How to Fit Radionuclide Therapy Planning into Your Department

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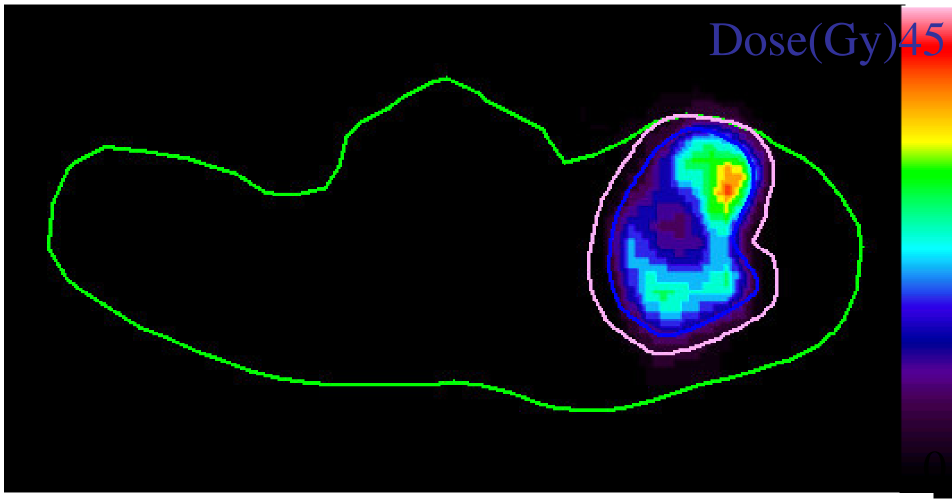
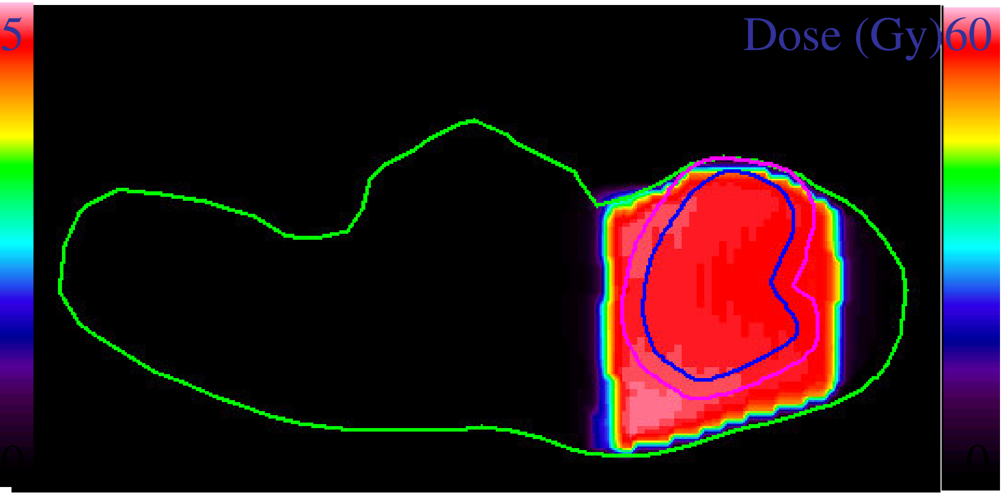
Targeted Radionuclide Therapy

- **Aims**
  - To deliver a tumourcidal dose to target volume
  - To minimise the dose to normal organs…
- Rapidly increasing method of treatment for a wide range of cancers
- Often given in conjunction with *Chemotherapy* or *External Beam Therapy*

Combined TRT & XRT Planning





Radionuclide Dose Map

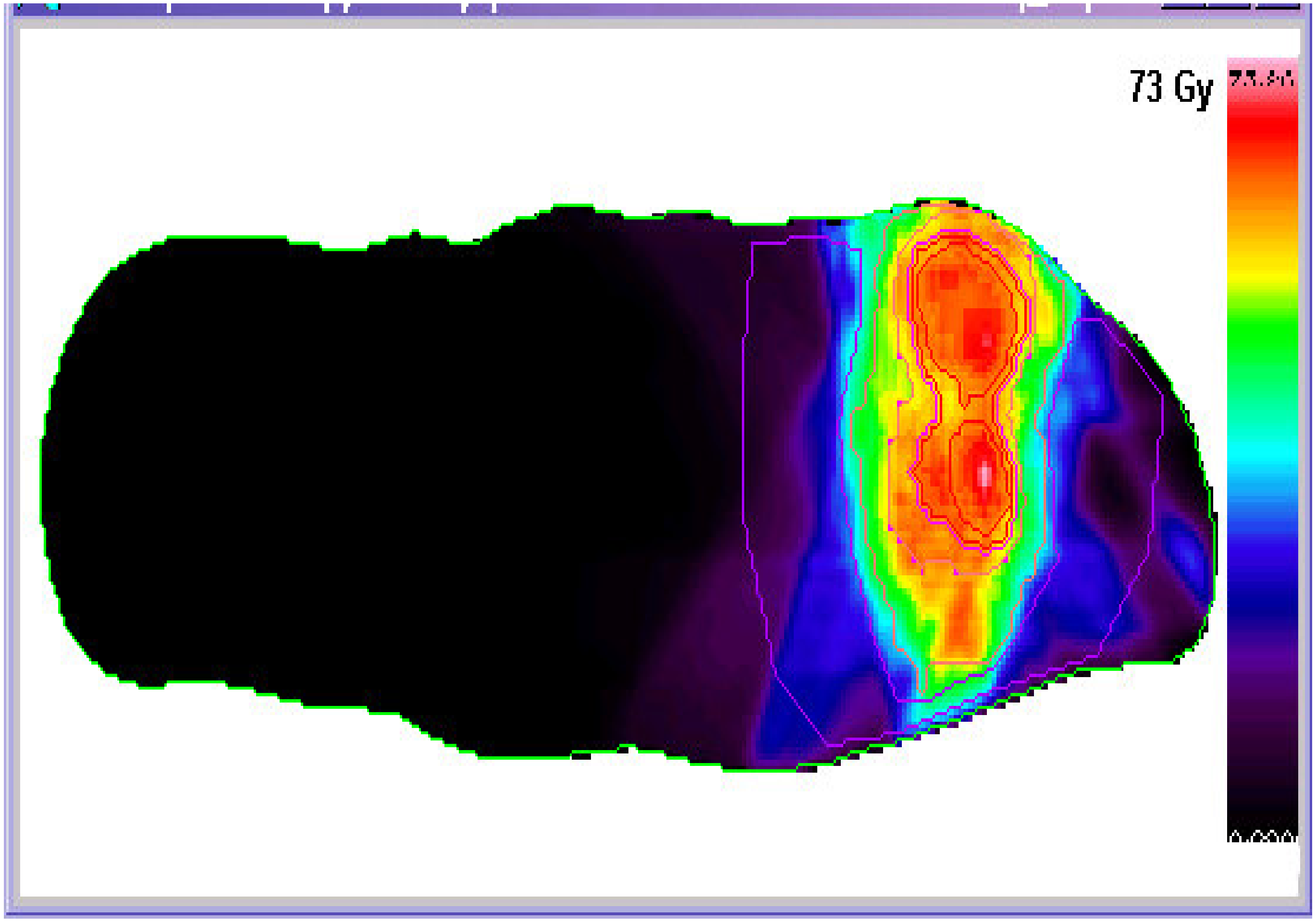
- Maximum Dose: 45 Gy
- Produced using RMDP (Radionuclide Multimodality Dosimetry Package)

External Beam Dose Map

- Dose to Isocentre: 60 Gy
- Parallel opposed pair

Images Courtesy Rachel Bodey, The Royal Marsden, London

Combined TRT & XRT Dose Map



Images Courtesy Rachel Bodey, The Royal Marsden, London

Targeted Radionuclide Therapy

- Alpha, **beta** or Auger electron emitters can be used with these general requirements:-
  - ~days < $T_{1/2}$ < ~month
  - Low gamma and x-ray emissions *(Imaging only)*
  - Stable chemical bond to targeting agent
- Why not utilise the High LET of a?
  - The a-recoil may break carrier-radionuclide bond, allowing daughter products *(often unstable)* to spread to normal tissue…
  - Targeting agent must bind very close to DNA *(as is also the case with Auger electrons)…*

Targeted Radionuclide Therapy

- Radioimmunotherapy (RIT) is the use of Monoclonal antibodies (Mabs)
- Pressman demonstrated back in 1946 tumour targeting using antibodies

Radionuclide	Primary photon energy /MeV	Average beta energy /MeV	Half-life
^{64}Cu	0.511	0.190	12.7 hours
^{124}I	0.511	0.686, 0.974 (e^+)	4.2 days
^{131}I	0.364	0.192	8.0 days
^{186}Re	0.137	0.320	90.6 hours
^{73}Se	0.511	0.001, 0.562 (e^+)	7.2 hours
^{90}Y	None	0.935	64.1 hours

Current Therapy Range at RSCH

- *Ca Thyroid and Thyrotoxicosis*
  - ^{131}I**NaI** (Amersham Health)
- *Bony Metastasis (~ Pain Palliation)*
  - ^{89}Sr Cl_2(**Metastron** - Amersham Health)
  - ^{153}Sm EDTMP (**Quadramet** - Schering)
- *Liver Metastasis*
  - ^{90}Y **Microspheres** (Sirtex)
- *Neuroblastoma, Phaeochromocytoma, Carcinoid*
  - ^{131}I **mIBG** (Amersham Health)

^{90}Y Zevalin®

- Non-Hodgkin's Lymphoma (NHL)
- Ibritumomab tiuxetan (Biogen IDEC - Schering)
  - CD20 antigen
  - found on the surface of normal and malignant B lymphocytes
- **FDA** Approved February 2002 (initially)
- **European** Approval imminent (before end 2003)
- *First* **radioimmunotherapy** agent for cancer treatment
  - Response rates ~80% (when combined with Rituxan®)
  - Apparent Complete Response in ~20%
  - Schering market as "*One Time Only*" treatment…
- Weight and platelet-based administration
- Severe or life-threatening adverse events in <5% of patients:
  - allergic reaction
  - gastrointestinal hemorrhage
  - tumour pain

Why Patient Specific Therapy?

- Conventional administration is **fixed** or **weight-based** activity:-
  - Q: Treats an **Average** Patient?
  - A: No: treats to ensure ~no high grade toxicity in patient group (subject to exclusion criteria)
  - Therefore, approach is **safe**: doses to organs at risk are kept low
  - However, (by definition) most patients are **under treated**

- Benefits of tailoring therapies to individual patients are well documented over many years for External Beam Radiotherapy

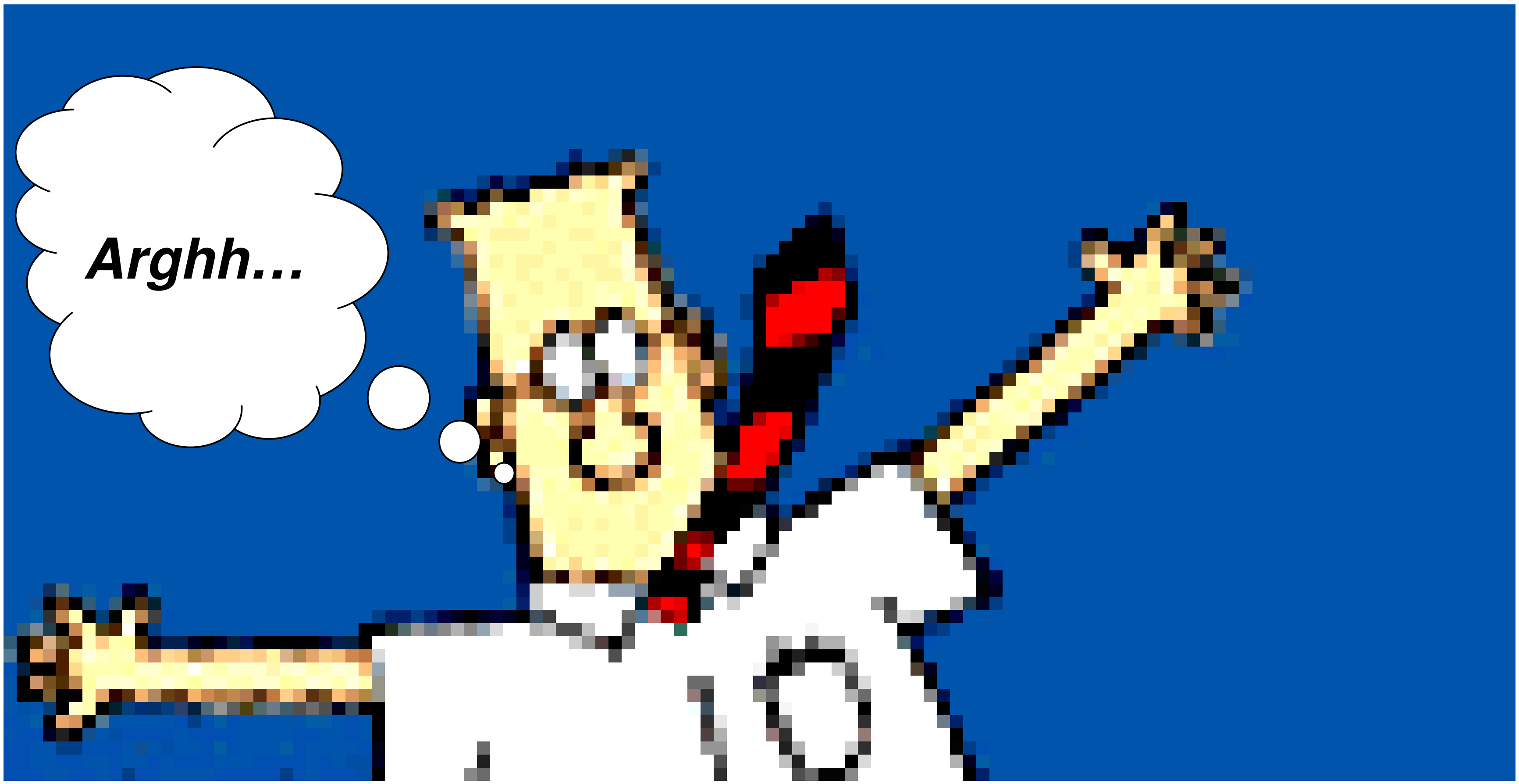
Patient Specific Therapy

- Radionuclide therapy can be optimised by varying:-
  - The **activity** administered
  - The **frequency** of therapies *("fractionation")*
  - The **radioisotope** used (a / ß ranges)
- These approaches require **planning** along similar lines to Radiotherapy Planning (RTP)

Patient Specific Input Required

- Multiple **wholebody** activity measurements
- Multiple NM datasets (preferably **SPECT**):
  - Must be **quantitative** (preferably **absolute**)
  - At least **three** sets *per* phase
  - Each dataset must be **registered**
- Anatomical dataset (preferably CT) for use in:
  - **Attenuation correction** (iterative recon)
  - **Localisation** of disease
  - **Registration** of SPECT scans

Sounds Like Hard Work…



Why Patient Specific Therapy?

- The Law within the European Union…
- Council Directive 97/43/Euratom 30/06/97
  - Defines *Radiotherapeutic* as

  Pertaining to radiotherapy including ***Nuclear Medicine*** *for therapeutic purposes*

  - It states that

  For ***all*** *radiotherapeutic purposes … exposures of target volumes shall be* ***individually*** *planned*

Medical Internal Radiation Dose

1 **Define**

source organ (containing activity) and

target organ (often the same)

2 Determine the cumulated activity in the source organ - $\tilde{A}$

3 Calculate the 'S' factor. Then $D = \tilde{A} \times S$

MIRD: The S Factor

where

$$S = \frac{1}{m_t}\sum_i \Delta_i \times \phi_i$$

m_t = mass of target organ

Δ_i = equilibrium dose constant for *i*th type radiation

ϕ_i = absorbed fraction for *i*th type radiation

MIRD: Assumptions

- Assumes **uniform** distribution
- Results quoted only as a **mean** tumour dose
- For all scans (input data) MIRD relies on
  - Volume determination
  - Localization
- Difficulty with **non-standard** organ geometries (*e.g. Tumours)*

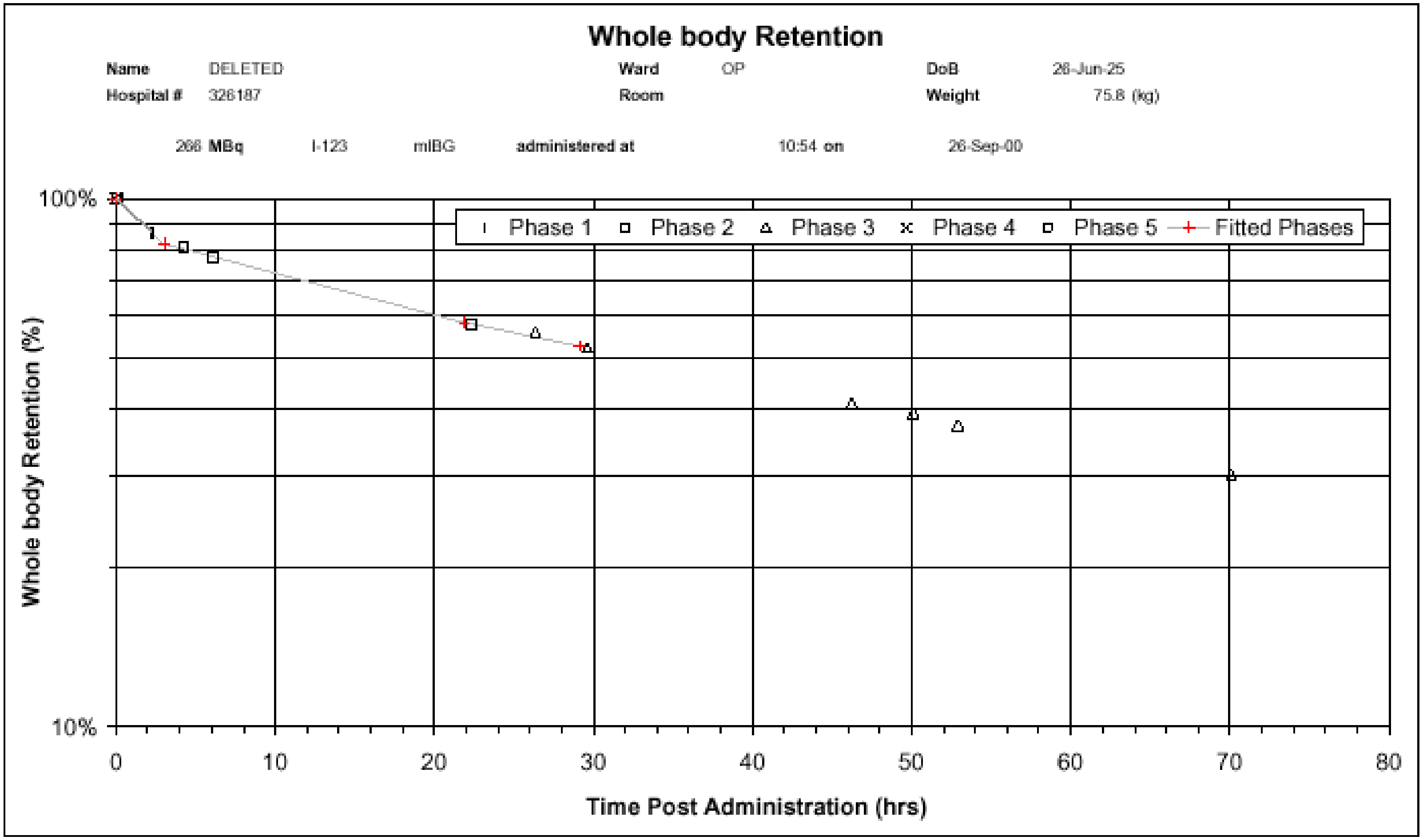
The MIRD Approach

- Despite limitations, MIRD offers fast results
- Require a straight-forward spreadsheet and MIRDOSE 3.1 *(NB Not FDA Approved)*
- In most cases **can** be used for calculating:
  - **Wholebody** dose (VERY important; a Red Marrow)
  - **Mean** or **Maximum** dose to organs at risk *(liver)*
- **Not suitable** for calculating TCP…

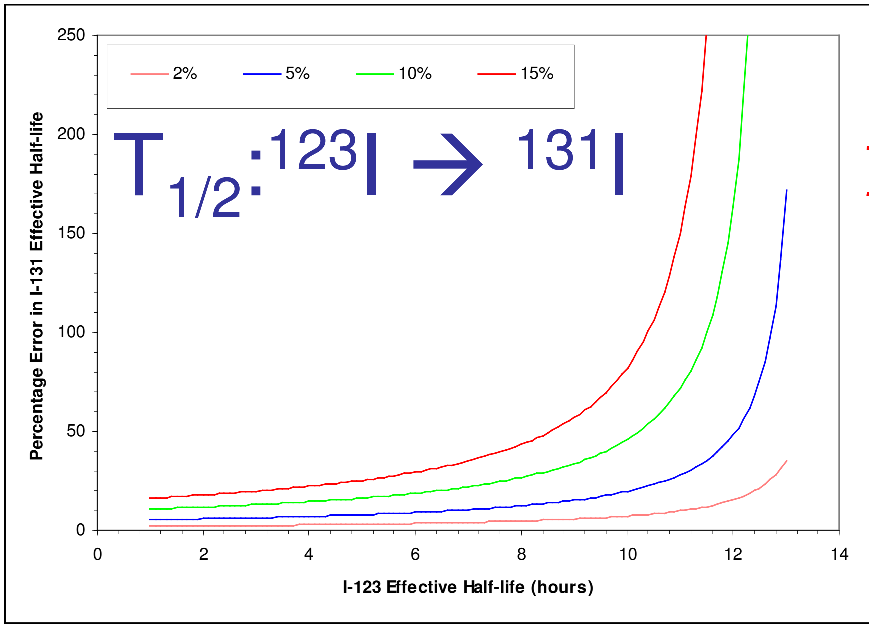
MIRD Example Case

- **Tracer ^{123}I** mIBG study on adult dosimetry patient
- **Wholebody** measurements made on 2m arc NaI
- **SPECT** studies acquired at 6, 26, 47 & 54 hours
- **Calibration** scans were carried out using activity distributions closely matching actual distribution
- **Predicted** administered activities of ^{131}I-mIBG to achieve preset wholebody doses are given
- Therapy tumour and liver (main organ at risk) doses predicted for given wholebody dose

MIRD Example: WB Retention



MIRD Example: WB Levels



Pre-Therapy Whole body Retention Report

Name	DELETED	*Ward*	OP	*DoB*	26-Jun-25
Hosp #	326187	*Room*		*Weight(kg)*	75.8

266 MBq I-123 mIBG *administered at* 10:54 *on* 26-Sep-00

TRACER Whole Body Retention (3 phases from graph *I-123* *Tphys 1/2* *13.1*

Phase #	Astart (Mbq)	Afinish (MBq)	Tstart (hrs)	Tfinish (hrs)	Teff 1/2(hrs)
1	266	186	0.000	3.067	5.939
2	186	49	3.067	21.889	9.748
3	49		21.889		10.354

THERAPY Activity Levels per Unit Activity Administered of... *I-131* *Tphys 1/2* *192.96*

Phase #	Astart (Mbq)	THERAPY Afinish (MBq)	Tstart (hrs)	Tfinish (hrs)	Teff 1/2(hrs)
1	1.000	0.813	0.000	3.067	10.284
2	0.813	0.540	3.067	21.889	31.813
3	0.540		21.889		39.334

Whole body S Factor

Using KP's Weight Dependent S-Factor (based on newborn, 1 year, 5 year and adult weights)

S Factor $_{WB\to WB}$ 1.35E-04 .Weight ^ -0.918 Gy / (MBq h)

Patient Weight (kg) = 75.8

S Factor $_{WB\to WB}$ **2.54E-06** Gy/(MBq h)

Whole body Dosimetry

Phase #	Dose per MBq per Phase (Gy/MBq)
1	7.056E-06
2	3.194E-05
3	7.791E-05

Whole body Dose (Gy)	**0.5**	**1.0**	**1.5**	**2.0**	**2.5**	**3.0**
Activity Required (MBq)	**4,277**	**8,554**	**12,831**	**17,108**	**21,385**	**25,662**
Dose Factor (Gy/MBq)	*1.169E-04 Gy*					

Comments

First Pre-Therapy

Weight Corrected $S_{wb\to wb}$

Maximum *therapy* WB dose is usually 2Gy

MIRD: Calibration Scans

- Must use the **same** camera as for the patient
- Match scan parameters as closely as possible
- The calibration scan is an admission that *absolute* ^{131}I quantification is difficult to achieve…

Tumour Dosimetry Calibration Phantom
IF APPLICABLE

Please fill in grey cells as required. Other coloured cells will be calculated for you.

Name DELETED
Hospital # 326187

Tracer	I-123		**Therapy**	I-131
Tphys 1/2	13.1 hours		Tphys 1/2	192.96 hours

VOI 1	Tumour	*(Label)*	**Type**	Max	*(Max/Mean)*		
General Description	4 cm dia plastic bottle in Temex Man						
Scan Acquired at	17:18	on	15-Nov-00	with	72	projs of (s)	20
***Phantom** Vol (cc) =*	Phantom Mass Full(g)		90.43	- Empty(g)	13.11	=	77.32
***Stock** Volume (cc) =*	Stock Mass Full (g)		204.68	- Empty(g)	200.80	=	3.88
***Stock** Activity (MBq)*	21.90	at time	15:55	on date	15-Nov-00	@1/2scan	20.14
***Syringe** Vol (cc)=*	Syringe Full (g)		5.77	- Empty(g)	3.96	=	1.81
***Activity** in Phantom at mid-point of Scan*			**9.395**	MBq.	*Concentration (MBq/cc)*		**0.12151**
Voxel Dimension (cm)		0.44164		**Voxel Volume (cc)**		0.08614	
	MVCCF	**TVCCF**		**Using Cal Factor (cnts/MBq)**		**MVCCF**	**355964**
Counts	3726	2368878		**Comments**			
Voxel #	1	898		128 x 128 on VG			
Counts/cc	43253	30637					
cnts/MBq	**355964**	**252137**					

VOI 2	Liver	*(Label)*	**Type**	Max	*(Max/Mean)*		
General Description	Liver Calibration Phantom						
Scan Acquired at	17:11	on	16-Aug-00	with	64	projs of (s)	20
***Phantom** Vol (cc) =*	Phantom Mass Full(g)		3425.32	- Empty(g)	0.00	=	3425.32
***Stock** Volume (cc) =*	Stock Mass Full (g)		5.51	- Empty(g)	3.92	=	1.59
***Stock** Activity (MBq)*	32.90	at time	15:18	on date	16-Aug-00	@1/2scan	29.50
***Syringe** Vol (cc)=*	Syringe Full (g)		5.51	- Empty(g)	3.92	=	1.59
***Activity** in Phantom at mid-point of Scan*			**29.501**	MBq.	*Concentration (MBq/cc)*		**0.00861**
Voxel Dimension (cm)		0.88328		**Voxel Volume (cc)**		0.689121	
	MVCCF	**TVCCF**		**Using Cal Factor (cnts/MBq)**		**MVCCF**	**240694**
Counts	1207831			**Comments**			
Voxel #	846	4971		64 x 64 on VG. Large Volume, so should be no problem. T			
Counts/cc	2073	0		Slightly (< 2%) different than value used in her file as			
cnts/MBq	**240694**	**0**		half scan time used here (TA file uses start scan time)			

Comments

MIRD Example: Summary

- Administration of 17.1 GBq ^{131}I mIBG was predicted to give:
  - 2.0 Gy **Wholebody** dose (target maximum)
  - 11.4 Gy Maximum **Liver** dose (acceptable)
  - 15.4 Gy Maximum Estimated **Tumour** dose

Patient was determined **not** suitable for therapy

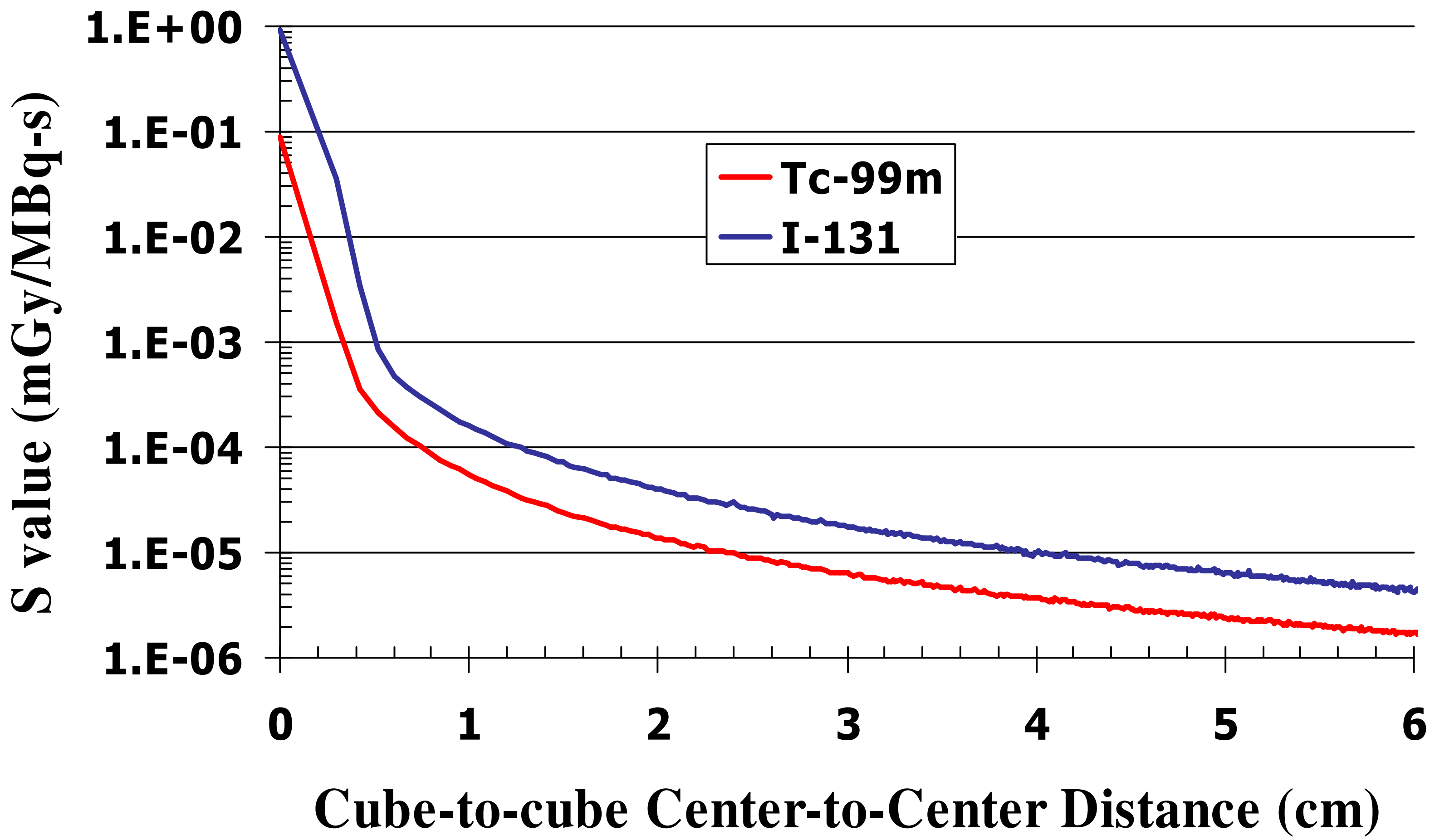
NB All calculations were independently checked on a separate system

MIRD: Limitations

- Recall, MIRD developed for **diagnostic** studies
- **Not** really suitable for therapy studies
- TCP (Tumour Control Probability) models show that the TCP of a tumour is heavily dependent on the TCP of its **lowest** voxel

$$TCP(\mathrm{D_i}) = \prod_{\mathrm{i=1}}^{\mathrm{N}} VCP(\mathrm{D_i})$$

3mm Voxel S Factors



Lionel Bouchet, University of Florida

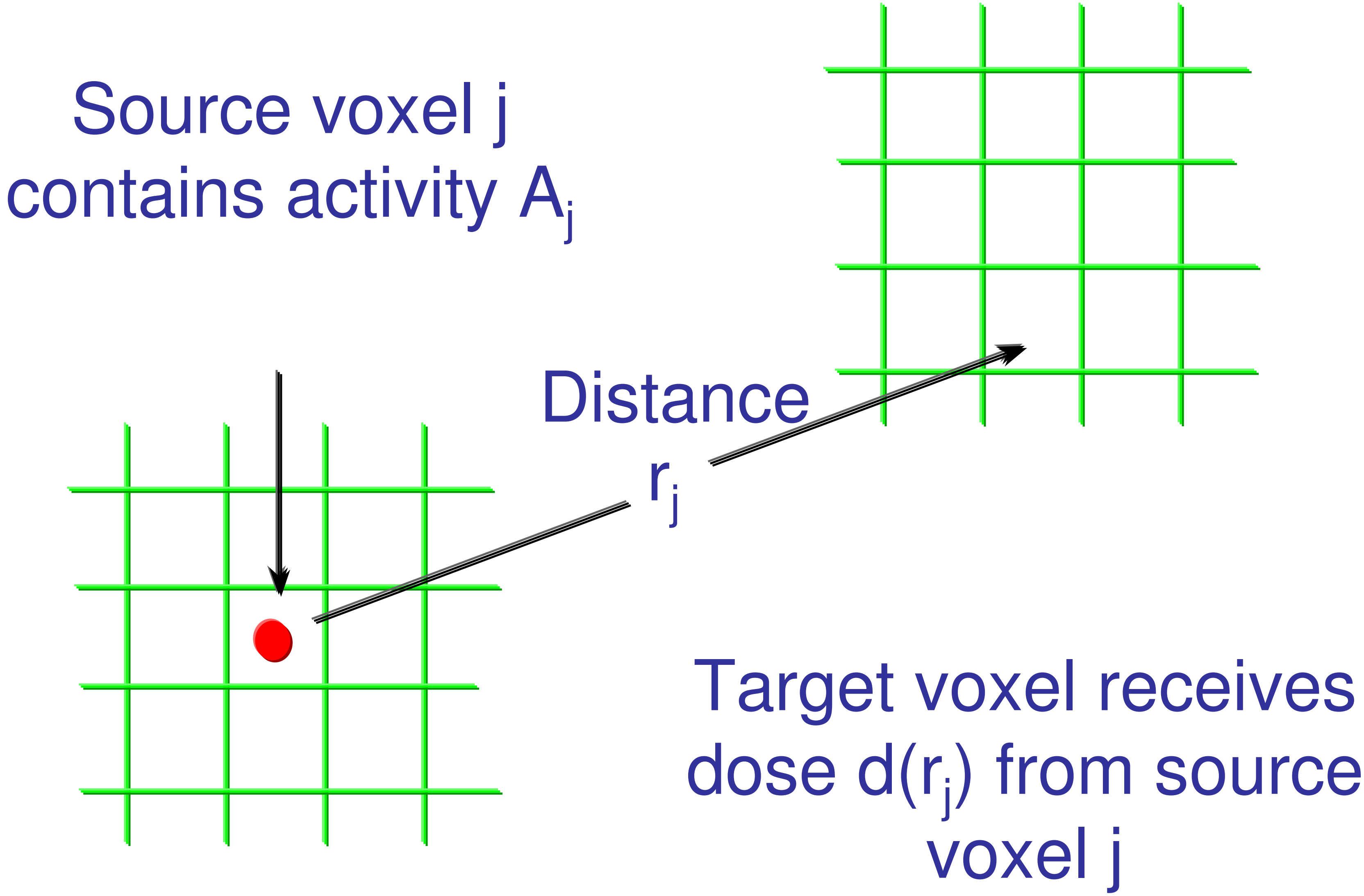
Dose Point Source Kernels

- Dose Point Source Kernels (PSK)
  - Monte Carlo generated tables or plots of absorbed dose as a function of distance from a point source of activity
- Convolve activity distribution with PSK to obtain absorbed dose distribution

$$D = \sum_{j} [A_j \times d(r_j)]$$

i.e. The dose to each target voxel is the sum of the dose contributions from each source voxel

Kernel Calculations



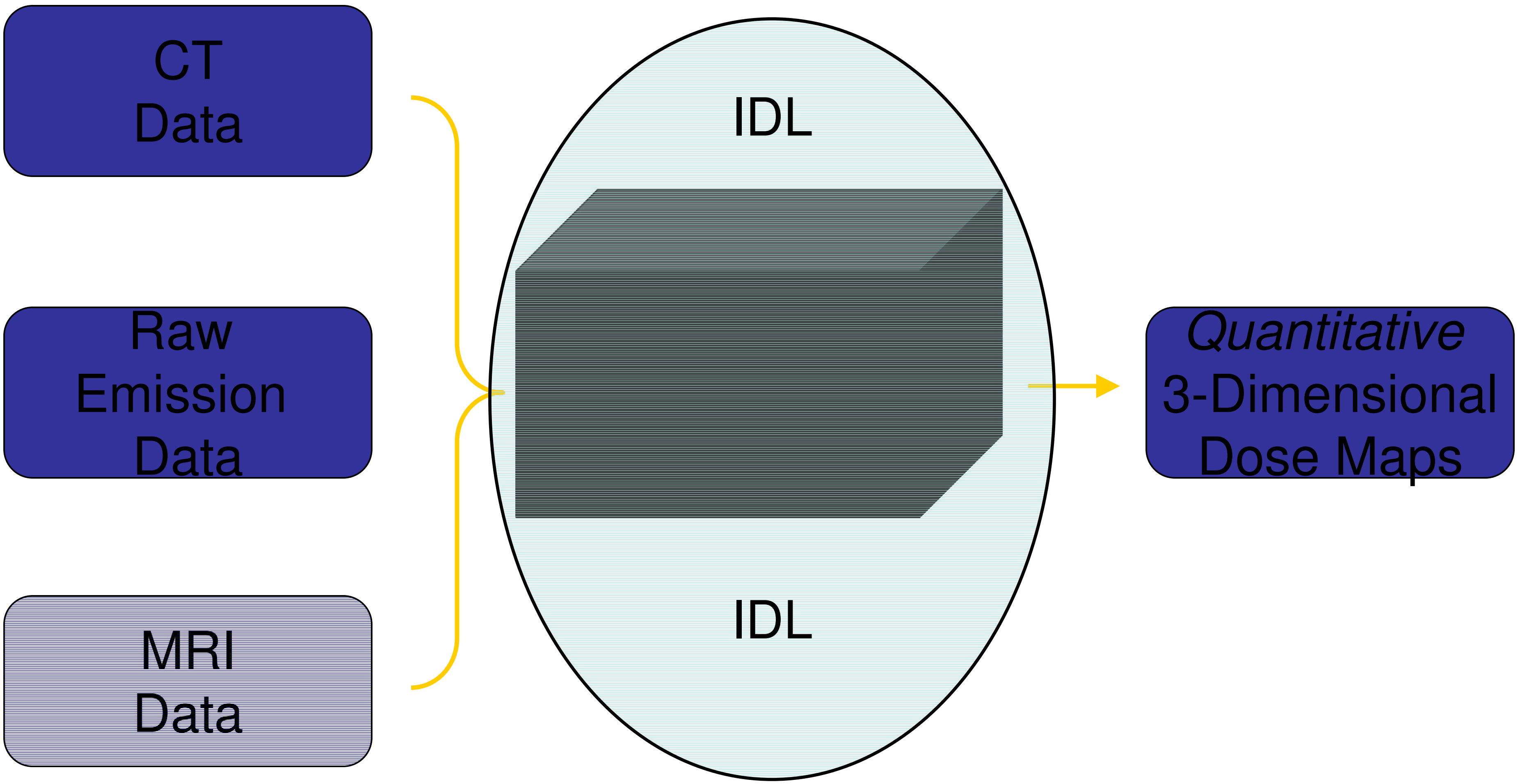
Monte Carlo Calculations

- PSK technique becomes difficult to implement in inhomogeneous media *(ie areas of body)*
- Kwok (1990)
  - Dose to tissue within 2mm of tissue-bone interface **underestimated** by **20-40%** due to backscatter
- Furhang (1997) used CT registered with SPECT and PET to obtain density map

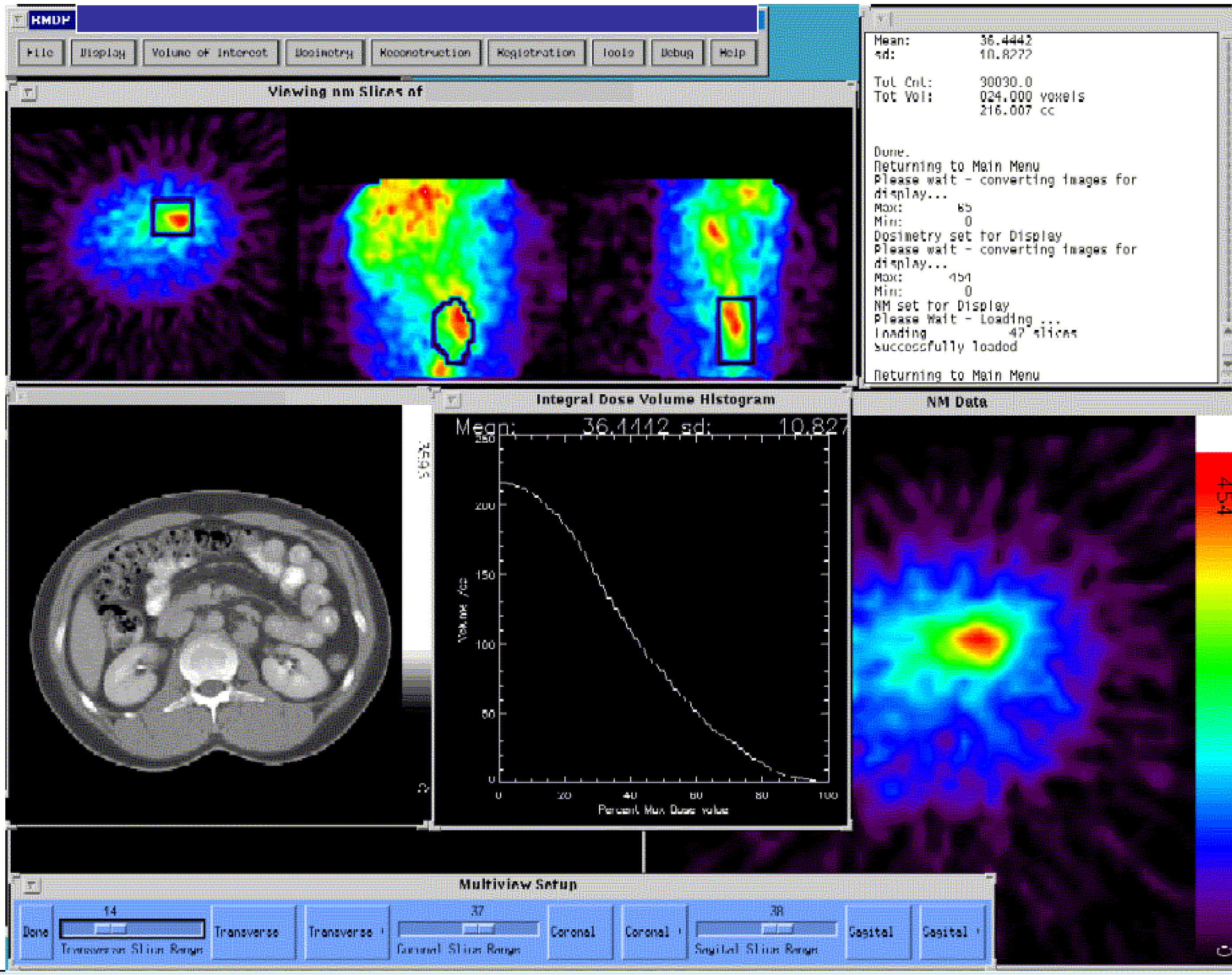
Resource Implications

- Wholebody data points – essential
- SPECT data sets – minimum 3 / phase
  - Possibly 1 SPECT + 2 planar…
    (Koral et al JNM 44(3):457, 2003)
- Quantitative Reconstruction – incl CT Reg
- SPECT-SPECT Registration
- Patient Specific Dosimetry
- Interpretation and Reporting

The Radioisotope Multimodality Dosimetry Package



RMDP - Overview



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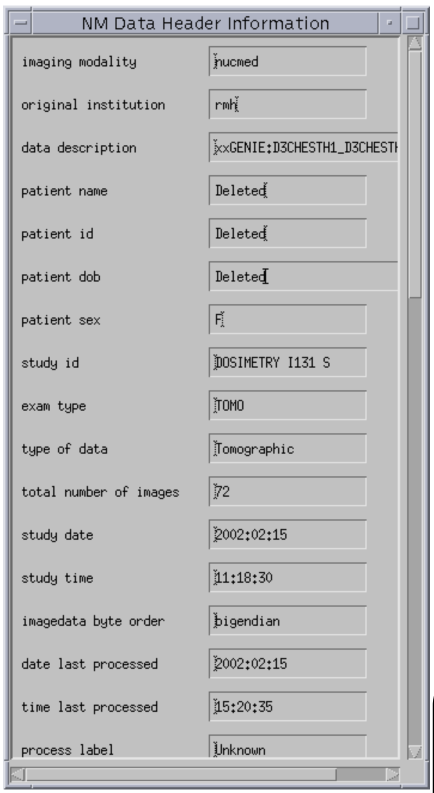
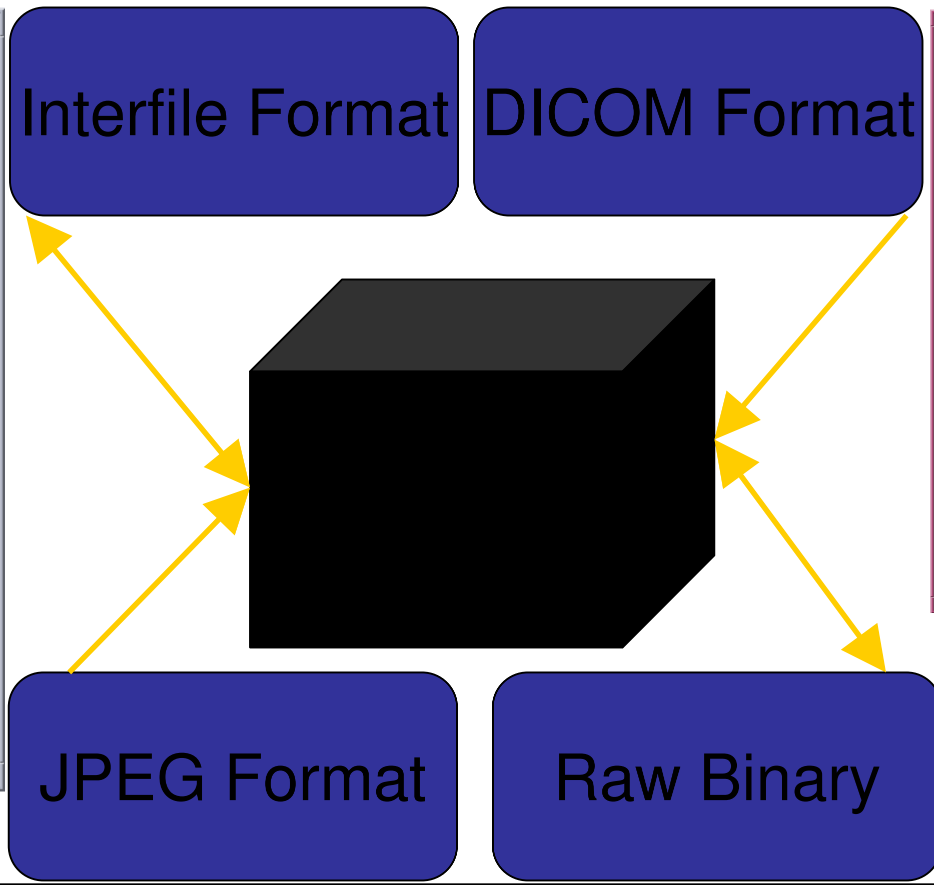
Inside the Box...

- Key Components:-
  - File Handling
  - Display
  - Interactive VOIs
  - Reconstruction
  - Registration
  - Dosimetry
- *Extras:-*
  - *Improved Quantitation for 2- & 3-D Images*
  - *List Mode Data*
  - *Monte-Carlo*
  - *Error Analysis*

File Handling





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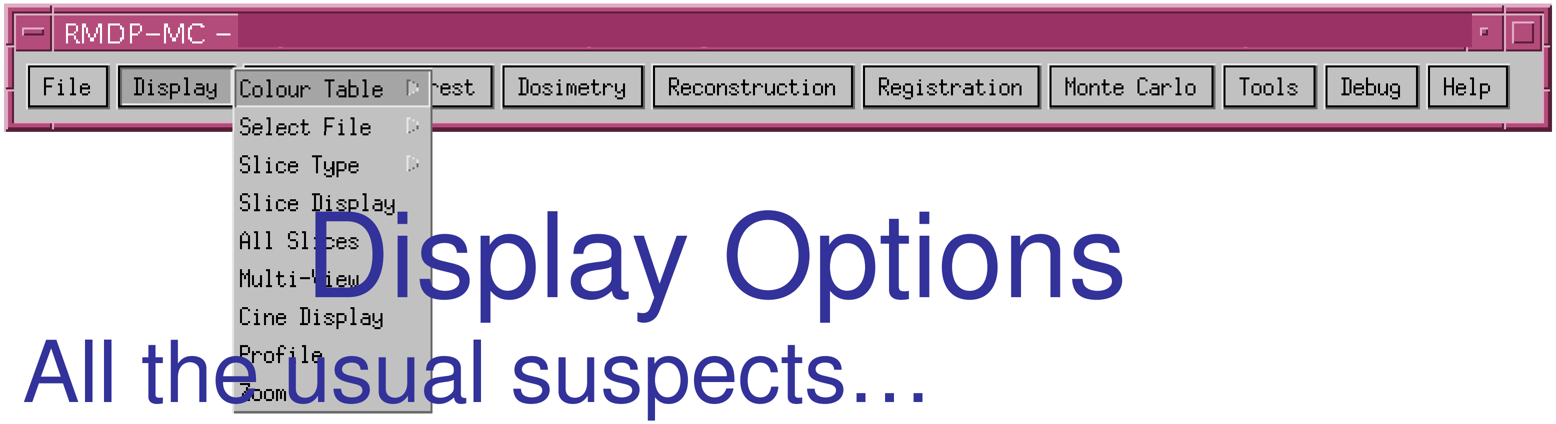

Display Options

- All the usual suspects…
  - Transverse, Coronal, Saggital
  - Multi-slice
  - Cine
  - 3-D rendered view of activity / dose iso-surface
- Imaging Tools
  - Profiles
  - Zooming and Resizing
  - Image Overlay / Linked Display

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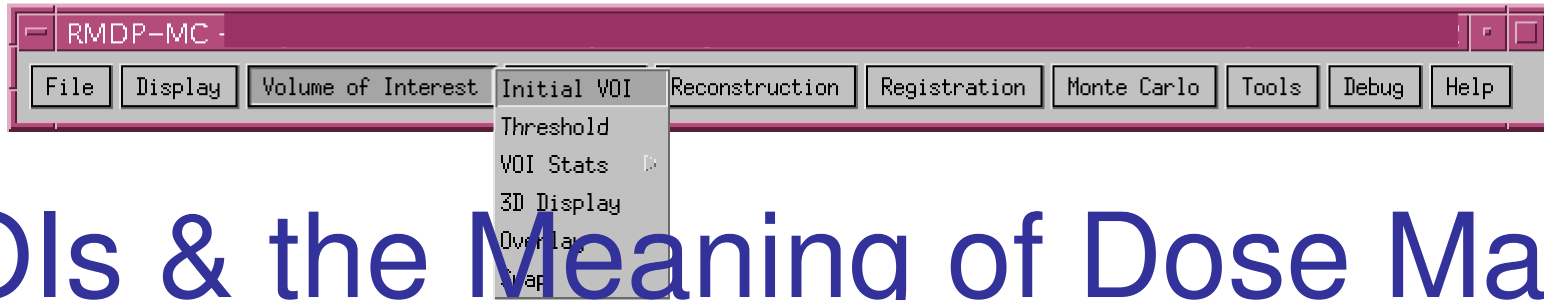
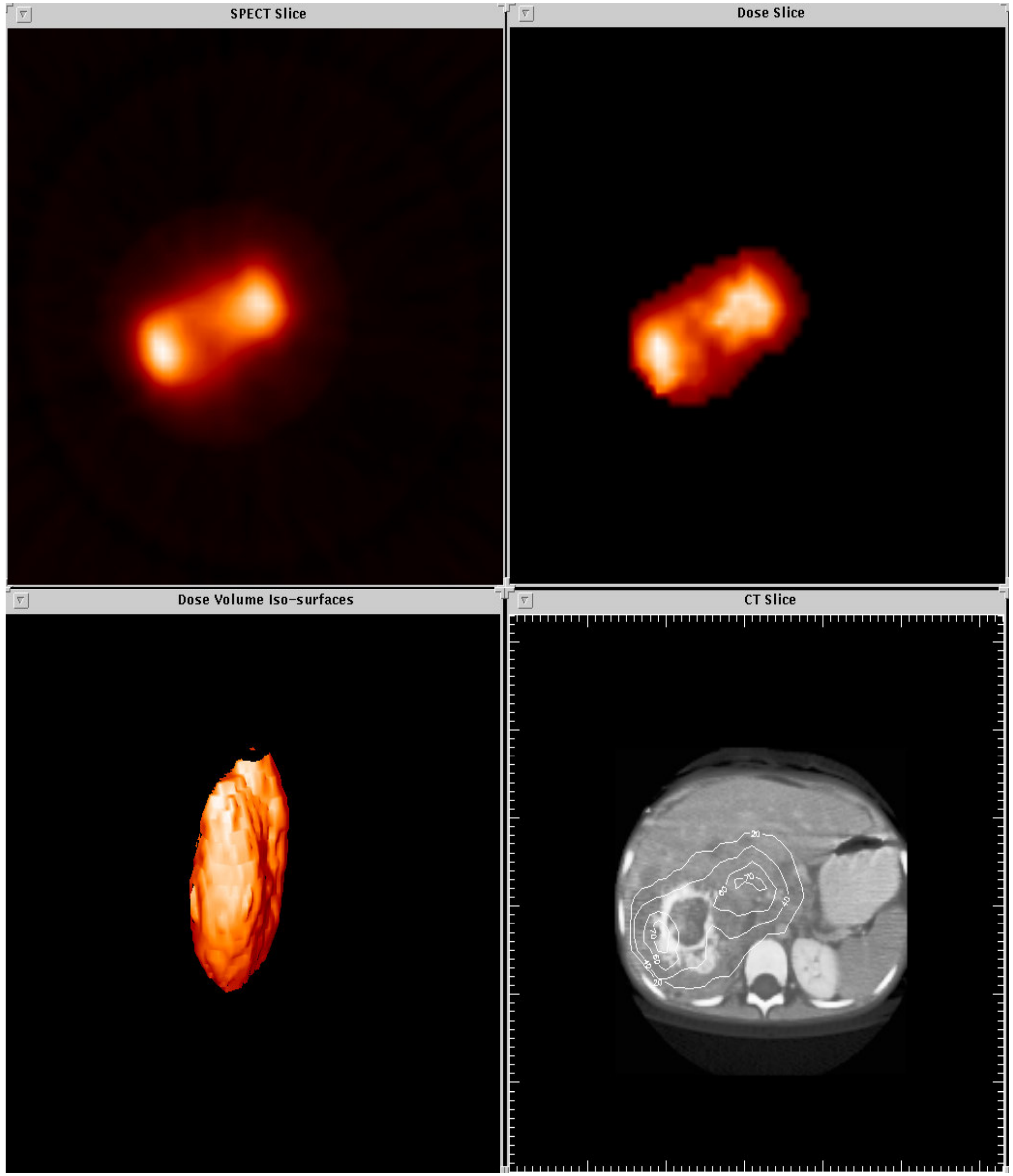


VOIs & the Meaning of Dose Maps

- Setting a VOI:
  - Manually drawn
  - Thresholded to a CT#/ activity/ dose level
  - Thresholded to a volume *(e.g. CT / RT vol)*
- Interpreting a VOI:
  - Integral and Differential Dose Volume Histograms (DVH)

I-131 SPECT

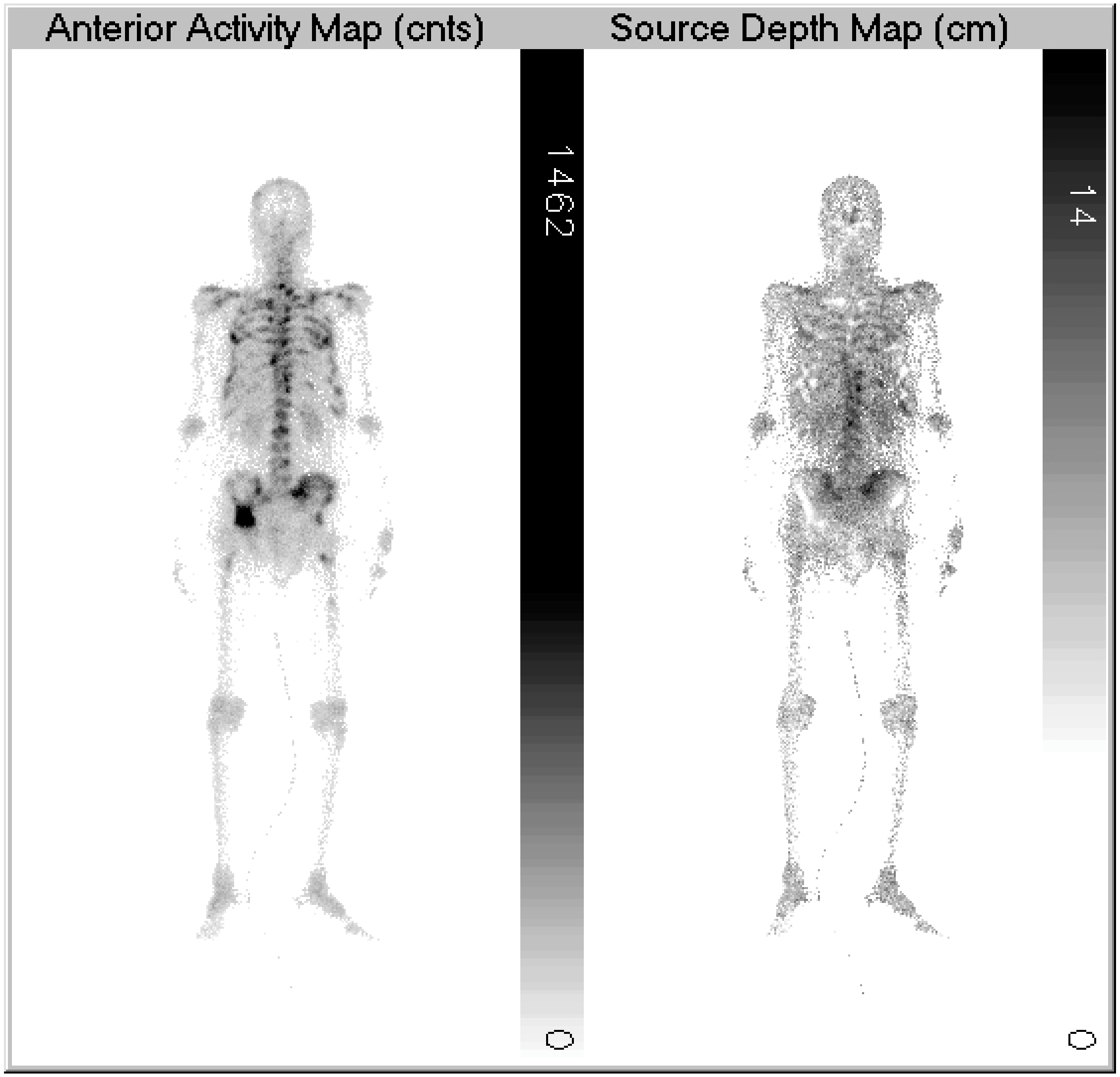
Absorbed dose



Rendered isodose

CT + isodose contours

2-D Image Quantification



- Developed for ^{186}Re HEDP - (applicable to other isotopes)[1]:

WB Images

+

Transmission Map

(CT / Scaled Phantom)

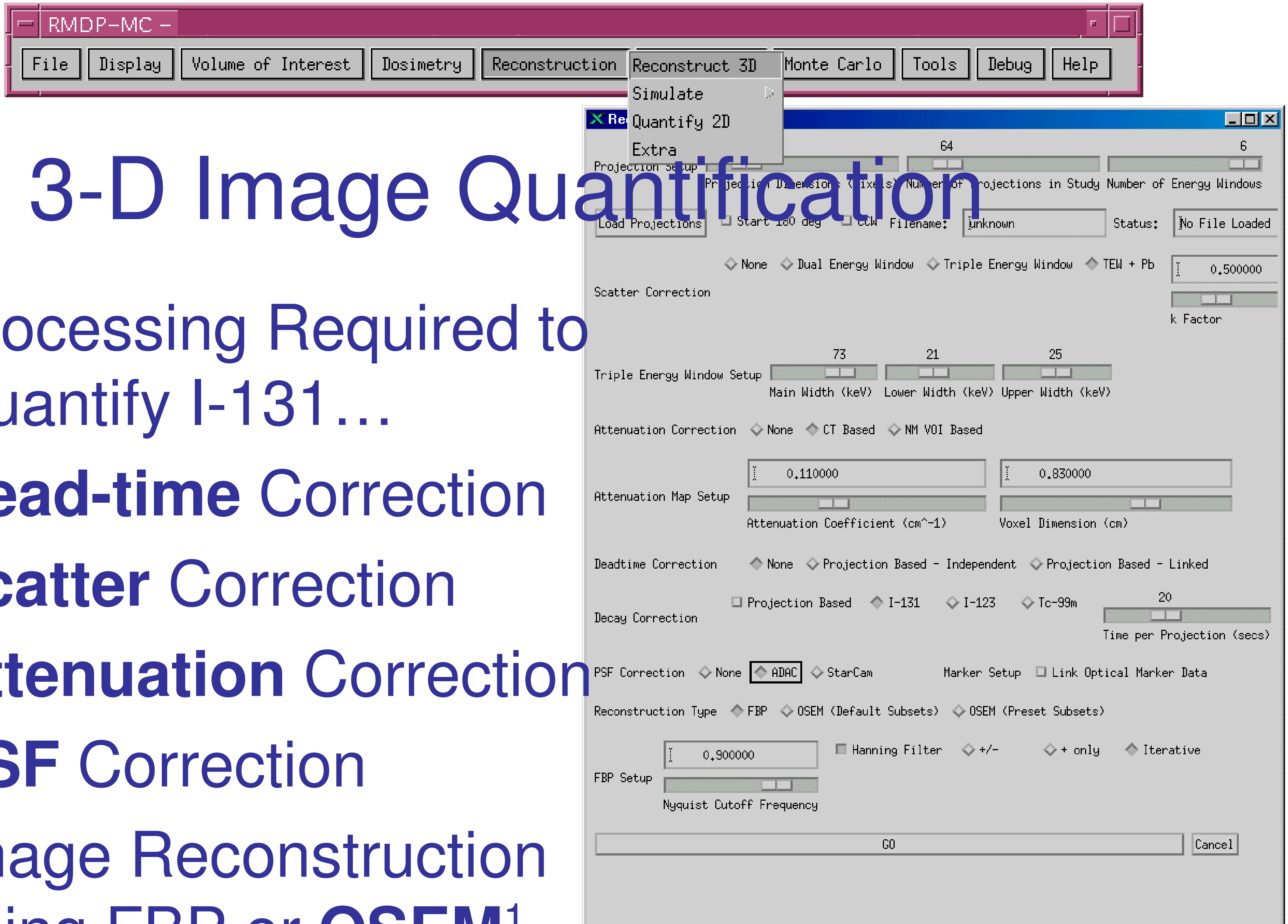
+

Build-Up Factor Data

=

Quantitative Activity Map *and* Source Depth Map

[1] Guy MJ *et al* J Nucl Med, 2001; 42: 822



3-D Image Quantification

- Processing Required to Quantify I-131…
- **Dead-time** Correction
- **Scatter** Correction
- **Attenuation** Correction
- **PSF** Correction
- Image Reconstruction using FBP or **OSEM**[1]

[1] Hudson HM, Larkin RS. IEEE TMI 1994; 13: 601-609

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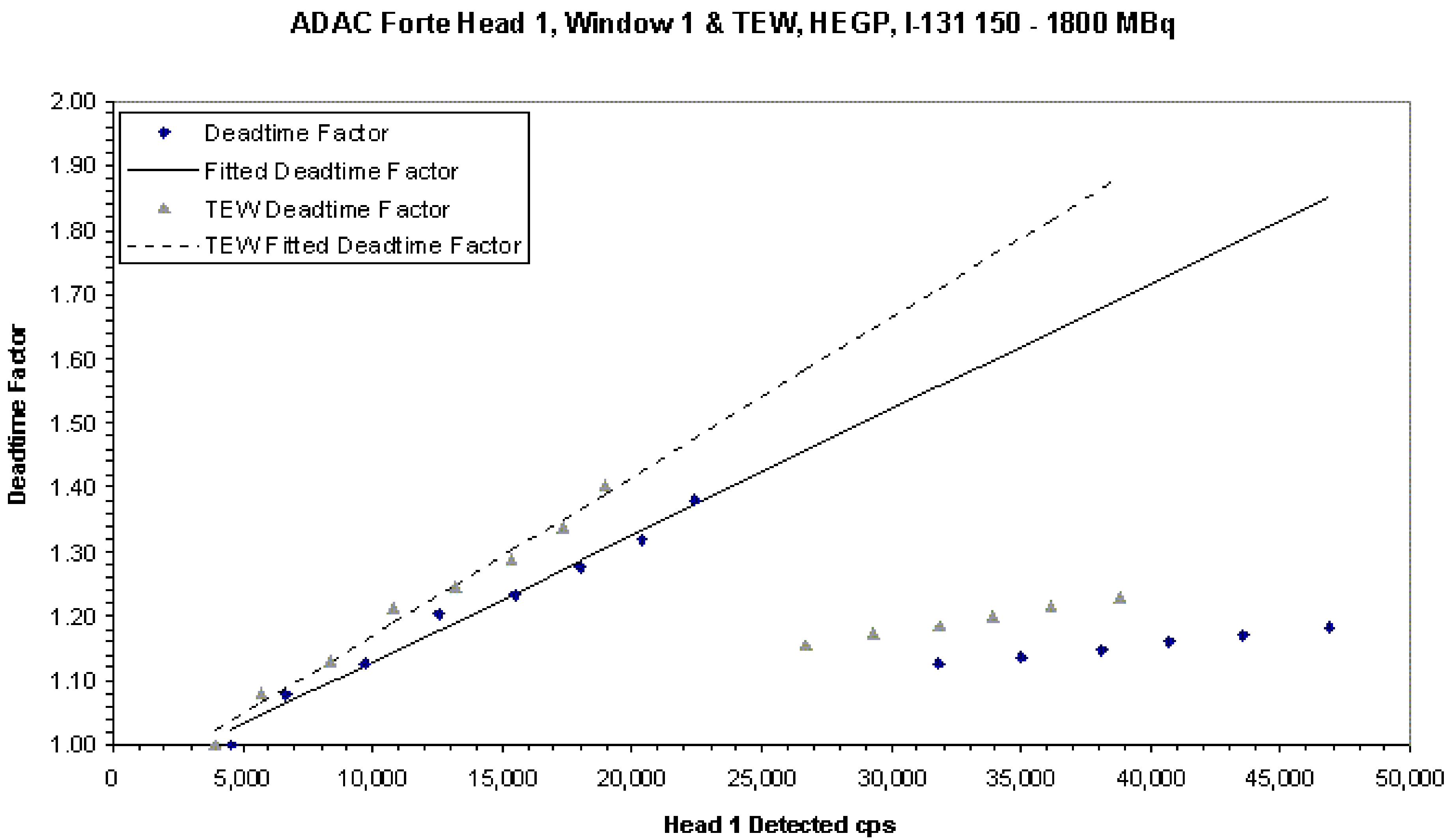
Dead-time Correction - Camera 1



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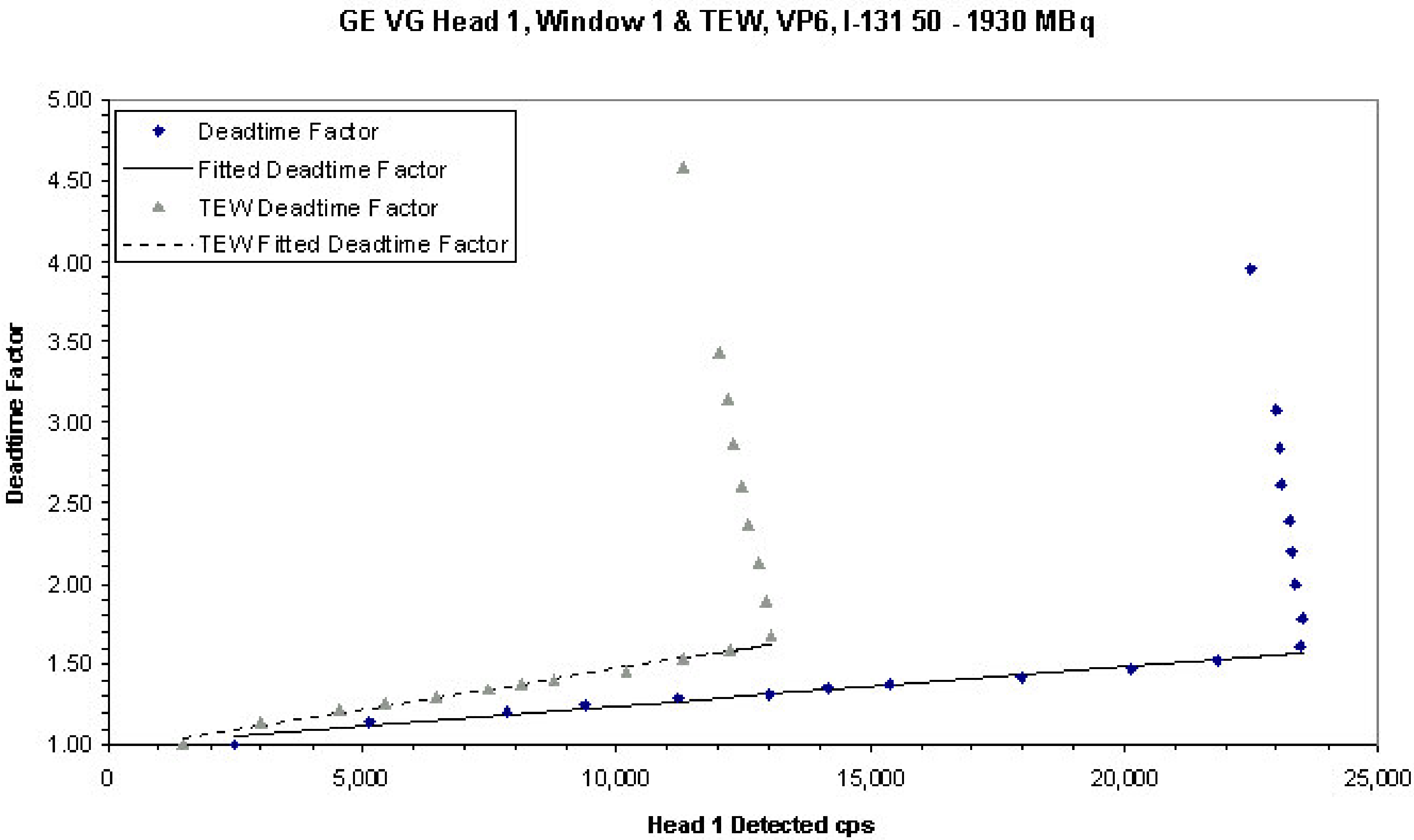
Dead-time Correction - Camera 2



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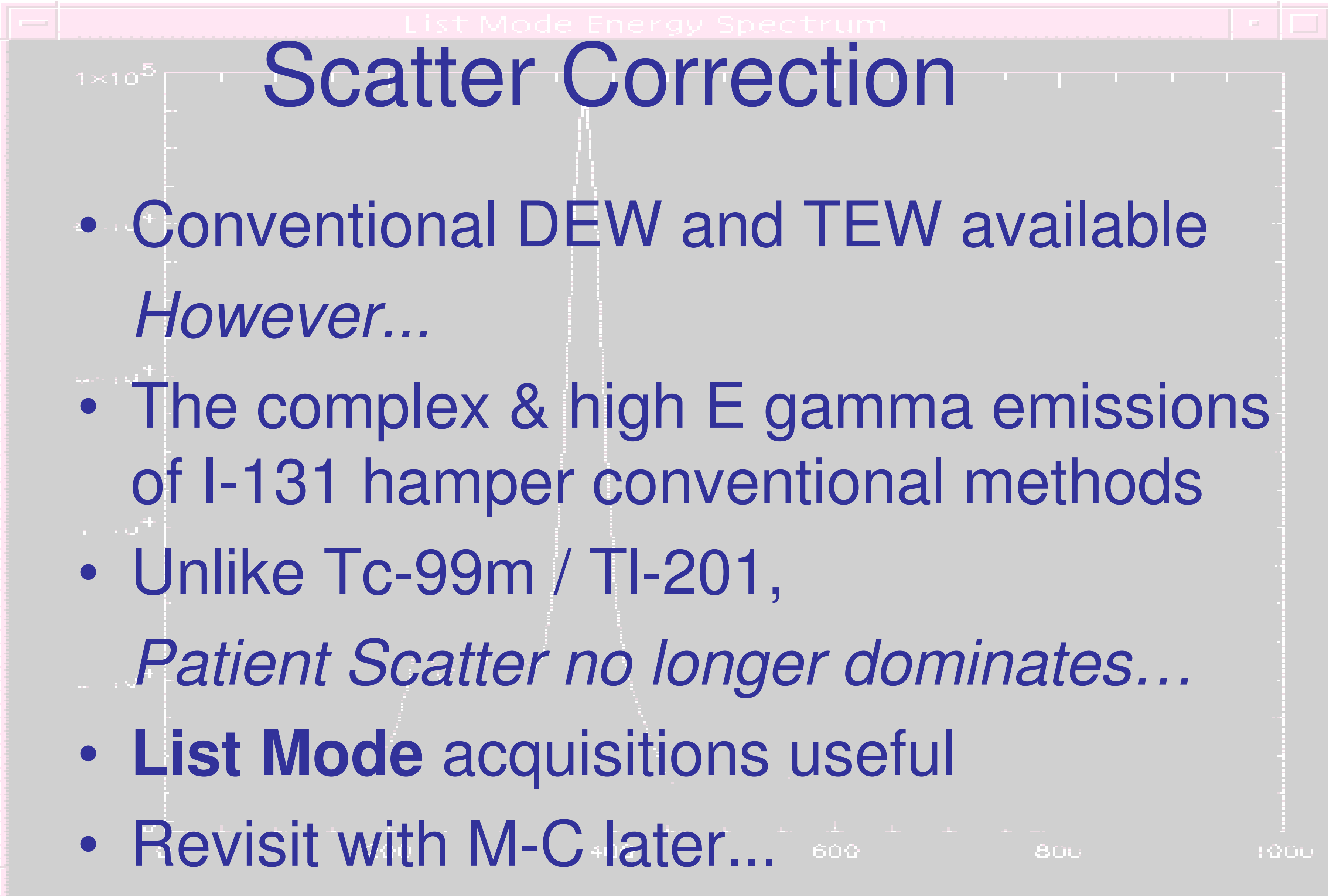
Scatter Correction



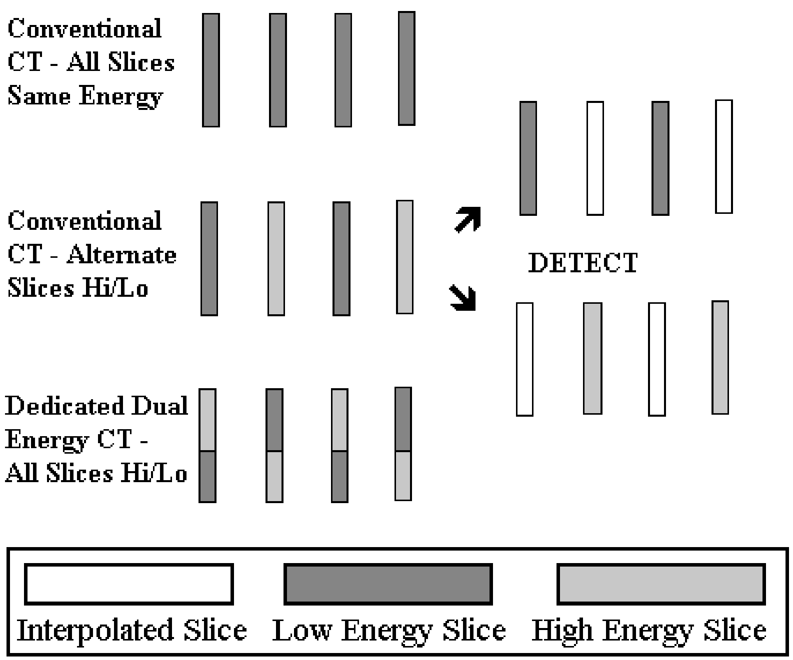
- Conventional DEW and TEW available

  However...
- The complex & high E gamma emissions of I-131 hamper conventional methods
- Unlike Tc-99m / Tl-201,

  Patient Scatter no longer dominates…
- **List Mode** acquisitions useful
- Revisit with M-C later...

Attenuation Correction

- CT-based attenuation correction(FBP & OSEM)
- Conventional Single Energy Scaling (120 or 140 kVp)
- *Single scan* Dual Energy Transmission Estimation CT[1]



•μ at CT $E_{effective}$ must be scaled to $E_{emission}$
•For H_2O & soft tissue, factor is ~constant

•But at low photon energies PE cross-section increases more rapidly for high effective Z materials, such as bone and use of a single scaling factor will cause errors
•Bone error=58% - leads to an overall error of 9% for typical $^{99}Tc^m$ myocardial data

[1] Guy MJ *et al* IEEE TNS 1998; 45: 1261-1267

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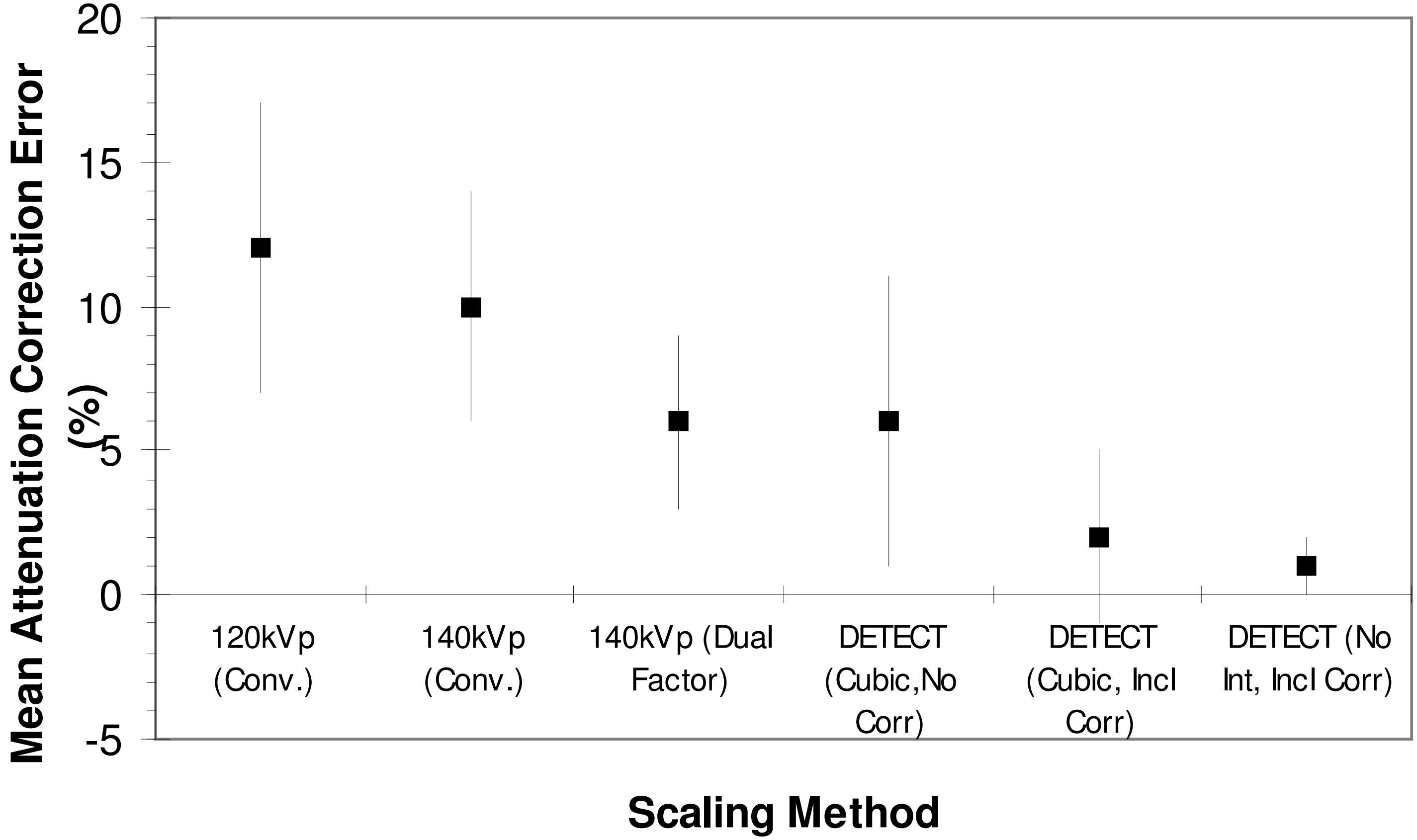
The DETECT Process

- Improves accuracy of high-energy attenuation maps without changing the clinical protocol



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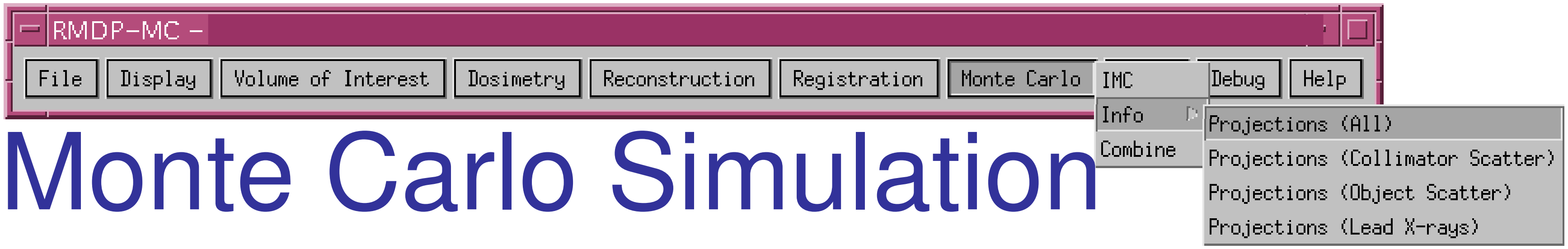
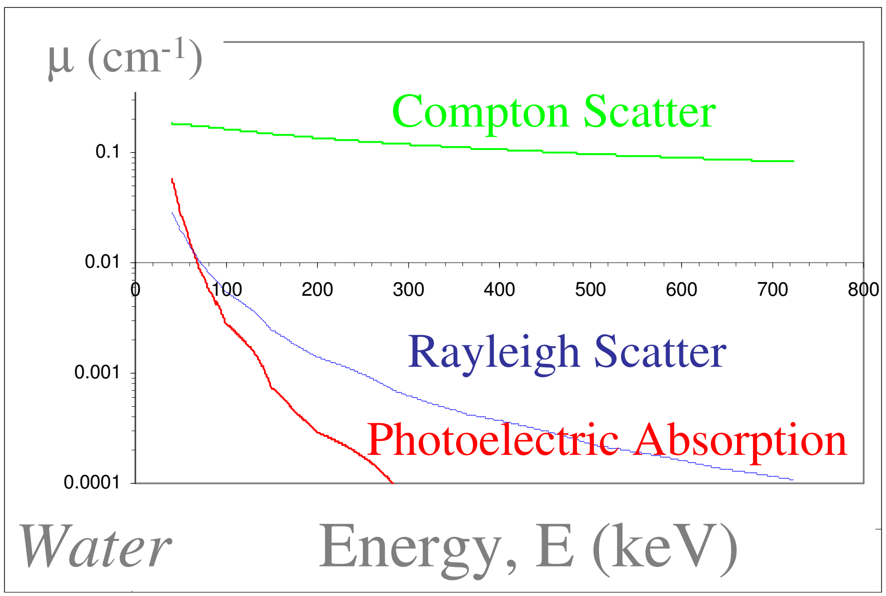
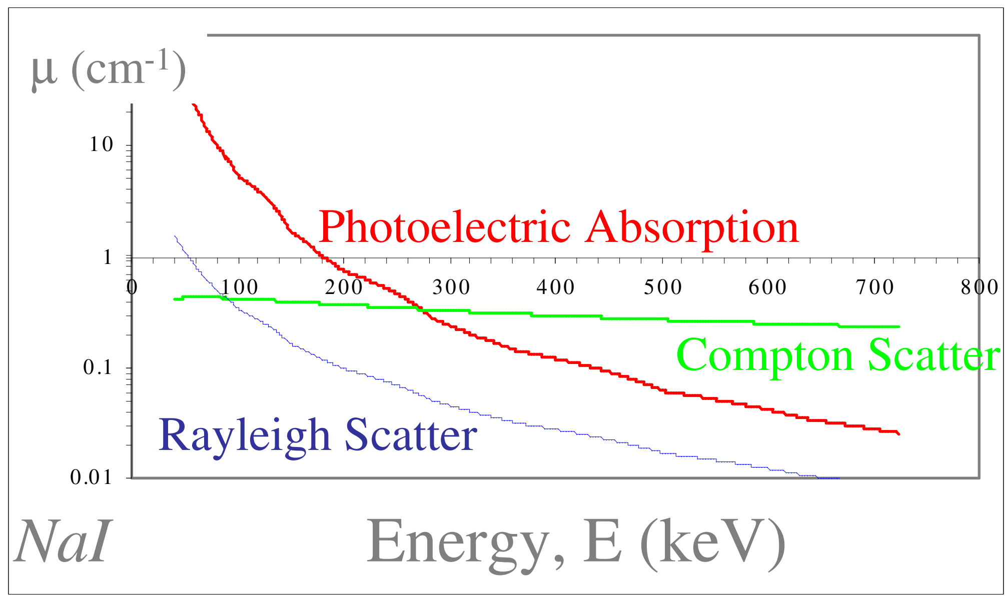


Monte Carlo Simulation

- 131-Iodine's High Energy Gamma-rays…
  - ∴Problems with collimator penetration
  - *Also* problems with scatter in patient and imaging system





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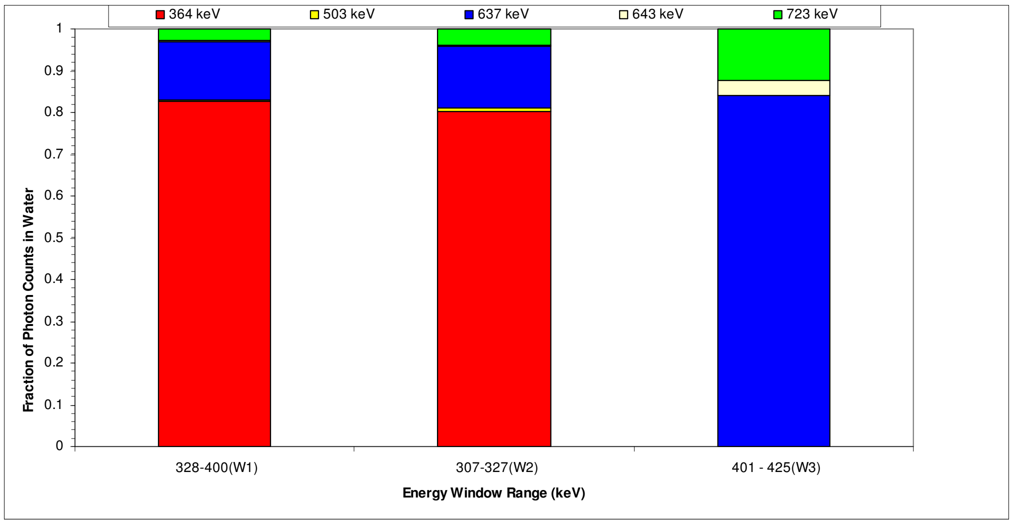
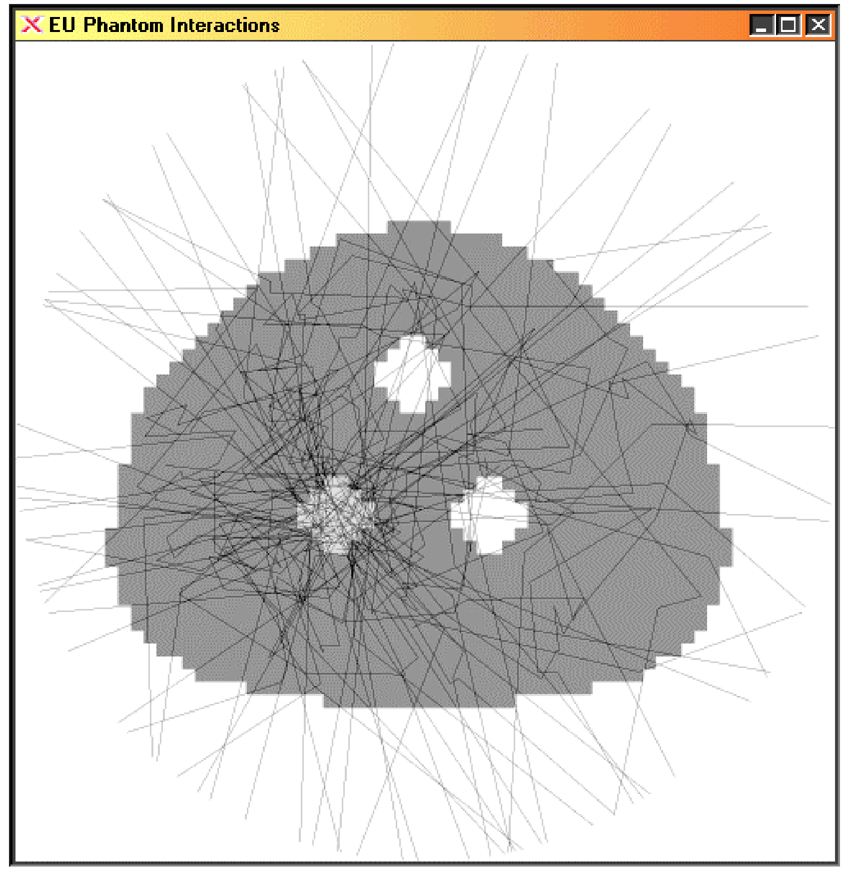
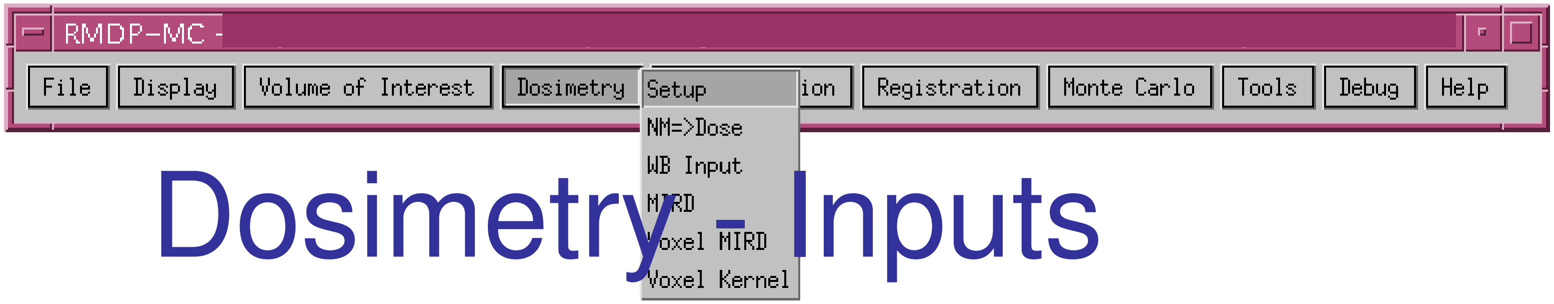
Monte Carlo Simulation Improved Quantification



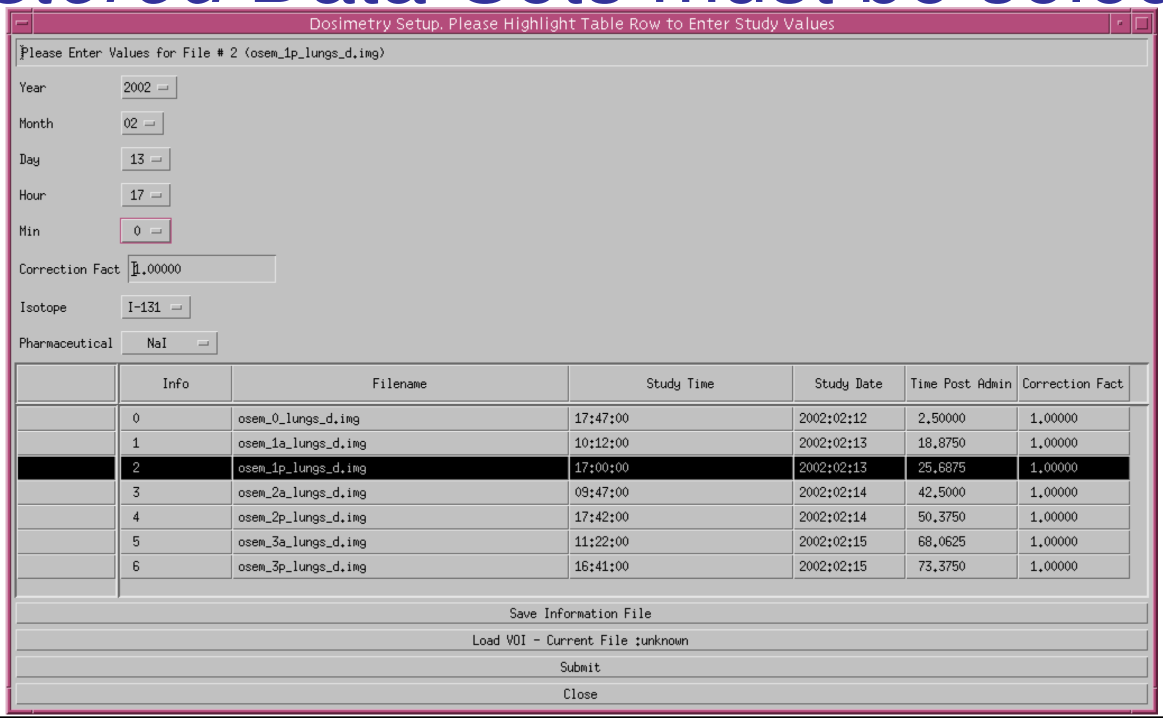


Analysing the interaction history of each photon and comparing the IMC data with that obtained from List Mode acquisitions should lead to improved image Quantification



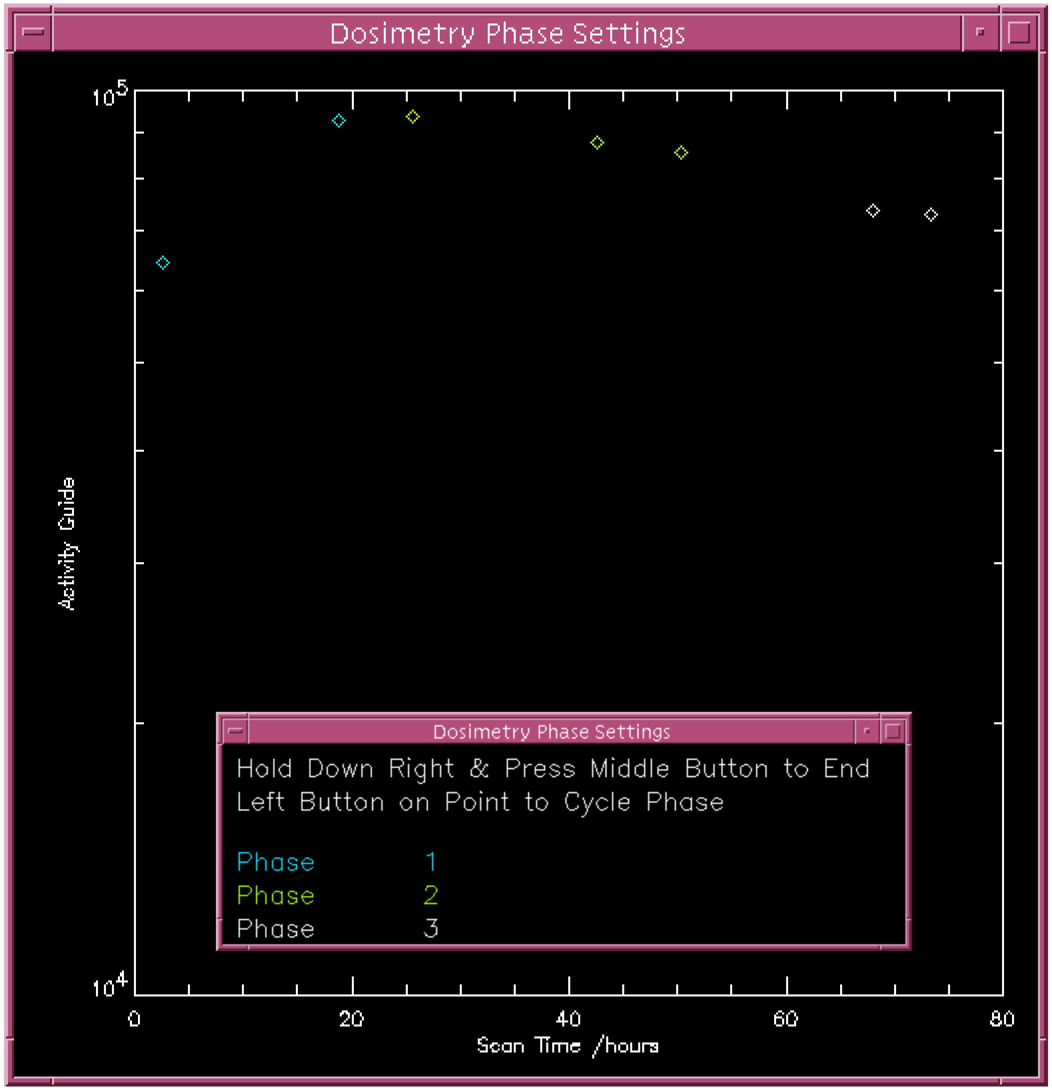
Dosimetry - Inputs

- To generate pixel- or voxel-based dose maps, a Series of 2- or 3-D *Quantified and Registered* Data-Sets must be selected



Dosimetry - Processing

- Cumulative Activity Map:
  - Artifacts caused by image noise or mis-registration can be controlled by phase-fitting



Dosimetry - Output

- 3-D Cumulative Activity to 3-D Dose Map...
  - Voxel S-Factor or kernel (β only) calculation
  - All material assumed to be soft-tissue at present
- 3-D **Biological** $T_{1/2}$ maps can be produced
- 3-D **Error** Maps based on $T_{1/2}$ & fit analysis are also generated

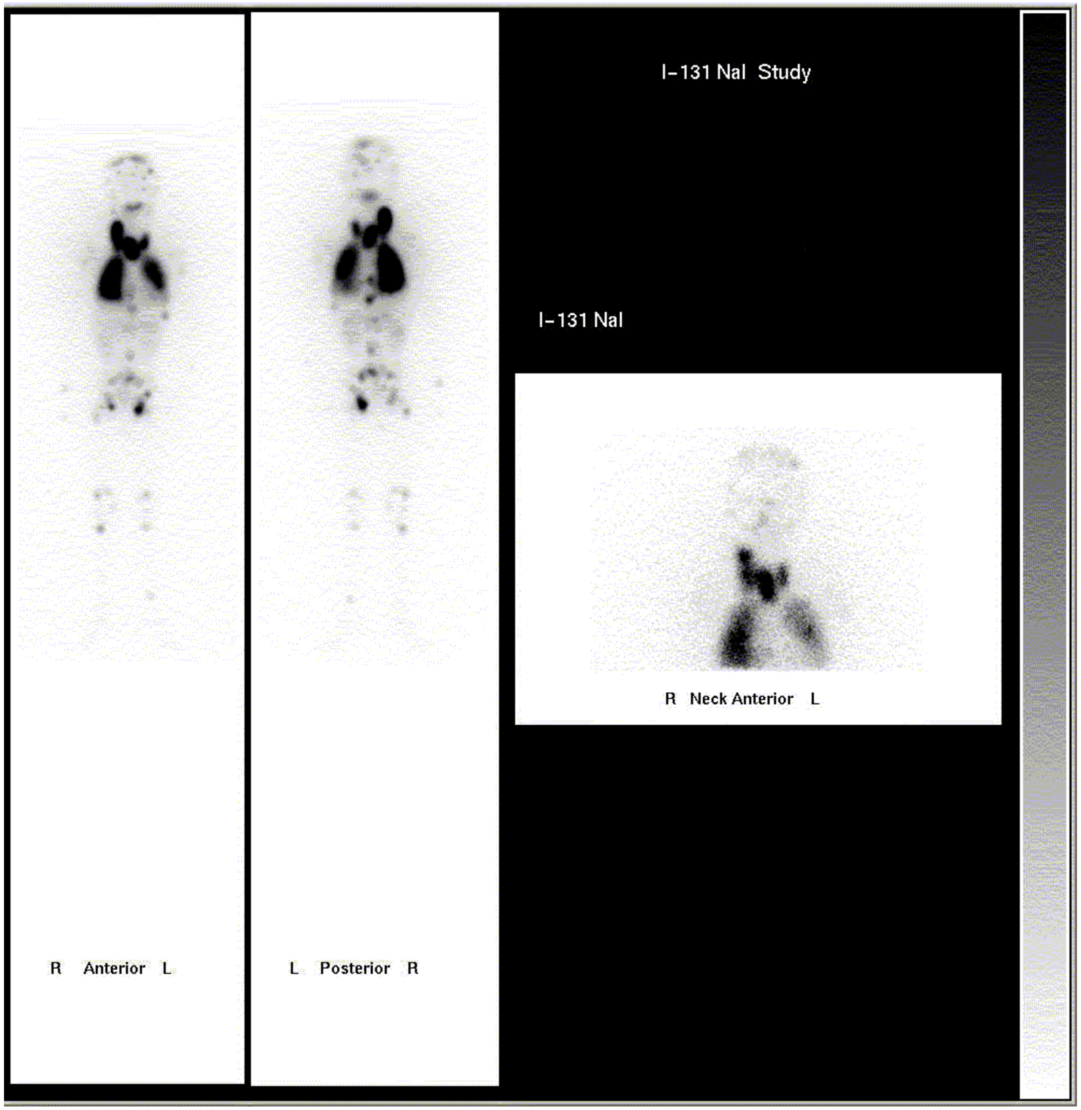
^{131}I Voxel Dosimetry - Case Study

- *A Quick Example…*
  - Pediatric Ca Thyroid Patient
  - Unable to operate due to heart defect
  - Treatment History:

10/00	NaI	400 MBq	(11 mCi)
04/01	NaI	400 MBq	(11 mCi)
06/01	NaI	1100 MBq	(30 mCi)
10/01	NaI	1100 MBq	(30 mCi)
02/02	NaI	1800 MBq	(49 mCi)

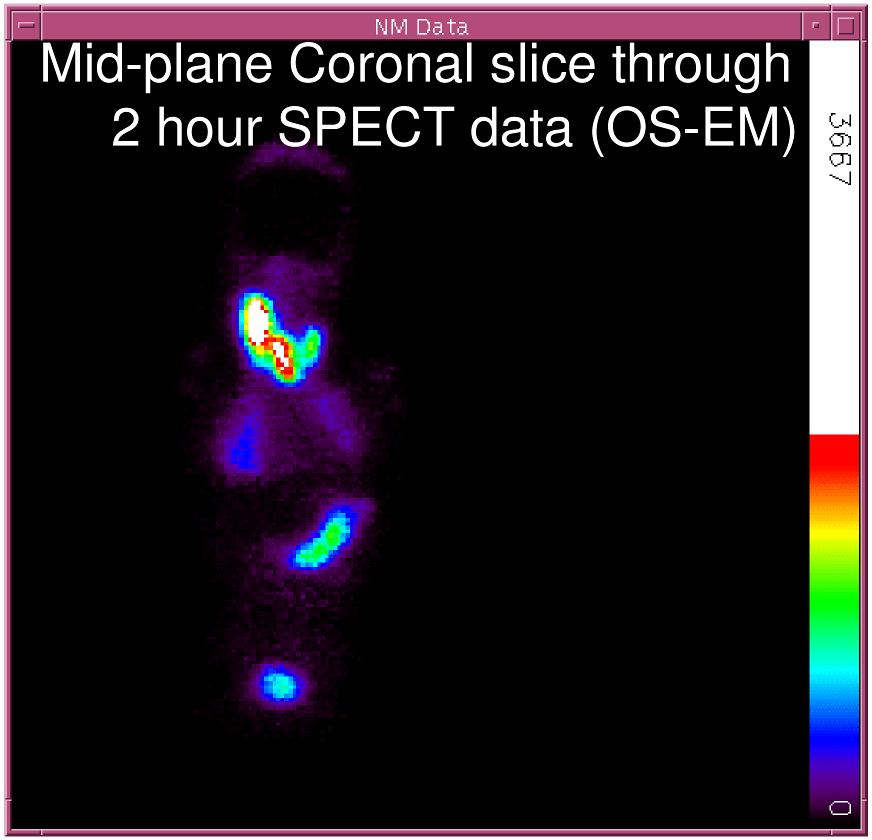
^{131}I Voxel Dosimetry - Case Study

- Clinical Protocol requires WB+Static - widespread metastatic disease
- RMDP requires sequence of SPECT acquisitions



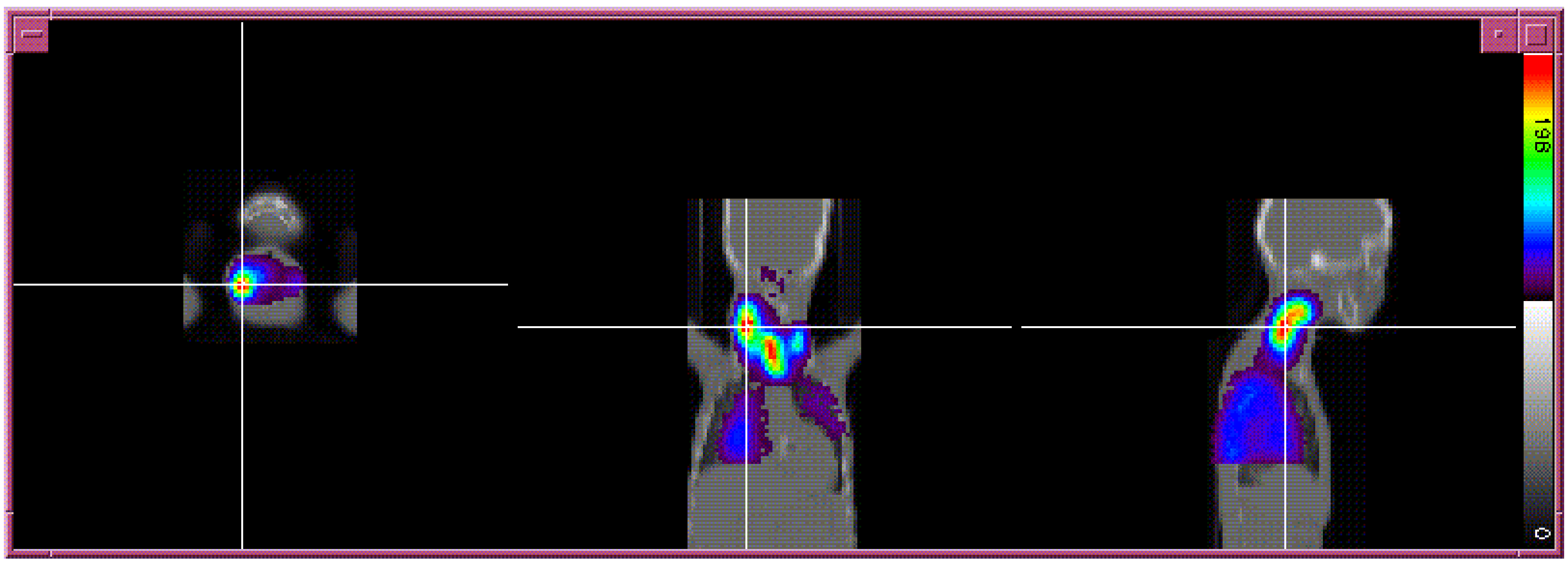
^{131}I Voxel Dosimetry - Case Study

- SPECT (covering neck, torso & abdo) acquired at 2, 18, 25, 42, 50, 68, 73 & 241 hours post admin.
- Dead-time Correction
- TEW Scatter Correction
- CT-based μ Correction
- OS-EM Reconstruction



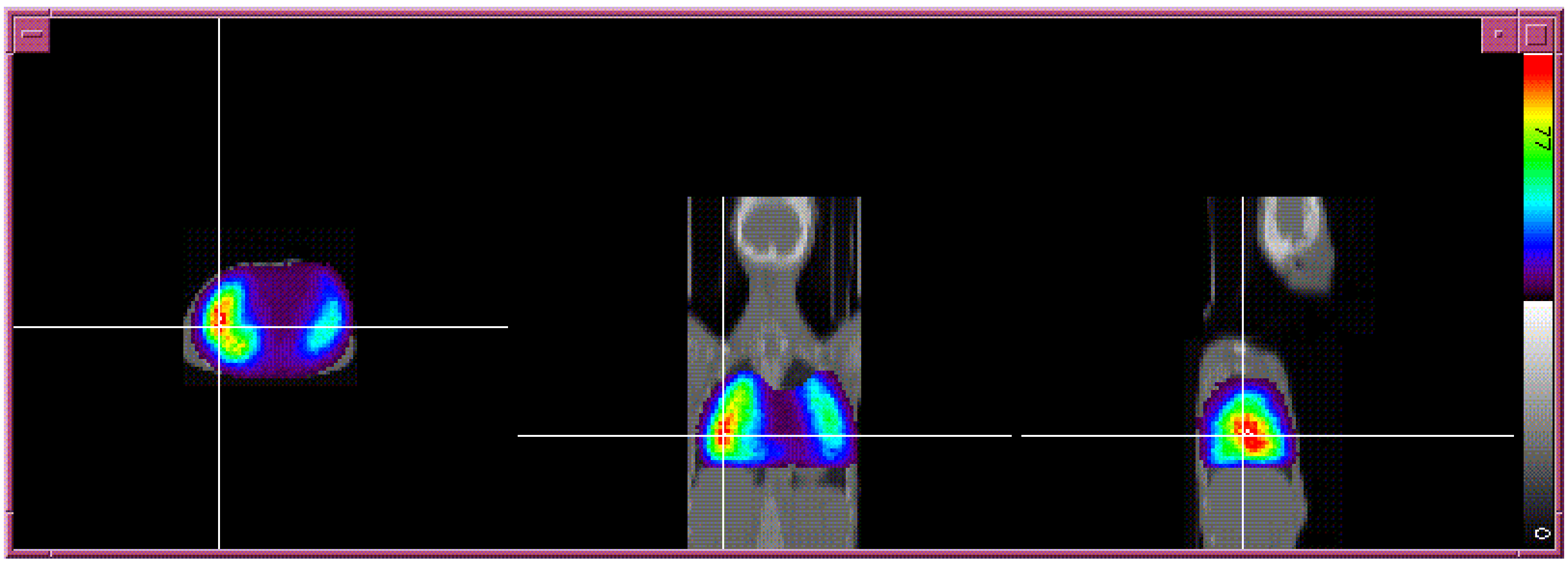
^{131}I Voxel Dosimetry - Case Study

- Neck Dosimetry
  - Fast uptake (~60% of maximum within 2 hours) and long biological $T_{1/2}$ lead to high dose around the thyroid bed and in the lymph nodes on the right-hand side



^{131}I Voxel Dosimetry - Case Study

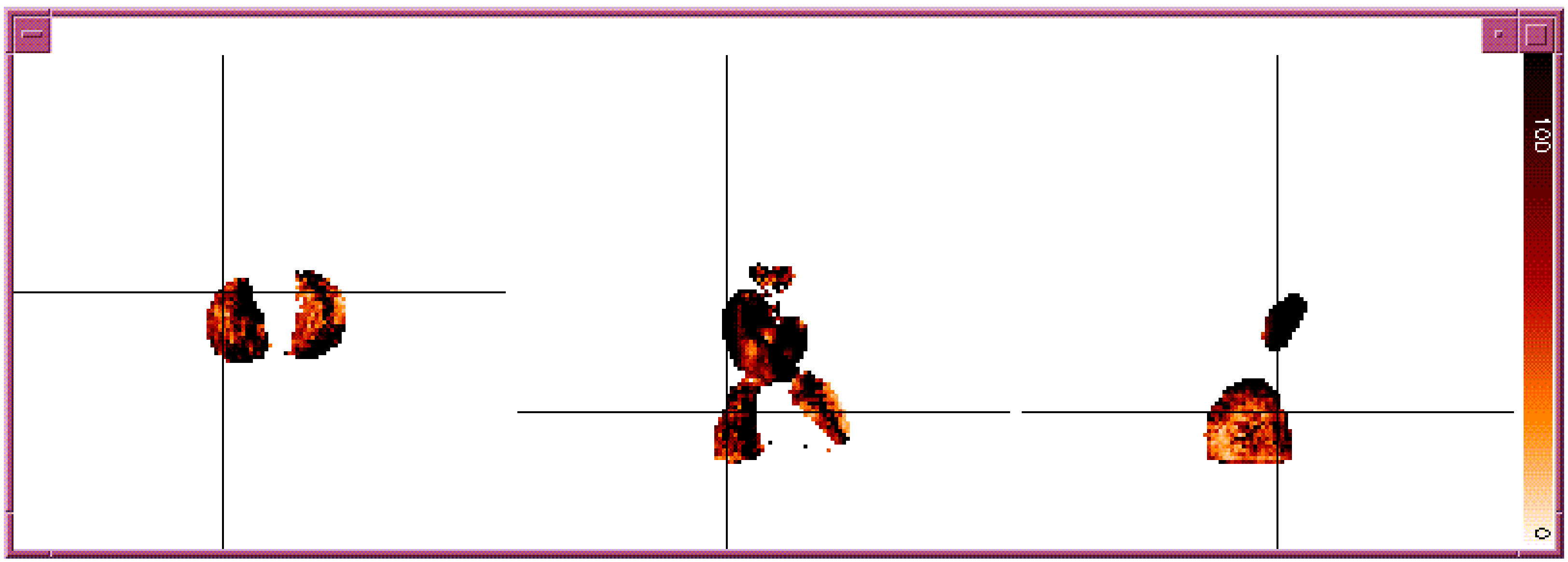
- Lung Dosimetry
  - The long retention times (Effective $T_{1/2}$ ~ 110hrs) for voxels in the left lung lead to high dose to the diseased lung



^{131}I Voxel Dosimetry - Case Study

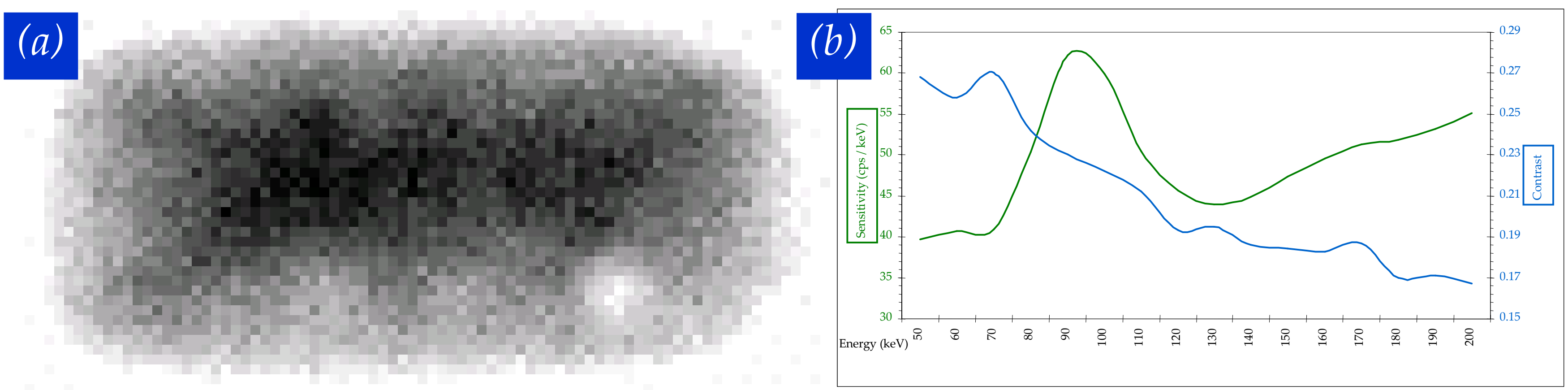
- 3-D Error Analysis
  - 3-D Error Maps are generated with each Dose Map
  - Registration & Phase-fitting optimised using these maps
  - *Eg Registration Optimised for Lungs, not Neck VOIs*

G.D. Flux et al PMB 2002;47:3211 & Cancer Biother Radpharm 2003;18:81



^{90}Y Dosimetry - *Imaging*

- ^{90}Y has no gamma emissions
- ^{90}Y Bremsstrahlung imaging is “challenging”…
- MEGP +low (<150 keV) windowing probably offers “best” imaging characteristics on gamma camera



Williams Liver Phantom. (a) ~3 cold spots visible (only 15mm dia clearly) in 50-150 keV inverse image. (b) Planar Sensitivity & Contrast measurements

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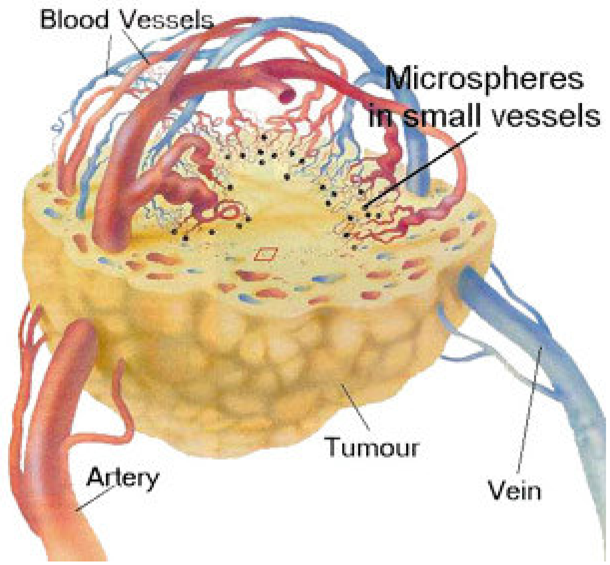
^{90}Y Microspheres - *Background*

- ^{90}Y SIR (Selective Internal Radiation)-Spheres® are designed for implantation into malignant liver tumours
- The spheres (20-40 μm dia) become lodged in the small blood vessels of the tumour
- RSCH is involved in first wave of UK treatments

- **Not curative** - aim is to destroy sufficient tumour to render previously non-resectable disease suitable for surgery
- Administered activity is prescribed solely on the degree of tumour involvement in the liver *(subject to negligible shunting to organs at risk)*



Research goals at RSCH for this study are to determine whether:-

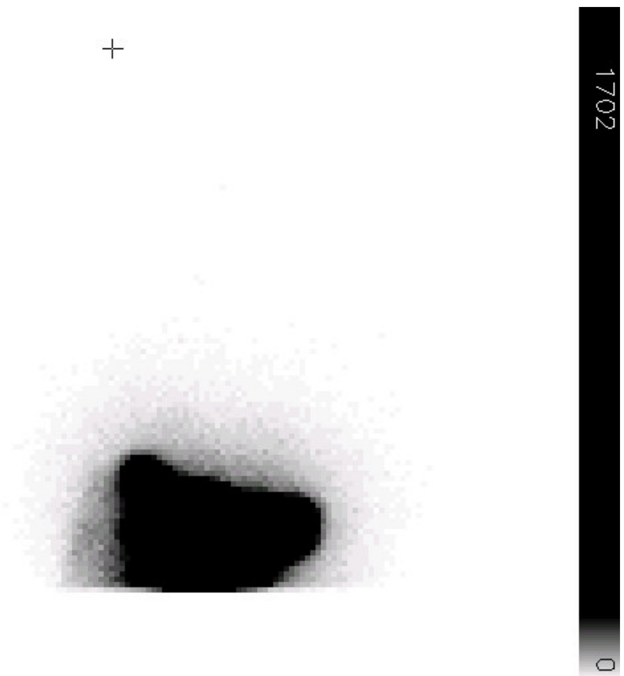
•^{90}Y SPECT of these patients is feasible, leading to post-therapy dosimetry

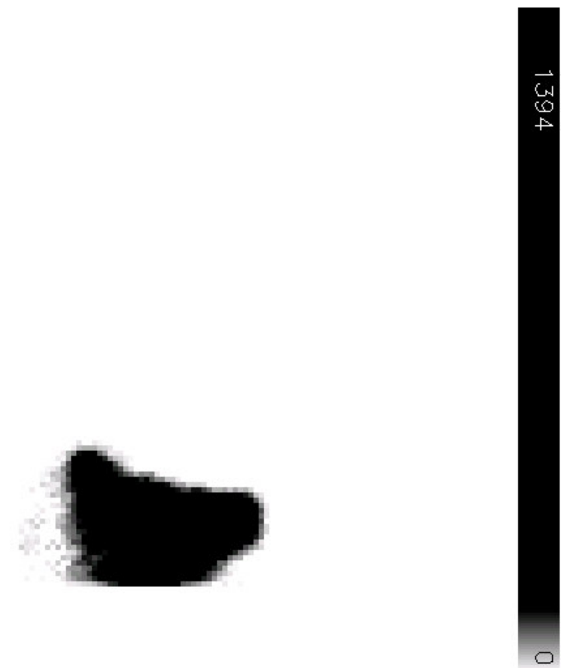
•the distribution of a pre-therapy administration of $^{99}Tc^{m}$ MAA could be used to predict the distribution of SIR-Spheres® (so acting as a Tracer Study)

^{90}Y Microspheres – *Lung Shunting*

- ~ 3% of patients are expected to have significant (>10%) shunting to the lung and therefore be at risk from radiation pneumonitis
- 100 MBq $^{99}Tc^{m}$ MAA was infused via a hepatic artery catheter under x-ray guidance
- Planar gamma camera imaging, including TEW (with noise control) and taking Geometric Mean, was used to estimate degree of lung shunting
- Up to 20% lung shunting is acceptable (though with reduced ^{90}Y activity)

^{90}Y Microspheres – Lung Shunting





No Scatter Correction

- Lung Shunt ~10.1%

→ **20%** ^{90}Y reduction

TEW Correction

- Lung Shunt ~0.1%

→ **0%** ^{90}Y reduction

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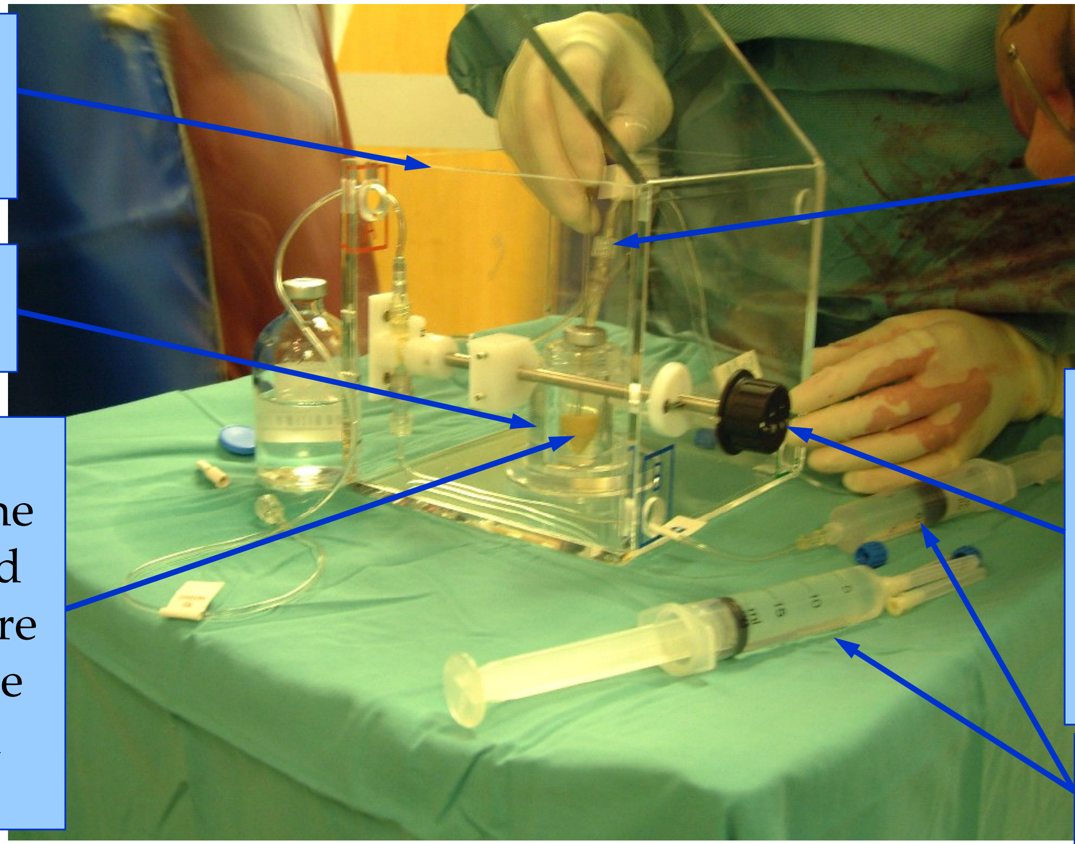
^{90}Y Microspheres - *Administration*



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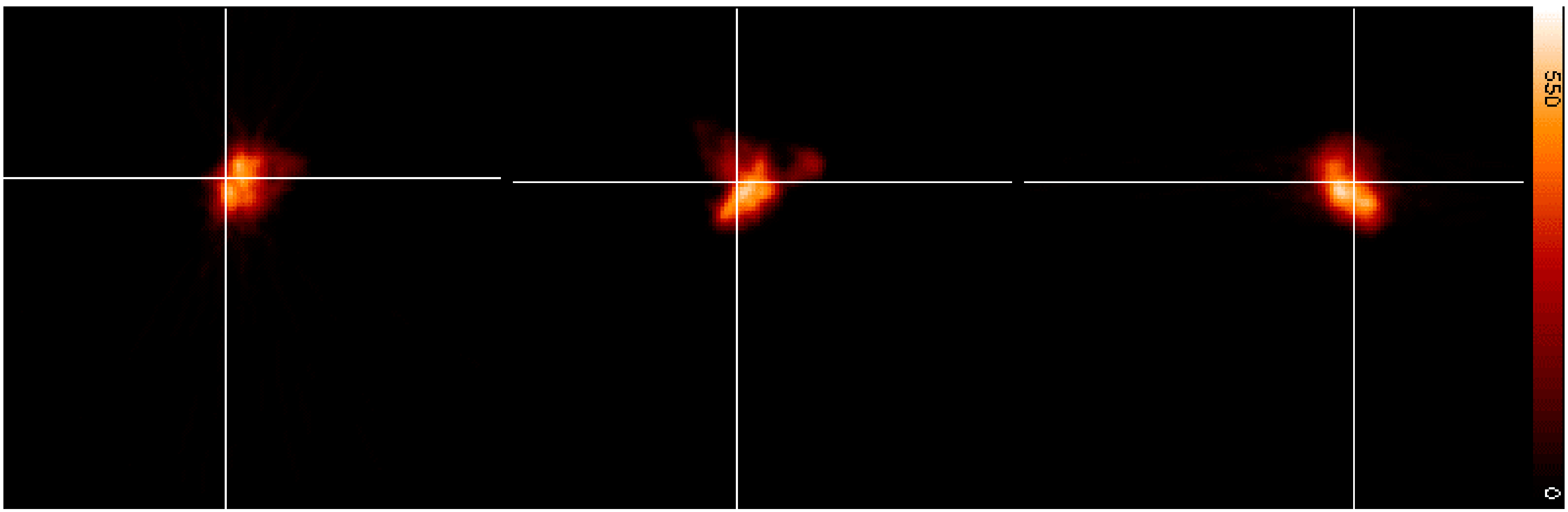
Microspheres - $^{99}Tc^{m}$ + ^{90}Y *Imaging*

- Simulated combined SPECT imaging of $^{99}Tc^{m}$ MAA (150 MBq) & ^{90}Y SIR-Sphere® (2000 MBq)
- Corrected to ***remove*** Bremsstrahlung from images
- Transverse, Coronal, Sagittal views from RMDP



^{90}Y Microspheres - *Dosimetry*

- As the spheres are permanently lodged in the liver and become immobile very quickly after administration, 3-D dosimetry is feasible with a ***single*** SPECT scan,
- Avoids some of the resource implications of performing multiple SPECT scans on each patient (such as in ^{131}I 3-D dosimetry)

Discussion

- TRT is resource (both staff & equipment) intensive, limiting its appeal & application
- Software similar to RMDP is essential for performing substantial numbers of 3D plans
  - is able to collate, accurately process and analyse raw acquired data
  - releases valuable resources
  - provides research ‘platform’ *(M-C, List-mode...)*
- Currently a lack of planning systems…

Discussion

- Some therapies are more favourable for patient specific dosimetry. For example:
  - ^{90}Y Microspheres (immobile, single SPECT)
  - ^{186}Re HEDP (skeletal, 2-D data satisfactory)
- Lack of **resources** is the limiting factor in TRT dosimetry, *not* the physics
- However, methodology is *not* established:
  - 3 centres calculate TCP → 3 *different* results
  - Image Quantification is current weak link

Discussion

- **Multi-centre** studies probably offer best chance of resolving current dosimetry issues
- **Dose-response** remains stubbornly elusive:
  - Poor input data (image quantification)
  - Poor dose model (beyond MIRD)
  - Poor understanding of **Micro-dosimetry** (what's going on at the cellular level…)

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World Cup Final, Sydney | Saturday 22 November 2003
Australia 17 England 20
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