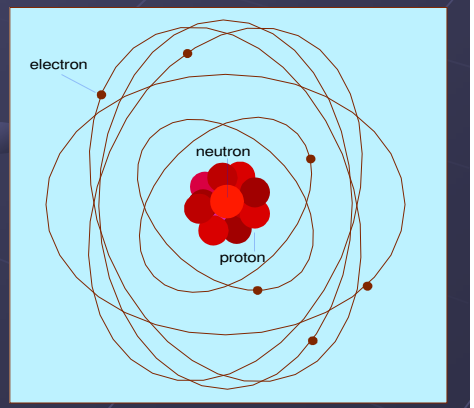


MEDICAL ISOTOPES



- isotopes are unstable → emissions
- electrons (beta radiation) used in nuclear medicine therapy
- positrons (antimatter electrons) annihilate to produce gamma rays for PET
- gamma rays: photons like X-rays but originate from nucleus, not the shell

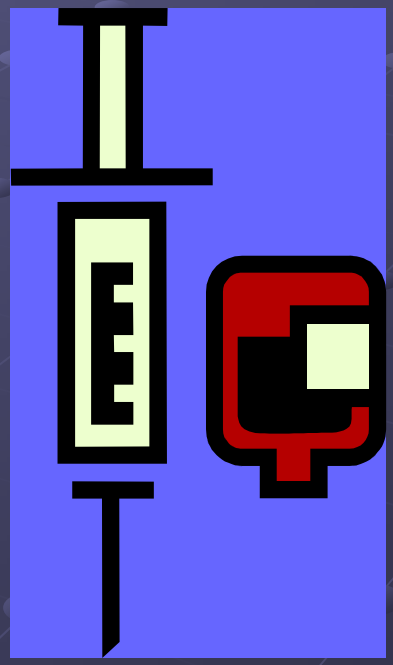




MEDICAL ISOTOPES

- Diagnostic
  - Tc^{99m}
  - I^{123}
  - Tl^{201}
  - Ga^{67}
  - In^{111}
  - I^{131}
  - Ga^{68}
  - F^{18}

- Therapeutic
  - I^{131}
  - Y^{90}
  - Lu^{177}
  - Sm^{153}
  - Sr^{89}
  - Rh^{188}
  - P^{32}



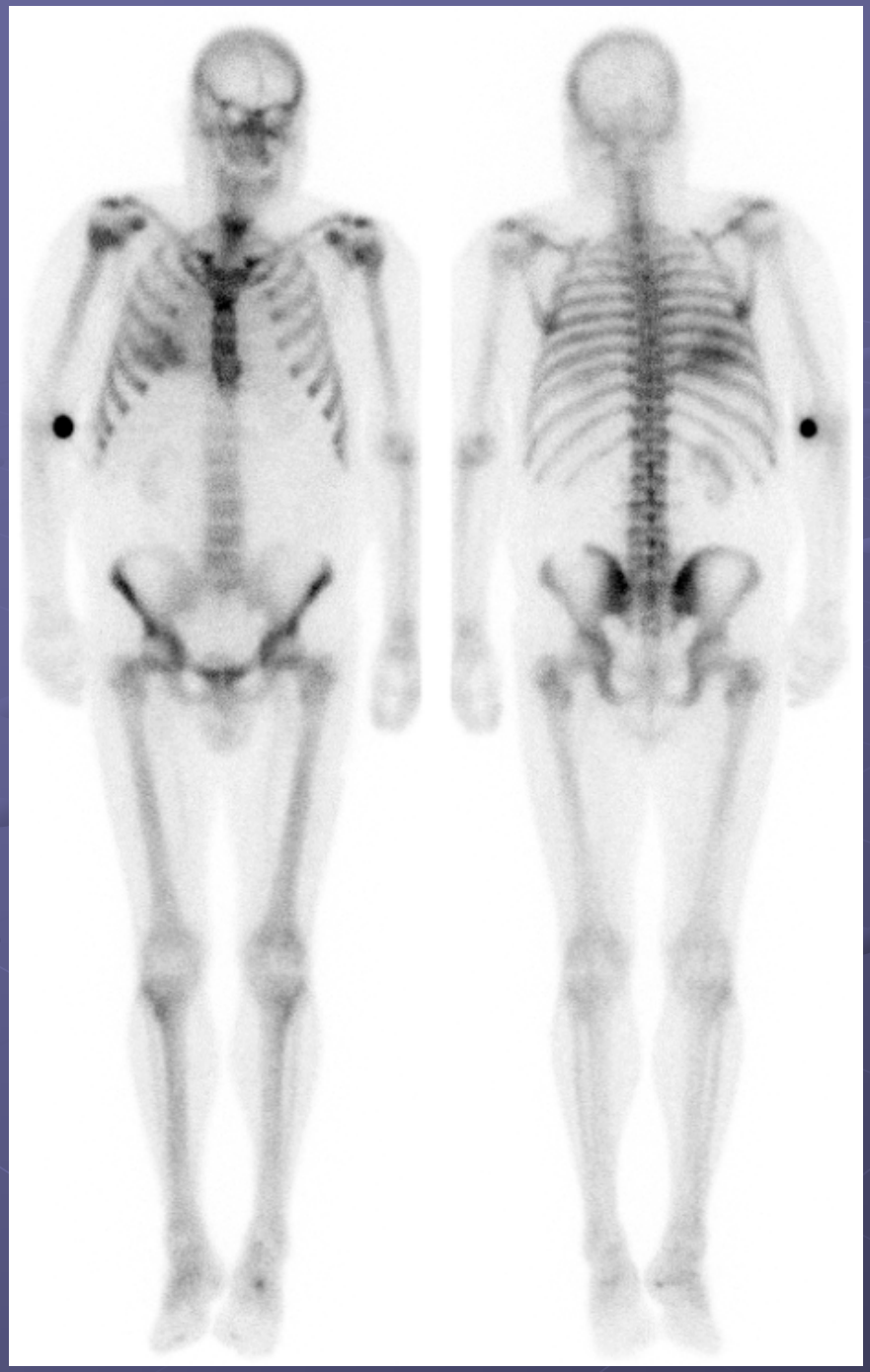
reactor and cyclotron produced radioactive isotopes; differing half lives and different electron, positron and gamma emissions

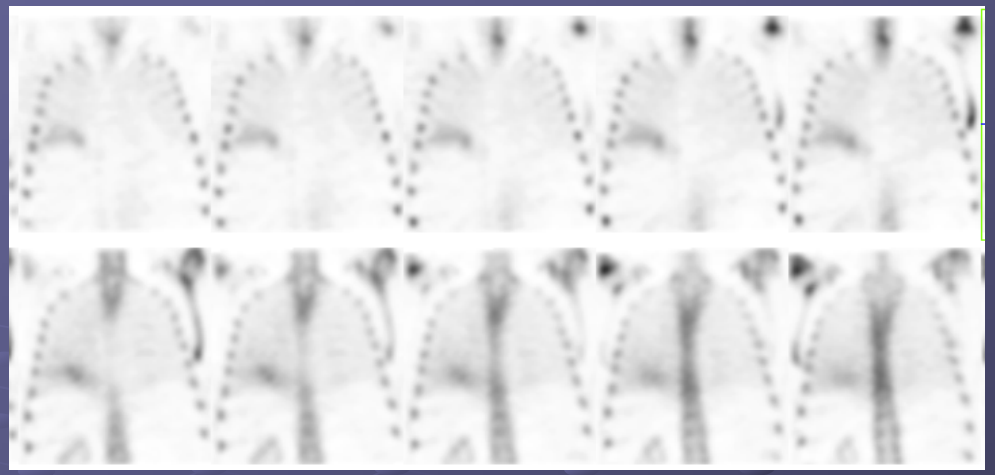
RADIOPHARMACEUTICALS

- isotope is directed to organ or target of interest via ligand
- scan name often derived from ligand eg MIBI scan, or from target organ eg lung scan

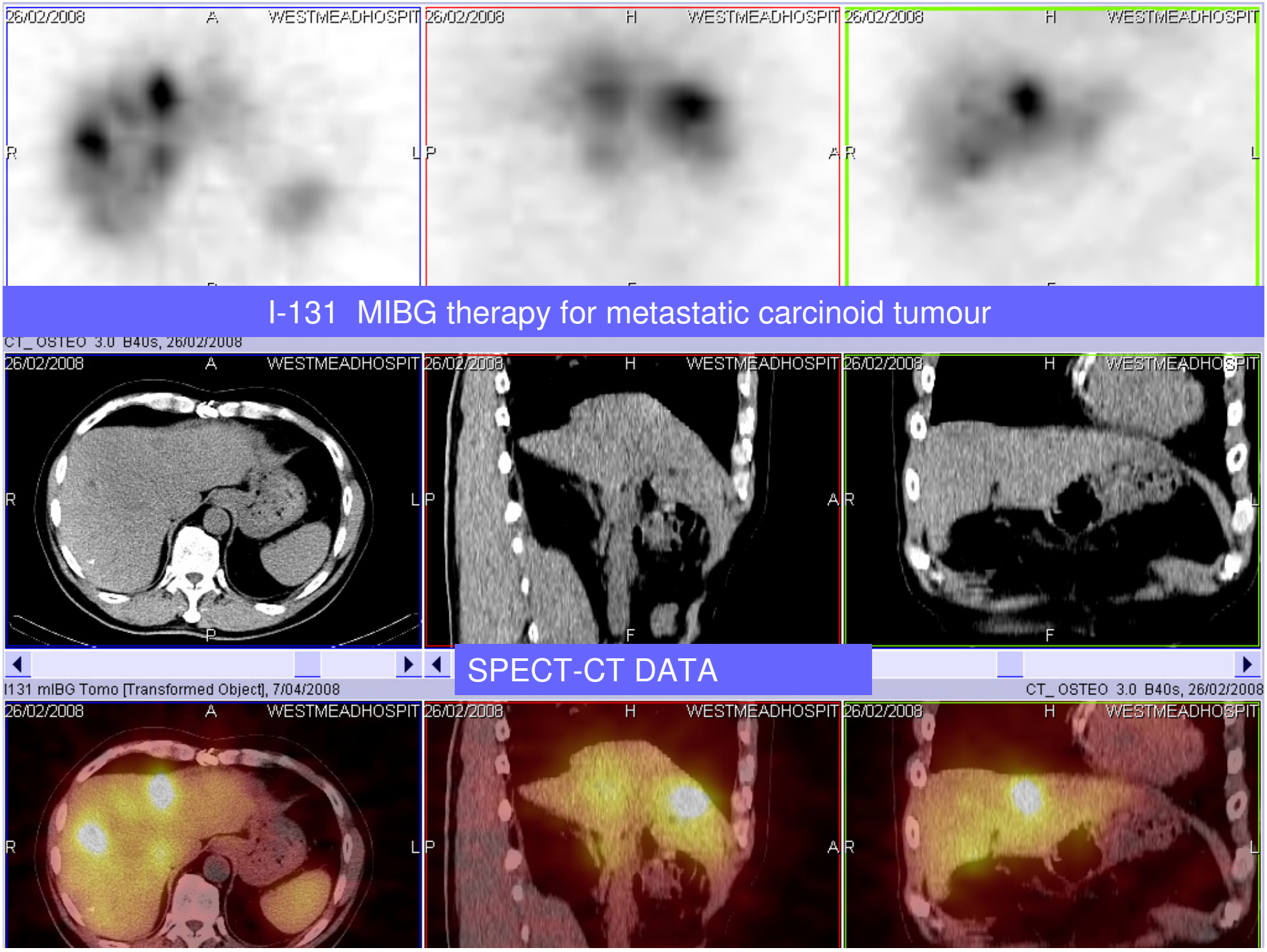
- Tc^{99m} HDP: for bone scan
- Tc^{99m} MIBI: cardiac perfusion scan
- F^{18} FDG: PET tumour scan (glu metabolism)
- Ga68 Octreotate: neuro-endocrine tumour scan, assessing SS receptor uptake


SIEMENS
1
Symbia





Single
Photon
Emission = SPECT
Computed
Tomography


26/02/2008 A WESTMEADHOSPIT
26/02/2008 H WESTMEADHOSPIT
26/02/2008 H WESTMEADHOSPIT
I-131 MIBG therapy for metastatic carcinoid tumour
CT_OSTEO 3.0 B40s, 26/02/2008
SPECT-CT DATA
I131 mIBG Tomo [Transformed Object], 7/04/2008
CT_OSTEO 3.0 B40s, 26/02/2008

PET-CT

- also images gamma rays arising from positron annihilations
- short half life isotopes eg C^{11}, N^{13}, F^{18}
- map basic metabolic pathways like glucose metabolism (F^{18}-FDG)
- now combined with CT (PET-CT)

NUCLEAR MEDICINE THERAPY

- Therapy isotopes emit beta radiation, with or without gammas
  - I-131
  - Y-90
  - Lu-177
- Same principle as diagnostic Nuc Med
  - ie target the isotope chemically to specific areas eg Lu-177 Octreotate (= Lutate)

NEURO-ENDOCRINE TUMOURS

- wide range of tumour types
  - carcinoid, phaeochomocytoma,meningioma, small cell lung cancer, medullary thyroid cancer, many others
- many are well differentiated, and slow growing
- wide range of treatment options
  - surgery, somatostatin treatment, chemotherapy, radiotherapy, radionuclide therapy
- Nuc Med/PET has diagnostic and therapeutic role in NETs

NUCLEAR MED IN NET

- Octreotide scans
  - In-111 Octreotide scan (SPECT-CT)
  - Ga-68 Octreotate scan (PET-CT_
- other scans eg bone scan
- Lu-177 Octreotate therapy
- other therapy
  - I-131 MIBG therapy
  - SirSphere therapy

MAKING A RADIOPHARMAECUTICAL

- isotope + link + Octreotide
- Ga-68 + DOTA + TOC
- In-111 + DTPA + Octreotide
- aim: link and isotope should not interfere with binding of octreotide compound
- half-life of isotope should approximately match uptake and binding characteristics of Octreotide compound

DON'T GET BOGGED IN DETAIL

Table 1. Affinity profiles (IC50) for human sst_1–sst_5 receptors of a series of somatostatin analogues.[31]

Peptide	sst_1	sst_2	sst_3	sst_4	sst_5
Somatostatin-28	5.2 ± 0.3 (19)	2.7 ± 0.3 (19)	7.7 ± 0.9 (15)	5.6 ± 0.4 (19)	4.0 ± 0.3 (19)
Octreotide	>10,000 (5)	2.0 ± 0.7 (5)	187 ± 55 (3)	>1000 (4)	22 ± 6 (5)
DTPA-octreotide	>10,000 (6)	12 ± 2 (5)	376 ± 84 (5)	>1000 (5)	299 ± 50 (6)
In-DTPA-octreotide	>10,000 (5)	22 ± 3.6 (5)	182 ± 13 (5)	>1000 (5)	237 ± 52 (5)
DOTA-TOC	>10,000 (7)	14 ± 2.6 (6)	880 ± 324 (4)	>1000 (6)	393 ± 84 (6)
Y-DOTA-TOC	>10,000 (4)	11 ± 1.7 (6)	389 ± 135 (5)	>10,000 (5)	114 ± 29 (5)
DOTA-LAN	>10,000 (7)	26 ± 3.4 (6)	771 ± 229 (6)	>10,000 (4)	73 ± 12 (6)
Y-DOTA-LAN	>10,000 (3)	23 ± 5 (4)	290 ± 105 (4)	>10,000 (4)	16 ± 3.4 (4)
DOTA-OC	>10,000 (3)	14 ± 3 (4)	27 ± 9 (4)	>1000 (4)	103 ± 39 (3)
Y-DOTA-OC	>10,000 (5)	20 ± 2 (5)	27 ± 8 (5)	>10,000 (4)	57 ± 22 (4)
Ga-DOTA-TOC	>10,000 (6)	2.5 ± 0.5 (7)	613 ± 140 (7)	>1000 (6)	73 ± 21 (6)
Ga-DOTA-OC	>10,000 (3)	7.3 ± 1.9 (4)	120 ± 45 (4)	>1000 (3)	60 ± 14 (4)
DTPA-[Tyr^3]octreotate	>10,000 (4)	3.9 ± 1 (4)	>10,000 (4)	>1000 (4)	>1000 (4)
DOTA-[Tyr^3]octreotate	>10,000 (3)	1.5 ± 0.4 (3)	>1000 (3)	453 ± 176 (3)	547 ± 160 (3)
In-DTPA-[Tyr^3]octreotate	>10,000 (3)	1.3 ± 0.2 (3)	>10,000 (3)	433 ± 16 (3)	>1000 (3)
Y-DOTA-[Tyr^3]octreotate	>10,000 (3)	1.6 ± 0.4 (3)	>1000 (3)	523 ± 239 (3)	187 ± 50 (3)
Ga-DOTA-[Tyr^3]octreotate	>10,000 (3)	0.2 ± 0.04 (3)	>1000 (3)	300 ± 140 (3)	377 ± 18 (3)

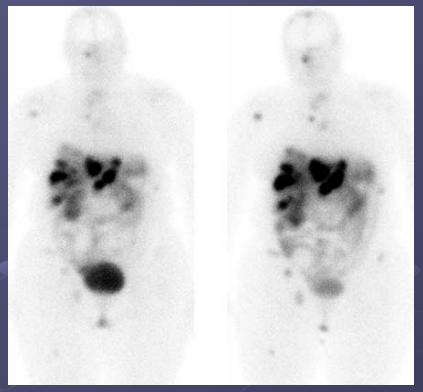
All values are half maximal inhibitory concentration (IC50) ± SEM in nM. The numbers of experiments are in parentheses.

Table 4 Results of the clinical application of somatostatin receptor imaging using various ligands in patients with gastroenteropancreatic neuroendocrine tumors

Radioligand	Reported results	Comments	References
[^{99m}Tc-EDDA/HYNIC^0]octreotate	Better than [^{111}In-DTPA^0] octreotide	[^{111}In-DTPA^0]octreotide scan protocol inadequate	Hubalewska-Dydejczyk *et al.* (2006)
[^{68}Ga-DOTA^0,Tyr^3]octreotide	[^{68}Ga-DOTA^0,Tyr^3]octreotide PET better than other two methods	No comparison to [^{111}In-DTPA^0]octreotide	Gabriel *et al.* (2007)
[^{99m}Tc-HYNIC^0]octreotide [^{111}In-DOTA^0]octreotide			
[^{68}Ga-DOTA^0,Tyr^3]octreotide	Better than [^{111}In-DTPA^0] octreotide SPECT	[^{111}In-DTPA^0]octreotide scan protocol inadequate	Buchmann *et al.* (2007)
[Gluc-Lys^0,[^{18}F]FP]octreotate	Better than [^{111}In-DTPA^0] octreotide		Meisetschläger *et al.* (2006)
[^{68}Ga-DOTA^0,Tyr^3]octreotide	Better than [^{111}In-DTPA^0] octreotide	[^{111}In-DTPA^0]octreotide scan protocol inadequate	Hofmann *et al.* (2001)
[^{68}Ga-DOTA,1-naphthylalanin^3] octreotide	Useful information additional to CT	No comparison to [^{111}In-DTPA^0]octreotide	Fanti *et al.* (2008)
[^{68}Ga-DOTA,1-naphthylalanin^3] octreotide	Better than ^{18}F-DOPA	No comparison to [^{111}In-DTPA^0]octreotide	Ambrosini *et al.* (2008)
^{99m}Tc-Depreotide	Inferior to [^{111}In-DTPA^0] octreotide		Lebtahi *et al.* (2002)
[^{111}In-DOTA]lanreotide	Inferior to [^{111}In-DOTA^0,Tyr^3] octreotide	No comparison to [^{111}In-DTPA^0]octreotide	Virgolini *et al.* (2002)

Peptide Receptor Radionuclide Therapy: Forrer et al. Best Practice & Research Clinical Endocrinology & Metabolism. 21; 111–129, 2007

OCTREOTIDE FAMILY



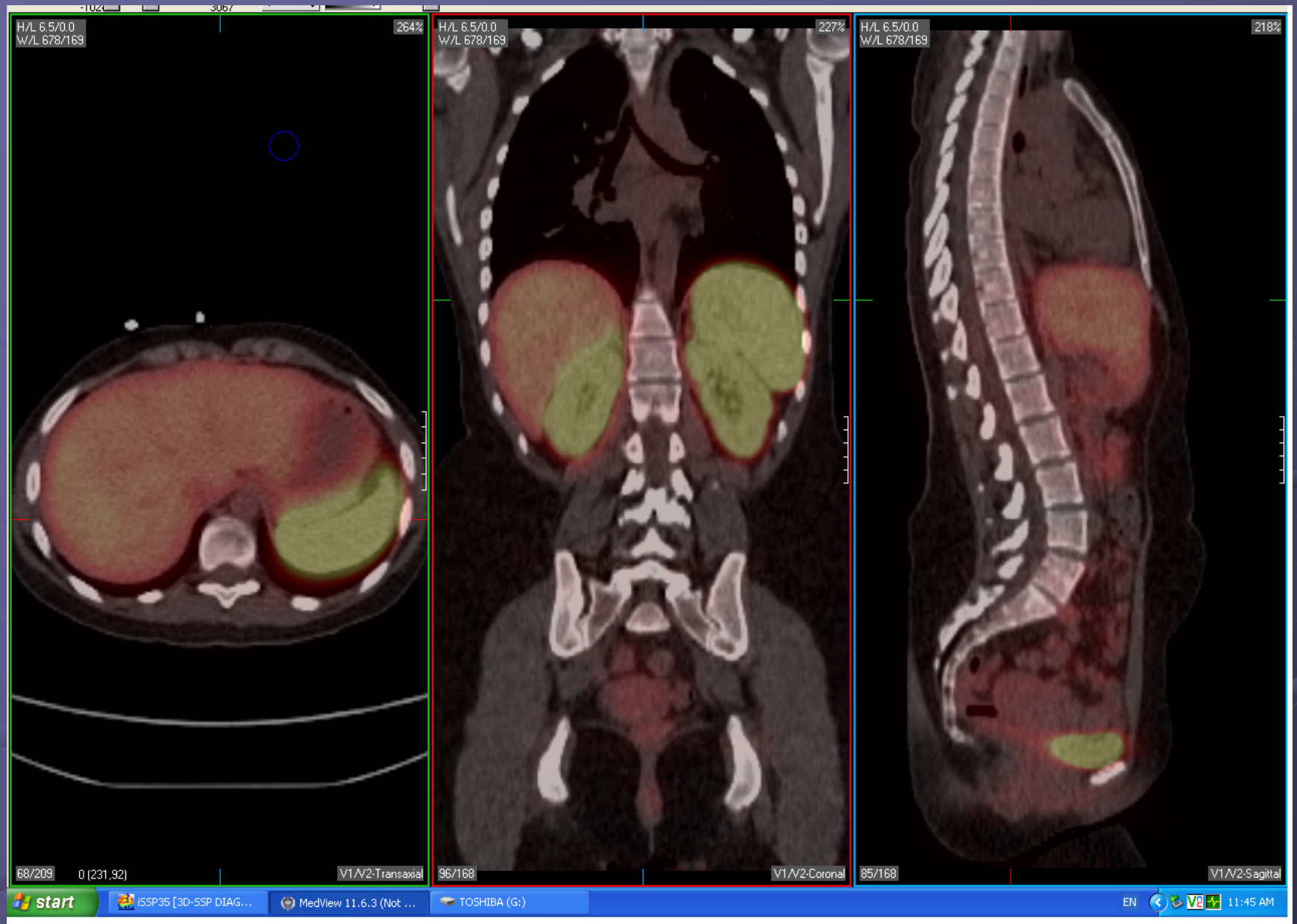
- different types of Octreotide
- different receptor binding
- different labelling capabilities
- Octreotate most commonly used in PET and therapy, while Octreotide most commonly used in SPECT.
- mixed formulations may evolve in future, for different tumour sub-types

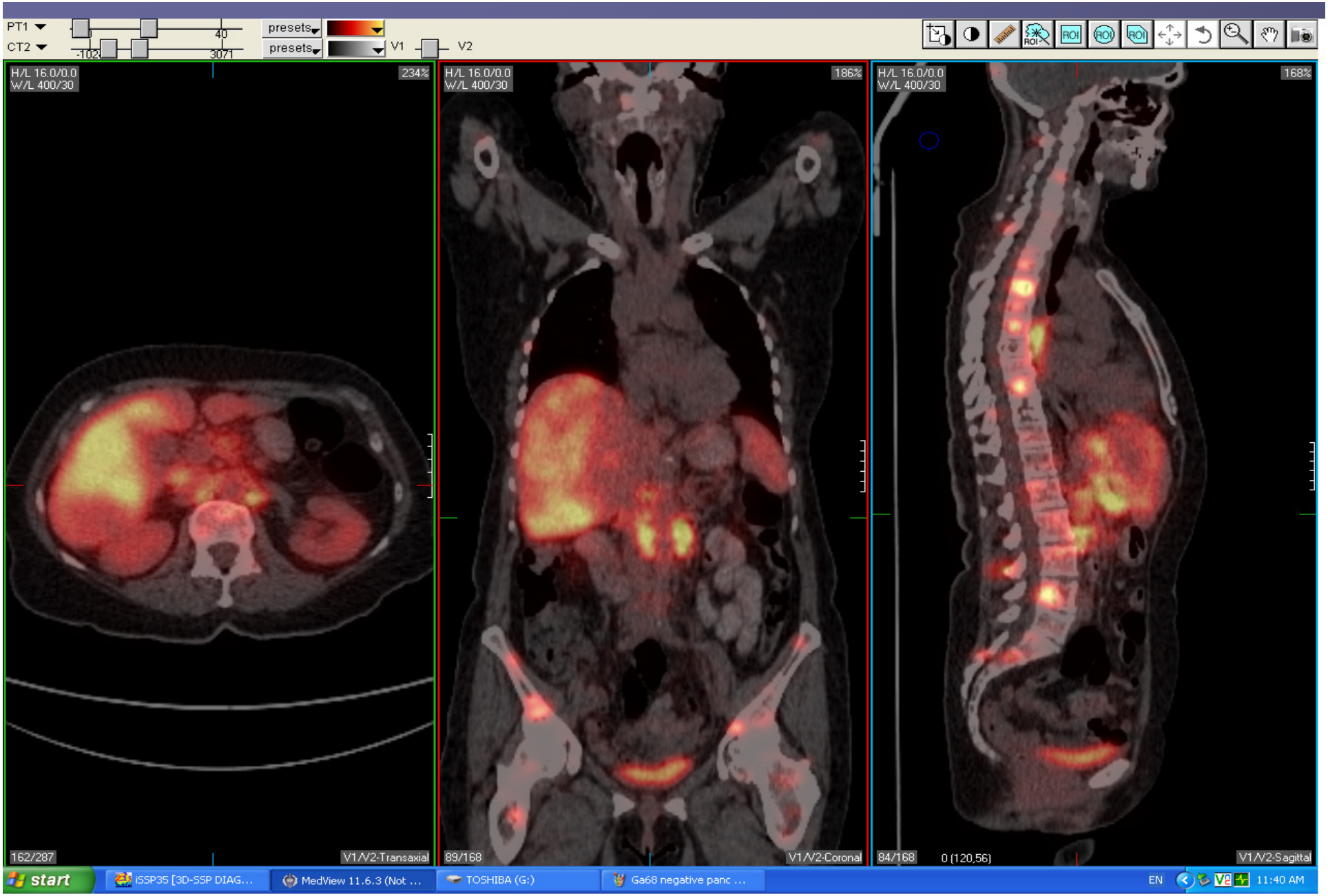
RADIOACTIVE ISOTOPES

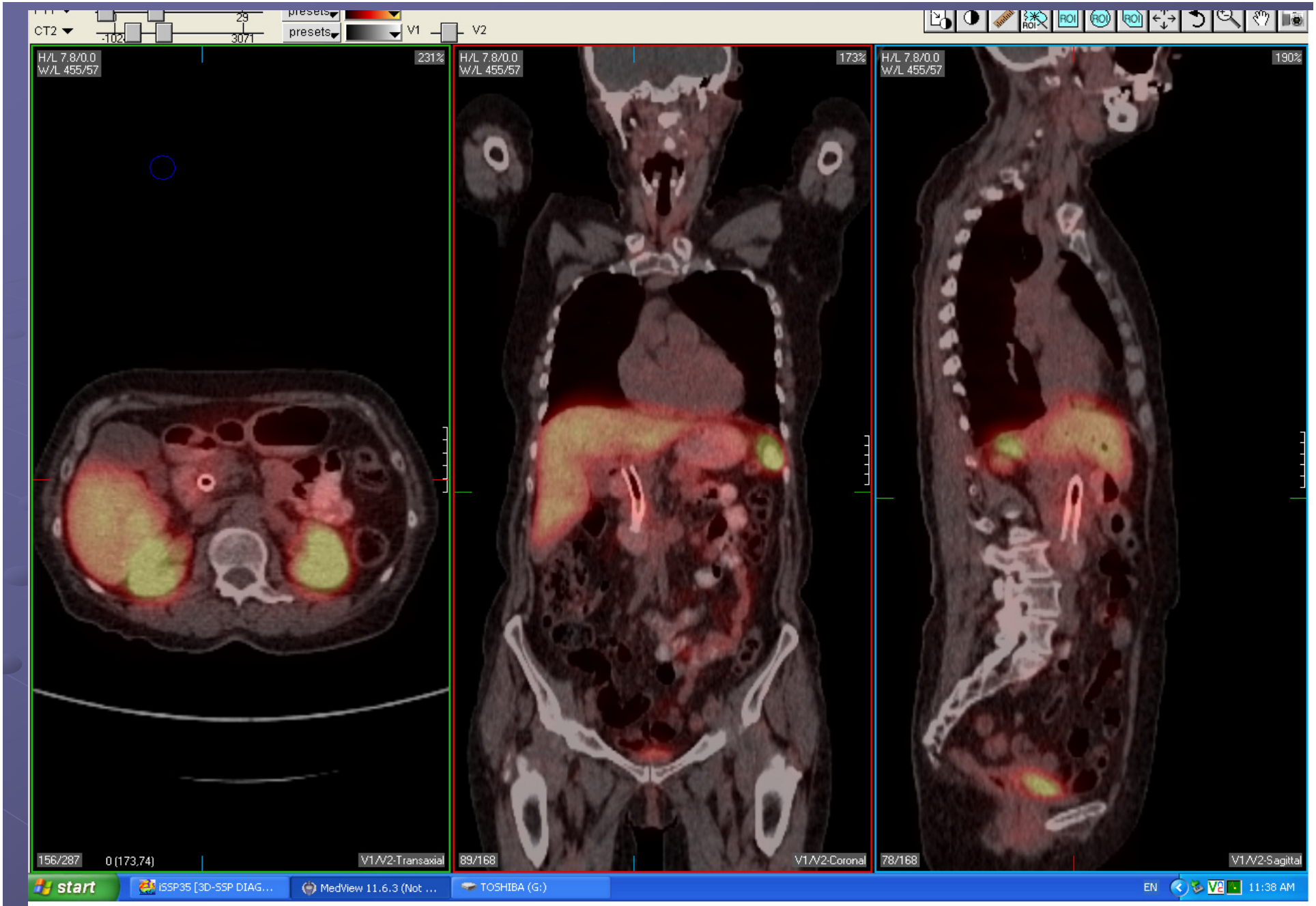
- Indium 111. Mostly a diagnostic agent, but some previous therapy use. Auger electrons have short tissue path (up to 10 microns)
- Y-90: high energy electrons, with tissue penetration of up to 12mm. No gammas so less radiation concerns for bystanders
- Lu-177: mid energy electrons, tissue penetration of up to 2mm. Some gammas for imaging.

OCTREOTIDE DIAGNOSTIC SCANS

- In-111 Octreotide scan with SPECT-CT is current standard, with good availability in most Nuclear Med Depts
- Ga-68 Octreotate PET-CT is superior: Westmead is only provider in NSW. Referrals accepted from all Oncologists. Other states have one centre each performing Ga68-Octreotate scans.
- RNSH wants to offer this service too.


H/L 6.5/0.0
W/L 678/169
264%
68/209
0 (231,92)
V1/V2-Transaxial
H/L 6.5/0.0
W/L 678/169
227%
96/168
V1/V2-Coronal
H/L 6.5/0.0
W/L 678/169
218%
85/168
V1/V2-Sagital
start
ISSP35 [3D-SSP DIAG...
MedView 11.6.3 (Not ...
TOSHIBA (G:)
EN
11:45 AM


PT1
CT2
-102
40
3071
presets
presets
V1
V2
H/L 16.0/0.0
W/L 400/30
234%
162/287
V1/V2-Transaxial
H/L 16.0/0.0
W/L 400/30
186%
89/168
V1/V2-Coronal
H/L 16.0/0.0
W/L 400/30
168%
84/168
0 (120,56)
V1/V2-Sagittal
start
iSSP35 [3D-SSP DIAG...
MedView 11.6.3 (Not ...
TOSHIBA (G:)
Ga68 negative panc ...
EN
11:40 AM


CT2
-102
29
3071
presets
presets
V1
V2
H/L 7.8/0.0
W/L 455/57
231%
156/287
0 (173,74)
V1/V2-Transaxial
H/L 7.8/0.0
W/L 455/57
173%
89/168
V1/V2-Coronal
H/L 7.8/0.0
W/L 455/57
190%
78/168
V1/V2-Sagittal
start
iSSP35 [3D-SSP DIAG...
MedView 11.6.3 (Not ...
TOSHIBA (G:)
EN
11:38 AM

OTHER NUCLEAR MED TECHNIQUES

- SirSphere therapy
  - used to treat liver metastases
  - Y-90 labelled microspheres to embolise and give local high dose radiotherapy
  - used when most of the disease is within the liver
  - Westmead Hospital and St Vincent's Private
  - expensive ($8K for SirSpheres plus costs of angiogram x 2, etc)

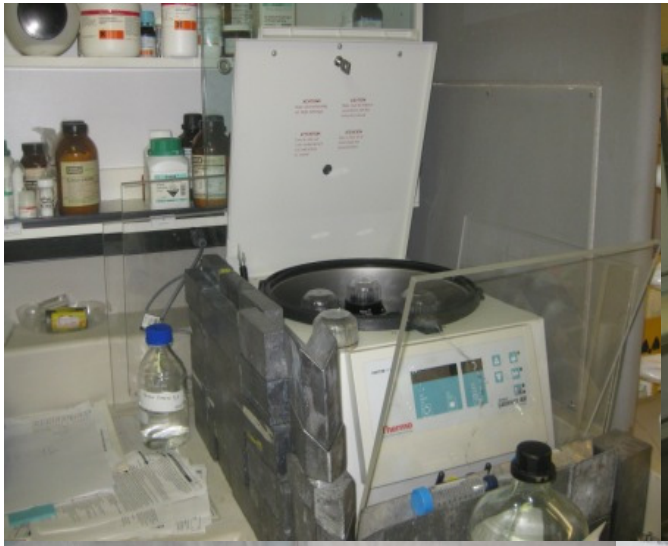
OTHER IMAGING

- CT scanning
- MRI
- ultrasound
- plain x-rays
- angiography
- interventional procedures eg line placement
- PET: F-Dopa, F-tryptophan: no therapy analogue

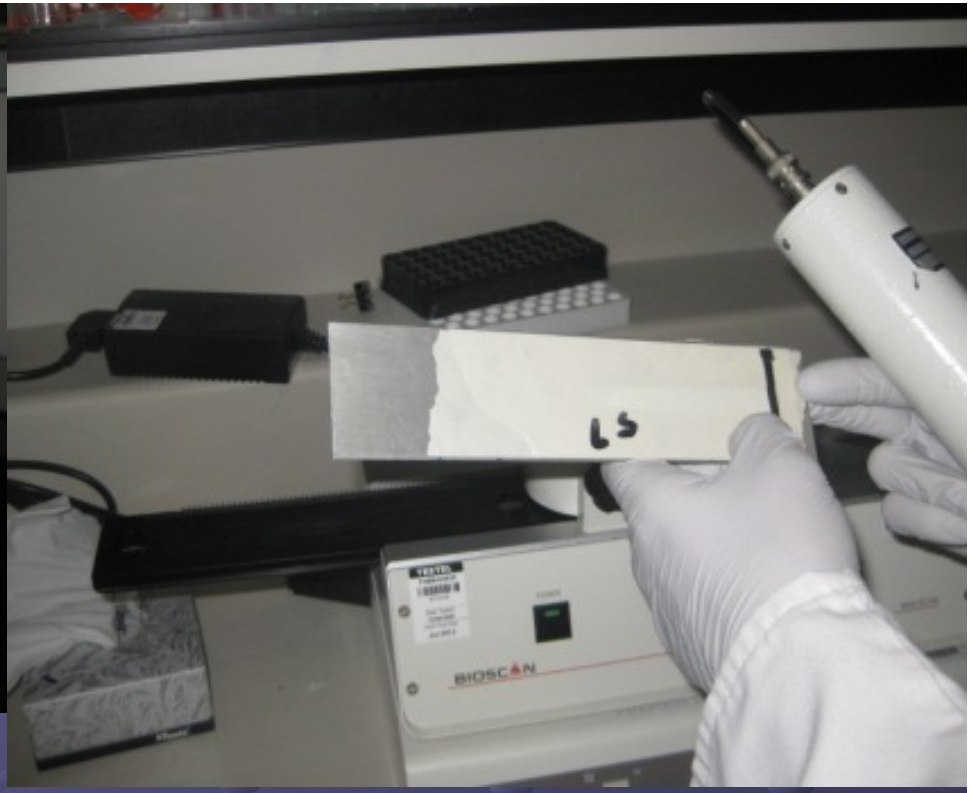
all provide essential anatomic information and allow procedures to be reliably performed

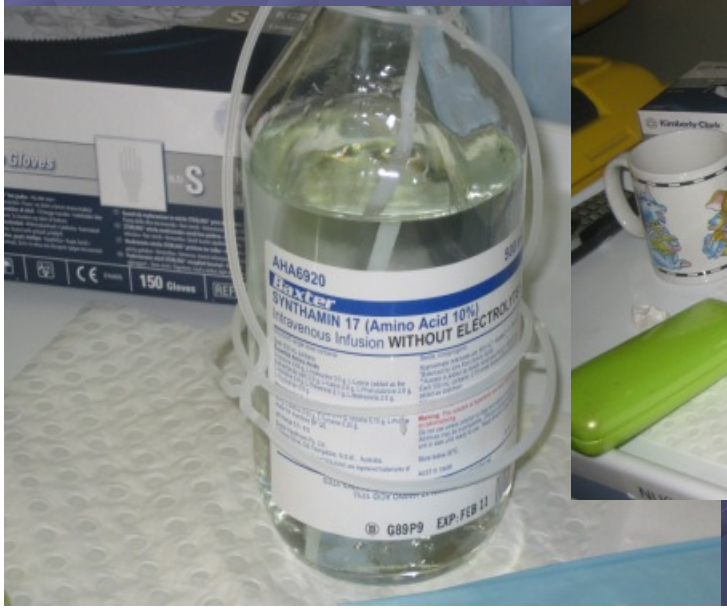
Lu-177 Octreotate

- most common peptide receptor therapy isotope used in Australia and Europe
- little used in US due to local regulations
- Lu-177 reactor produced; imported from Holland
- Lucas Heights reactor just starting to produce small amounts (first test shipments)

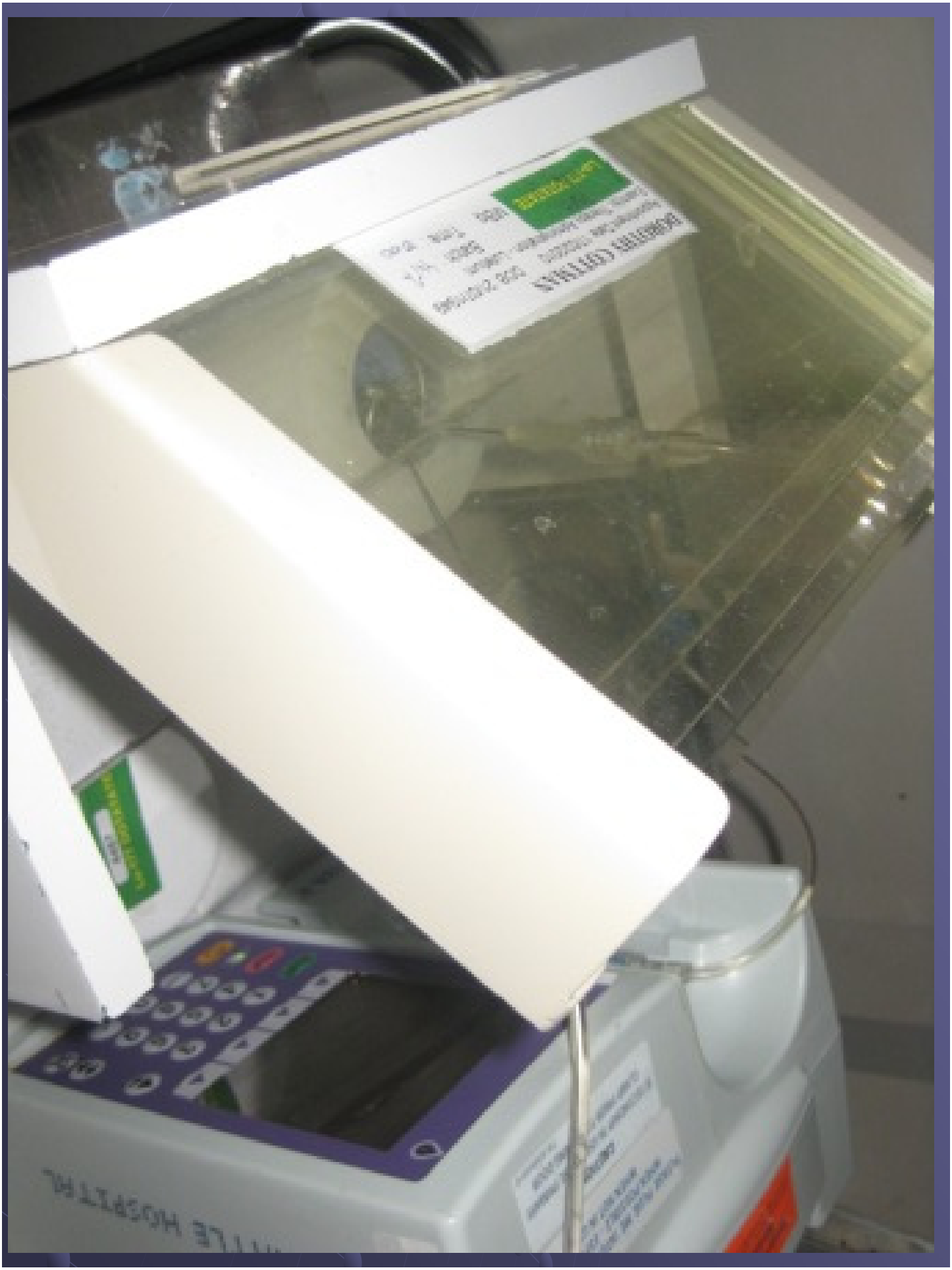



Sterile Room

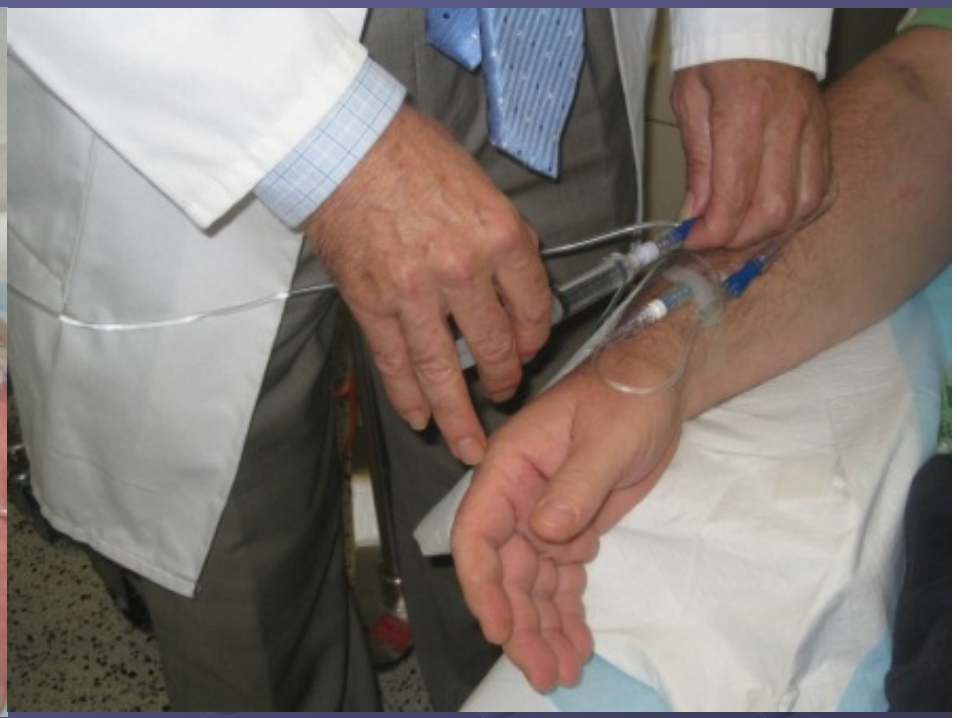

BIOSCAN


AHA6920
Baxter
SYNTHAMIN 17 (Amino Acid 10%)
Intravenous Infusion WITHOUT ELECTROLYTES
G89P9
EXP. FEB 11


OPERATING INSTRUCTIONS
CAUTION: Verify all values before beginning infusion!
START



saline flush to check for leaks



tropisetron to block nausea + vomiting

LUTATE THERAPY

Sequential post Lutate therapy whole body scans over 16 weeks

Reduction in size and activity of carcinoid metastases

Lutate Therapy Indications

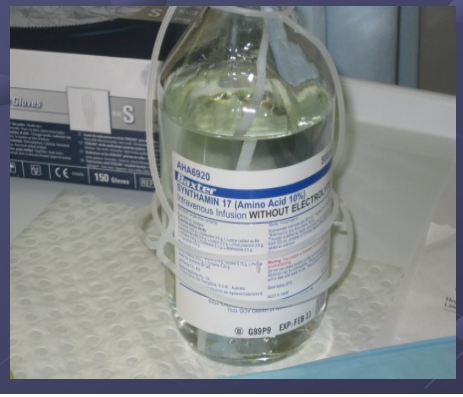
- NET
- well differentiated; Ki-67 index < 10 (proliferative rate)
- disseminated and not surgically amenable
- progressive disease (symptoms, CT, markers eg chromogranin A)

TREATMENT PHILOSOPHY

- cure not achieved with disseminated disease by mono-therapy
- combine Lutate with biotherapy / chemotherapy
  - eg capecitabine, temozolamide, everolimus
- dose: 7.8 GBq x 4 cycles @ 8 week intervals
- expect gradual response

PATIENT PREP

- day Oncology ward admission
- light breakfast
- 22G cannula
- oral benzodiazepine premed because it is a long day (can't drive home).
- 4 hour amino acid infusion for reno-protection



INFUSION

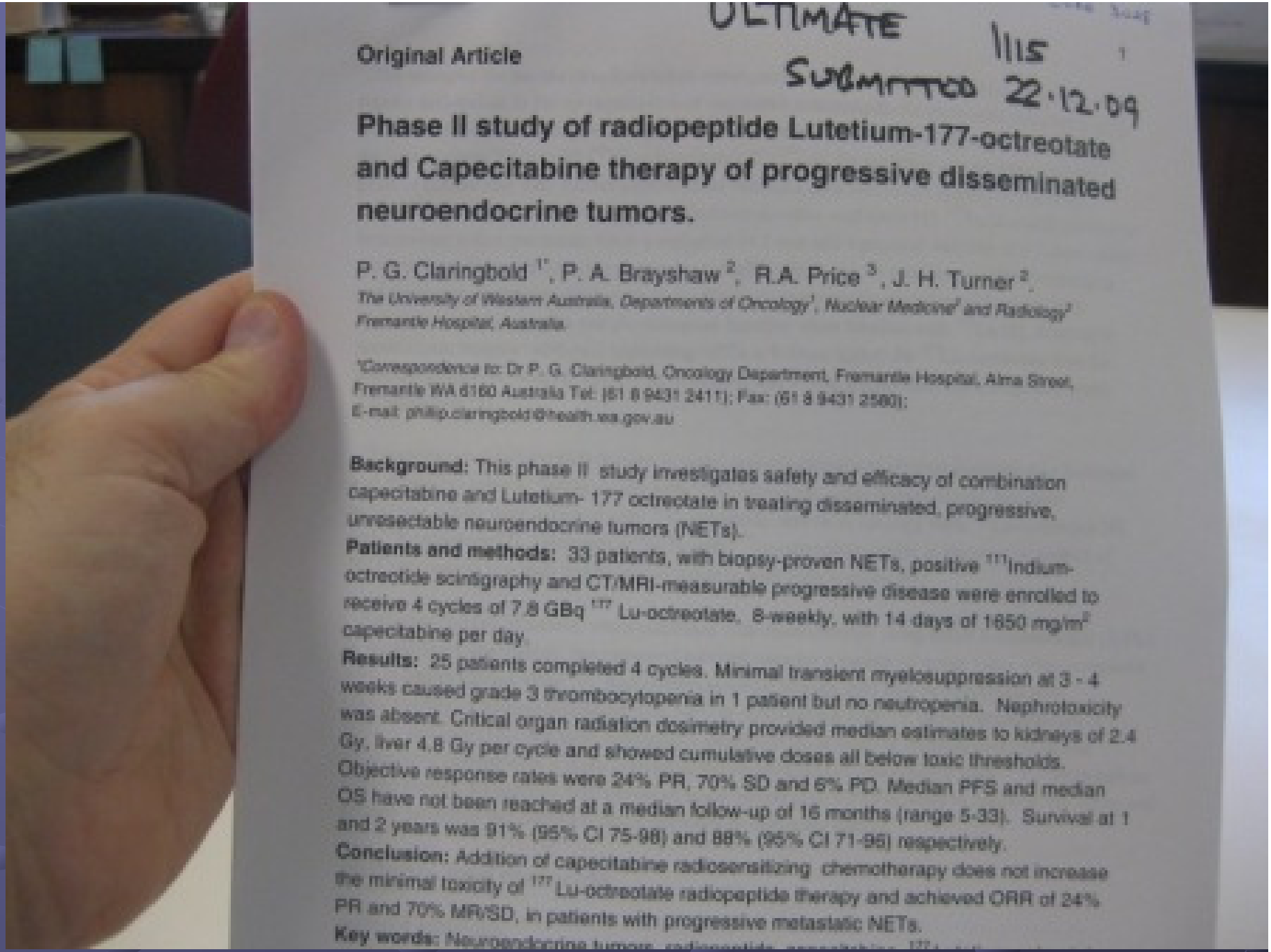
- Lutate infused over 10 mins, 3.5ml of injectate made up to 10ml with normal saline
- 40 ml saline flush
- infusion via pump
- vial behind shield on trolley
- via same cannula as amino acid infusion

DISCHARGE CRITERIA

- average discharge can occur at 3.46 hours (dose rate = 25 microSv / hr at 1 m)
- 100% can go home at 6 hours
- coffee and sandwiches as soon as the patient wishes
- family member can stay with patient for day

SIDE EFFECTS

- immediate
  - nausea and vomiting (requires IV tropisetron)
  - due to AA and peptide (5m tropisetron for AA infusion, then up to 7mg for Lutate infusion at 20-30 ml
  - arm swelling (AA infusion)
- delayed
  - side effects of chemo and radionuclide therapy only
  - some marrow impairment (transient marrow suppression)
  - no renal impairment
- similar results to large published studies internationally



ULTIMATE MS SUBMITTED 22.12.09

Original Article

Phase II study of radiopeptide Lutetium-177-octreotate and Capecitabine therapy of progressive disseminated neuroendocrine tumors.

P. G. Claringbold [1*], P. A. Brayshaw [2], R.A. Price [3], J. H. Turner [2].

The University of Western Australia, Departments of Oncology[1], Nuclear Medicine[2] and Radiology[3] Fremantle Hospital, Australia.

Correspondence to: Dr P. G. Claringbold, Oncology Department, Fremantle Hospital, Alma Street, Fremantle WA 6160 Australia Tel: (61 8 9431 2411); Fax: (61 8 9431 2580); E-mail: phillip.claringbold@health.wa.gov.au

Background: This phase II study investigates safety and efficacy of combination capecitabine and Lutetium- 177 octreotate in treating disseminated, progressive, unresectable neuroendocrine tumors (NETs).

Patients and methods: 33 patients, with biopsy-proven NETs, positive ^{111}Indium-octreotide scintigraphy and CT/MRI-measurable progressive disease were enrolled to receive 4 cycles of 7.8 GBq ^{177} Lu-octreotate, 8-weekly, with 14 days of 1650 mg/m^2 capecitabine per day.

Results: 25 patients completed 4 cycles. Minimal transient myelosuppression at 3 - 4 weeks caused grade 3 thrombocytopenia in 1 patient but no neutropenia. Nephrotoxicity was absent. Critical organ radiation dosimetry provided median estimates to kidneys of 2.4 Gy, liver 4.8 Gy per cycle and showed cumulative doses all below toxic thresholds. Objective response rates were 24% PR, 70% SD and 6% PD. Median PFS and median OS have not been reached at a median follow-up of 16 months (range 5-33). Survival at 1 and 2 years was 91% (95% CI 75-98) and 88% (95% CI 71-95) respectively.

Conclusion: Addition of capecitabine radiosensitizing chemotherapy does not increase the minimal toxicity of ^{177}Lu-octreotate radiopeptide therapy and achieved ORR of 24% PR and 70% MR/SD, in patients with progressive metastatic NETs.

Key words: Neuroendocrine tumors, radiopeptide, capecitabine, ^{177}Lu

PERTH LUTATE OUTCOMES

- 33 patients with biopsy proven metastatic NET, progressive despite regular therapy, unresectable.
- mean age 60 years (32-82 y)
- 4 cycles of Lutate given
- objective responses
  - 24% partial response
  - 70% stable disease
  - 6% progressive disease
- 1 and 2 year survival rates: 91% and 88%

NSW SITUATION

- most hospitals provide In-111 Octreotide SPECT-CT service
- Westmead provides Ga-68 Octreotate PET-CT scans (and F18-FDG scans for NET)
- no NSW site provides Lutate therapy
- radionuclide therapy business case submitted to NSW Health (for Lutate funding, plus other therapies).

LUTATE THERAPY

- funding required for Lutate service ($1-3m per annum).
- Westmead is a suitable site for such a therapy service, but other hospitals also suitable
- ? one or two sites in NSW
- Cost = $20-30K per patient.
- Expensive but similar in cost to sandostatin and cost offsets common