Dosimetry of RAI in Treatment of Differentiated Thyroid Cancer (DTC)

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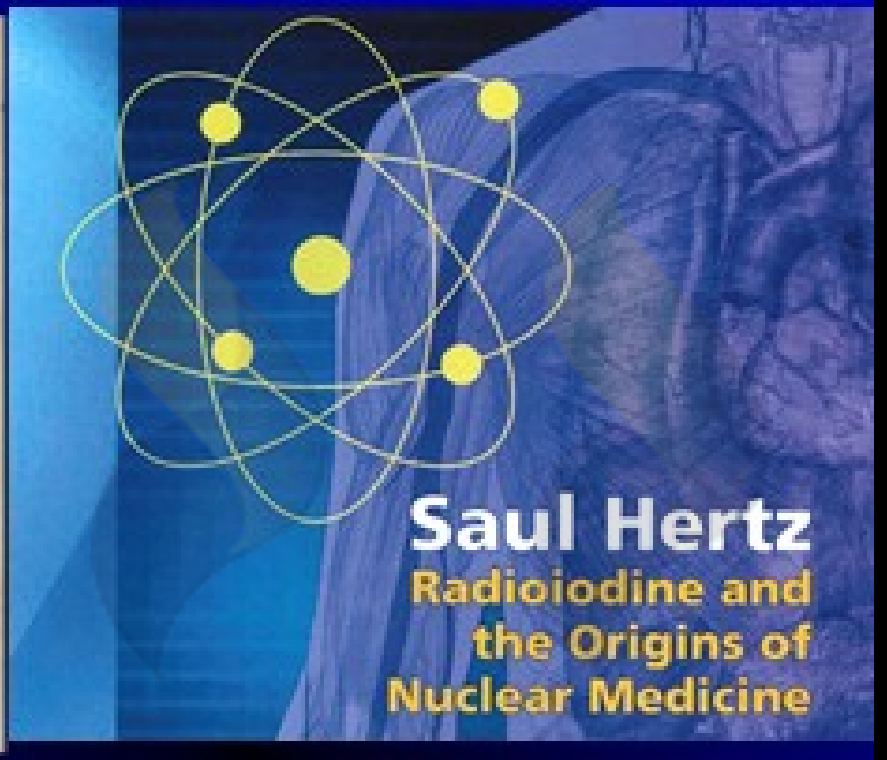
Saul Hertz – The Father of Radioiodine Therapy

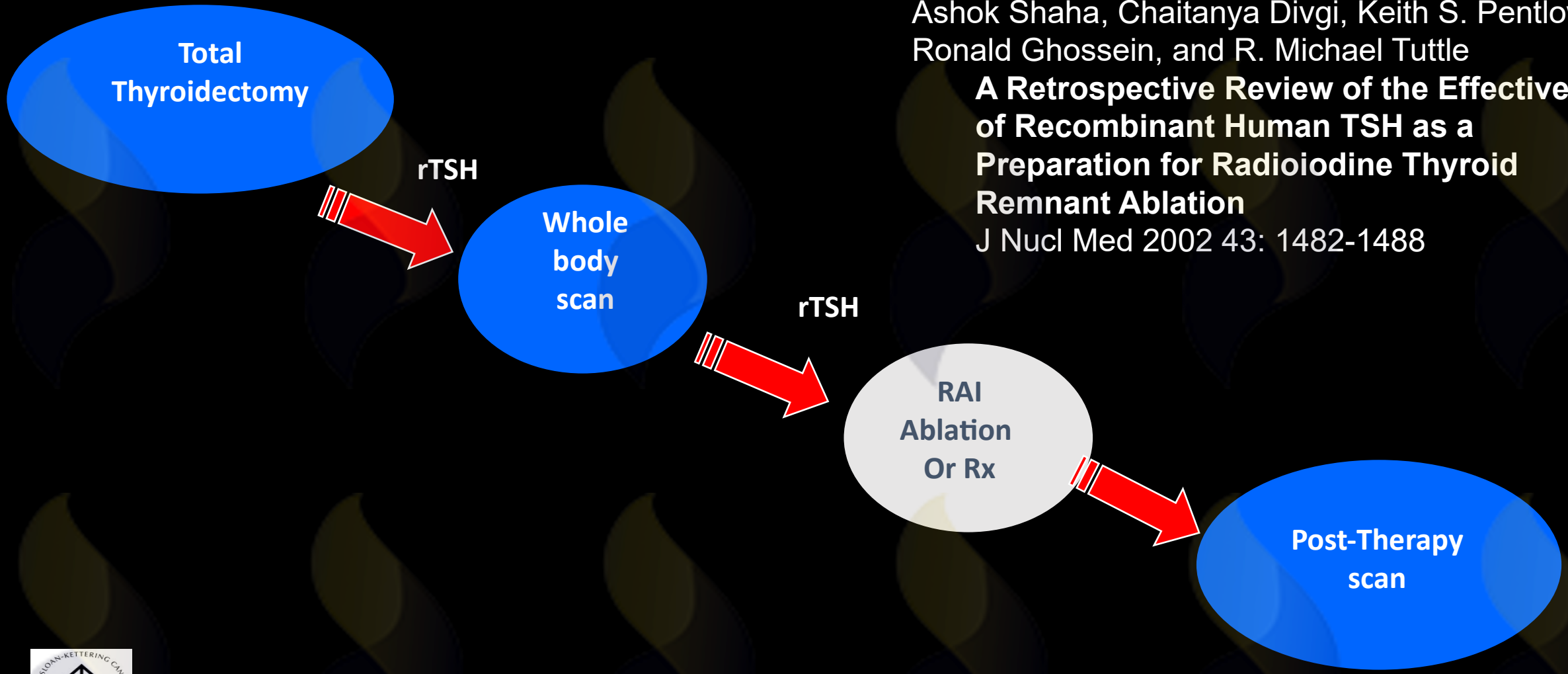


The first application of Theranostics for molecular targeted radiotherapy in history and the cornerstone of nuclear medicine therapy

A Practice Changing Paradigm – effective, affordable, practicable

First Saul Hertz Award Symposium June 2016 in San Diego @SNMMI AM honoring the achievements of Steve Larson (who also performed the 1st radioimmunotherapy using monoclonal antibodies in the 80s)

MSKCC Practice Guidelines

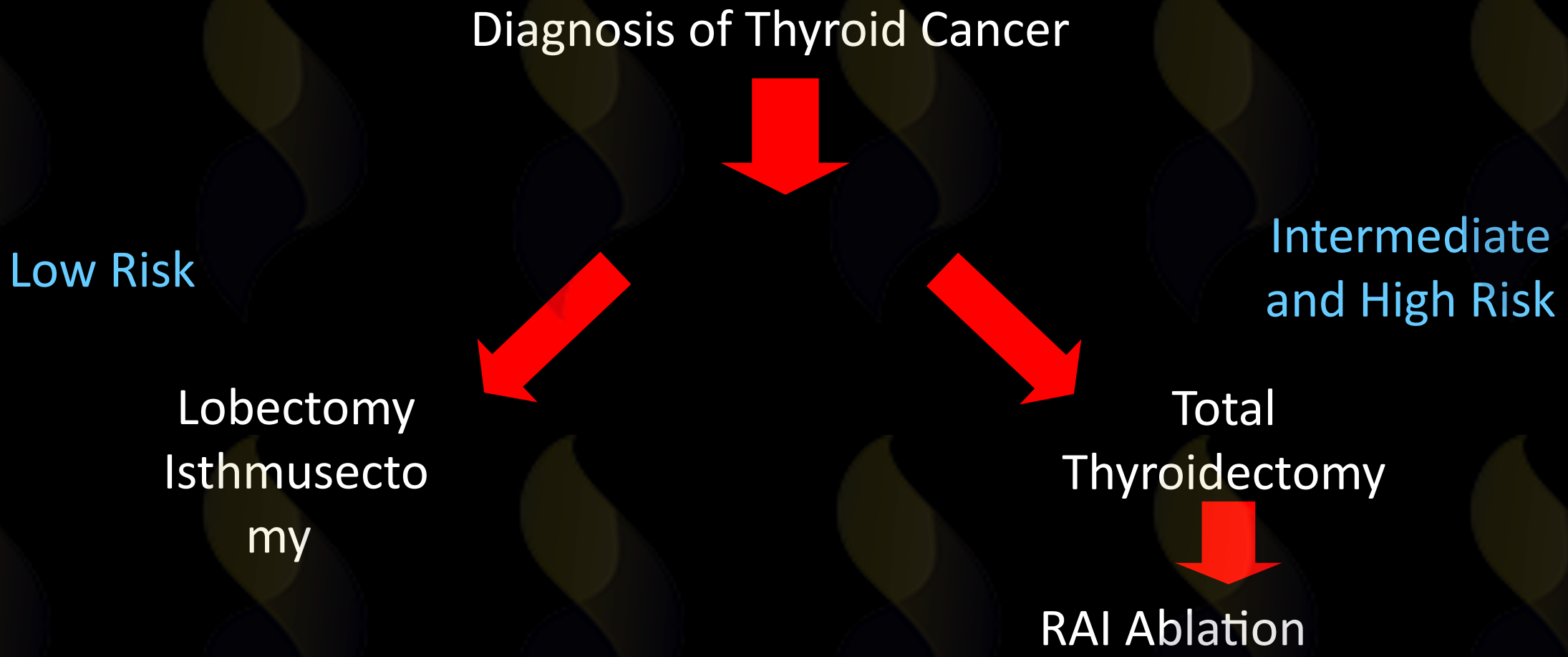


Richard J. Robbins, Steven M. Larson, Naina Sinha, Ashok Shaha, Chaitanya Divgi, Keith S. Pentlow, Ronald Ghossein, and R. Michael Tuttle

A Retrospective Review of the Effectiveness of Recombinant Human TSH as a Preparation for Radioiodine Thyroid Remnant Ablation

J Nucl Med 2002 43: 1482-1488

Thyroid Cancer
Initial Treatment Strategy



High Dose I-131 Therapy of Thyroid Cancer at MSKCC

Ablation (30-50 mCi), Adjuvant (100 mCi), Therapy (150 mCi)

WB Dosimetry

Whole Body (WB)

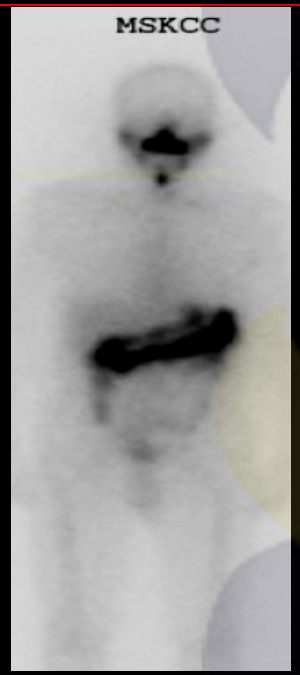
“Maximum Tolerated Activity (MTA)” for Mets (vis a vis bone marrow, lungs)

Role for RAI in Different Clinical States of Thyroid Cancer

PRIMARY TUMOR

POST-THYROIDECTOMY

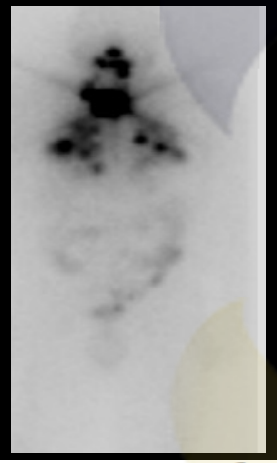
RAI remnant ablation/adjuvant therapy
(Curative Intent)



RECURRENT/METASTATIC DISEASE

RAIA

RAI
(Curative or Palliative Intent)

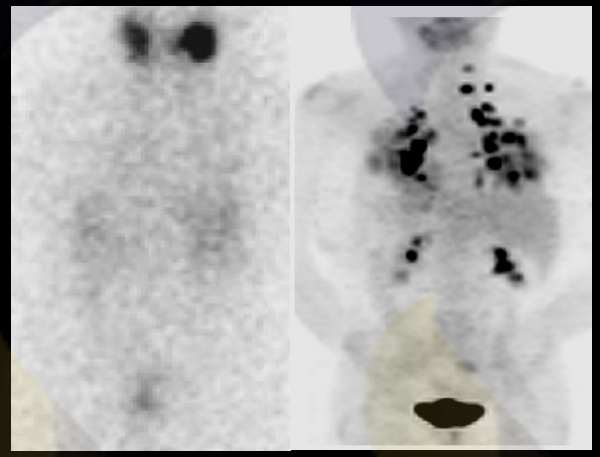


Structural response of distant metastasis to RAI ablation

Stable disease	35%
Progressive disease	30%
Partial response	19%
No structural disease	16%

RAIR

No role for RAI?
- RAS MUT
- BRAF MUT
- BRAF/RAS WT



I-131 FDG

MSKCC
High Risk Group Full Dosimetry

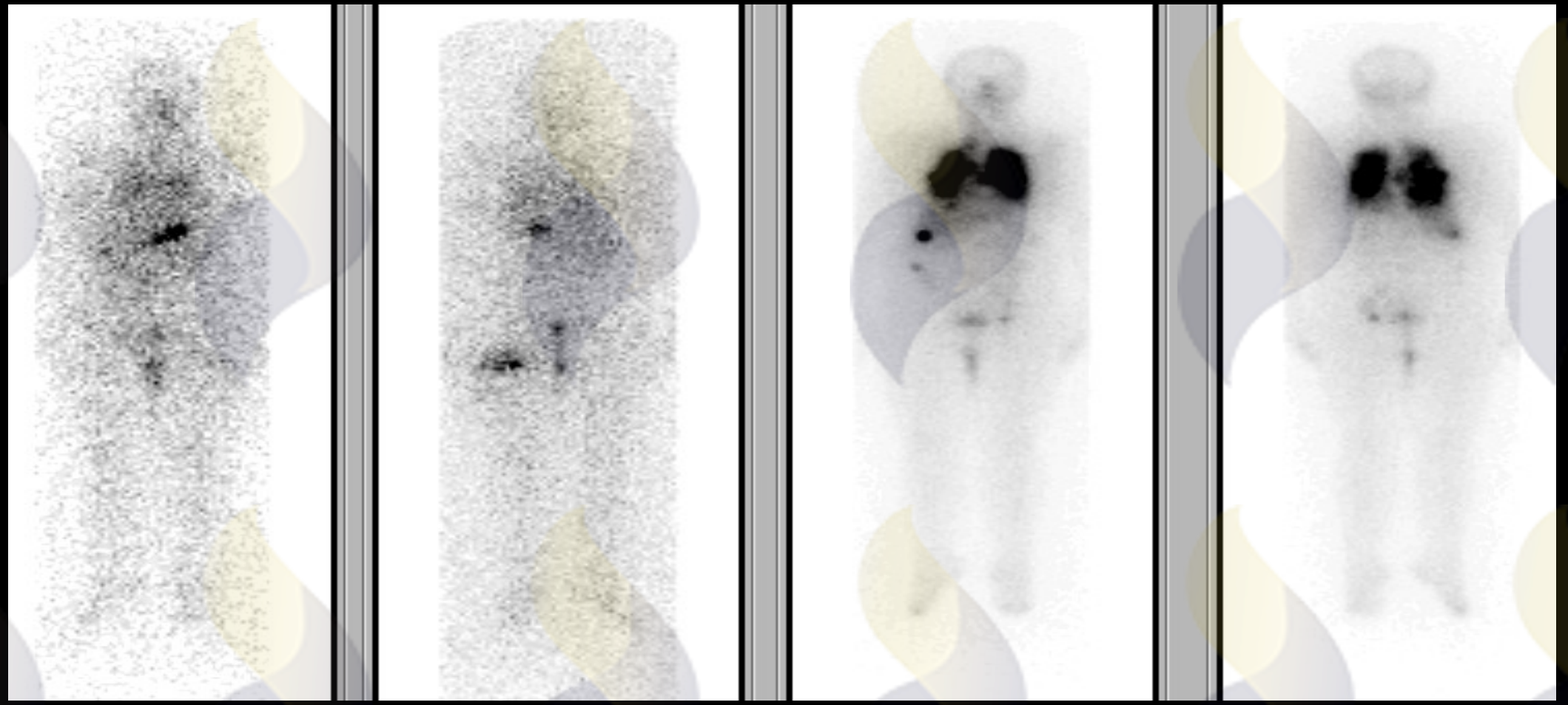
- Day 1 Thyrogen injection and blood work (Green top for background blood clearance), Red top (CBC, TFT, Tg, Preg test)
- Day 2 Thyrogen injection
- Day 3 5 mCi I131, whole body sweep (30 cm/min) at 0, 2 and 4 hrs, Blood work (Red top TSH, Tg) and Green top (Blood clearance)
- Day 4 Whole body sweep, 24 hr diagnostic scan (neck and chest views, Neck uptake), Green Top (Blood clearance)
- Day 5 Whole body sweep, Red top (stimulated Tg), Green Top (Blood clearance)
- Day 6 Whole Body sweep, 72 hr Whole body diagnostic scan, neck and chest views, Green top (Blood clearance)

MSKCC Largest Safe Treatment Dose* Emphasize Normal Organs

- Dosimetry measurements based on total and blood clearances 200 rads to blood
- Body retention less 120 mCi in 48 hrs, 80 mCi in diffuse lung diseases
- No limit of single dose
  - Usually under 0.5 Ci
  - Less than 300 mCi if salivary complication is concern

* Aka MTA. Benua , Sonenberg, Rawson et al: American J Roentgenology Radium Therapy and Nuclear Medicine 1962; 87 (1): 171-182.

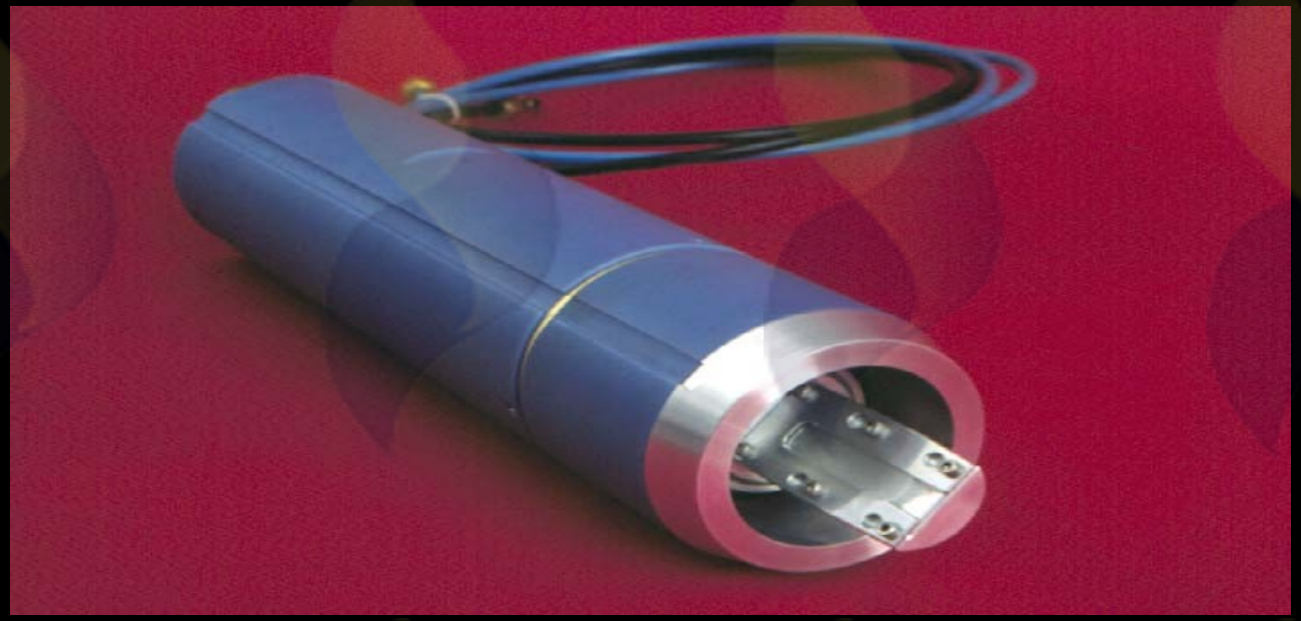
73 year-old female with thyroid carcinoma, status
post total thyroidectomy, elevated Tg and I-131 therapy with 400 mCi



Ant Post Ant Post

Diagnostic scan Post Therapy scan Day 5

MSKCC Solid Target Assembly



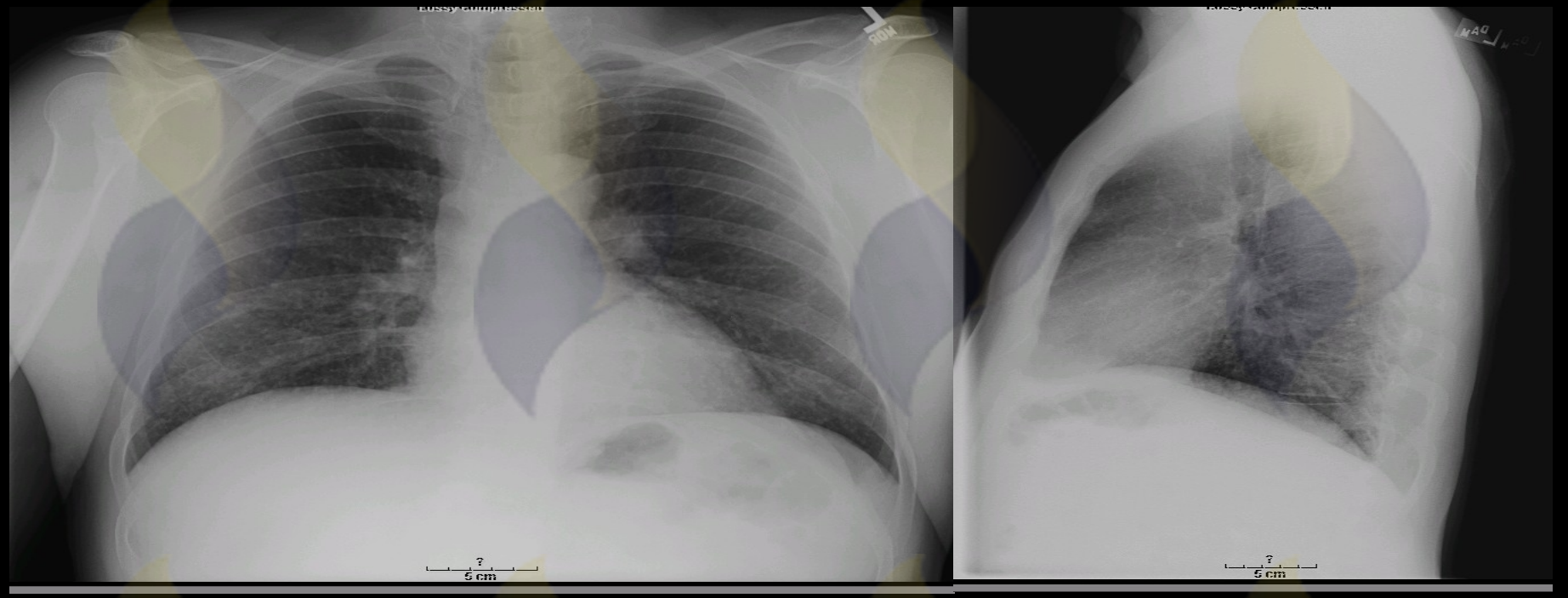
$^{124}Te(p,n)^{124}I$ (incident energy 15 MeV)*

* U.S. Department of Energy contract DE-FGO2-86ER60407.

Advanced Thyroid Cancer

- 53 yo white male with numerous pulmonary nodules discovered on routine CXR, while being W/U for prostate Ca
- Papillary thyroid Ca, moderately differentiated, locally invasive, 2.0 cm in diameter, with 13/23 lymph nodes
- Referred for Dosimetry

THYROID CA



^{124}I-Iodine in Thyroid Cancer

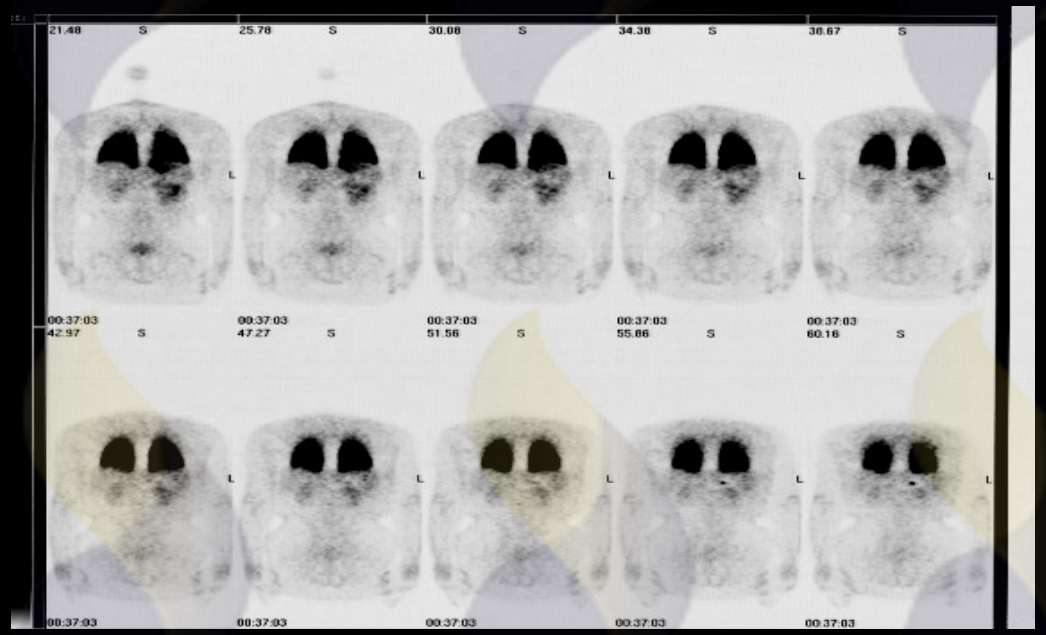
At time of surgery, WD thyroid Ca 2.0 cm
Mets to neck nodes and lung

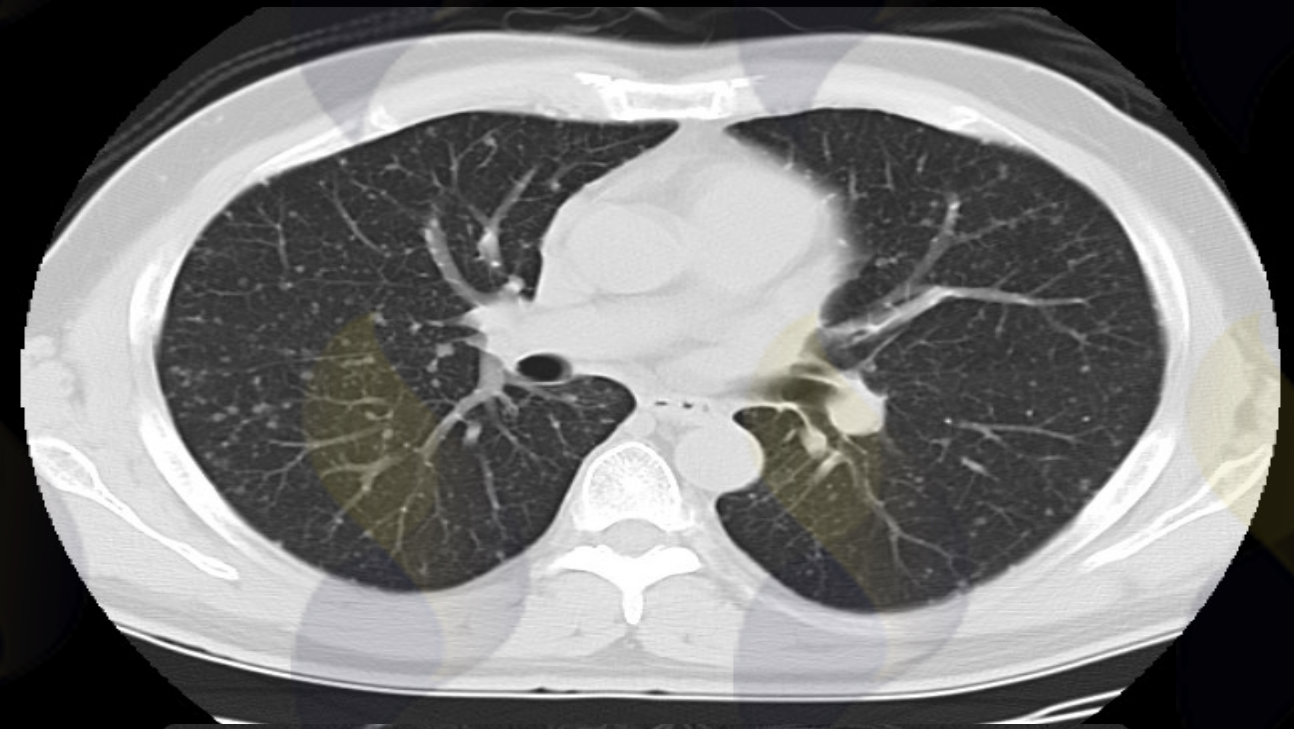
4.28.2000 TG 11,000
12.2003 TG 7
3.14.2013 TG < .2

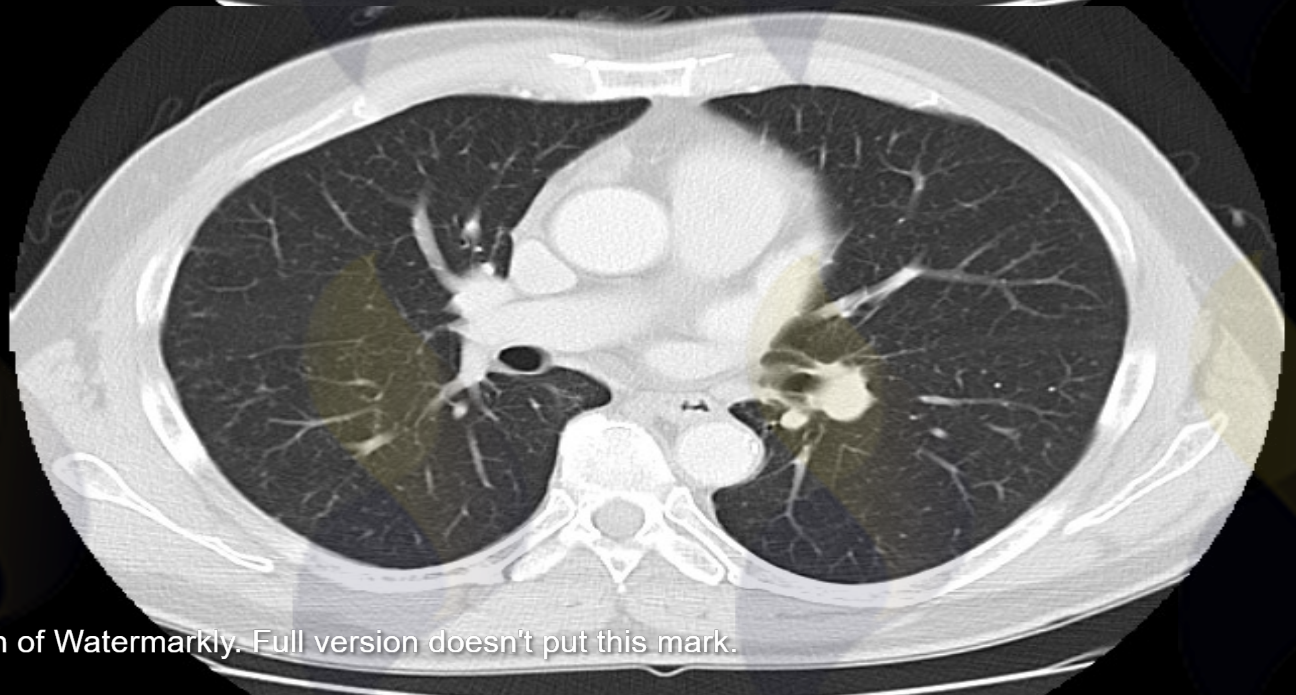
12/2000-10/2003 131I Rx in 4 doses to 1527 mCi. Est dose > 50,000

Last F/U 6/16/2017 TG 0.3
NED (CURE?) many punctate
bilateral CT lesions
Dry mouth, otherwise no sequelae

Pre-Treatment PET







Dosimetry

- total and blood clearances 200 rads to blood
- Body retention less 120 mCi in @48 hrs,
- WB 80 mCi in diffuse lung diseases @48 hr.

Targeted Radiotherapy can be curative in patients

A matter of radiation dose and Therapeutic Index (TI) : “Hitting the sweet spot”

Targeted Radiotherapy of Solid Tumors "Hitting the Sweet-Spot"*

- Curative Tumor Dose> 10,000 cGy
- Renal dose < 1500 cGy
  - ~7-10 Therapeutic Index (TI)
- Bone Marrow dose < 150 cGy
  - ~40-100 TI
- Colon mucosa dose < 250 cGy
  - ~40-60 TI

***Larson SM**, Cheal SM. New Insights in Theragnostics: Pre-targeted Radioimmunotherapy for Cure of Solid Human Tumors. World Journal of Nuclear Medicine / Volume 18 / Issue 2 / April-June 2019, pages 206-207.

Major Unmet Need

Individual Lesion and Normal Tissue Radiation absorbed dose with targeted radiotherapy in thyroid cancer

I choose a block of marble and chop off whatever I don't need. ..Rodin

On Invention and Development

James Fagin

Alan Ho

Mike Tuttle

Laura Boucai

The Clinical Problem: RAI-Refractory Thyroid Cancer

- Distant metastases are the most frequent cause of death for patients with differentiated thyroid cancer[1]
- Decreased RAI incorporation into metastatic sites is associated with higher mortality[2]
- New therapies for RAI-refractory thyroid cancer are desperately needed

[1]Mazzaferri E.L., *J Clin Endocrinol Metabol*, 86:1447-63, 2001.

[2]Durante, C. *J Clin Endocrinol Metab*, 91:2892-9, 2006.

John Humm

Ravinder Grewal , PI 18-253

Alan Ho PI 20-053

Audrey Mauguen

Lesional Dosimetry in Thyroid Cancer
18-253
20-053

^{124}I-NaI Theranostic

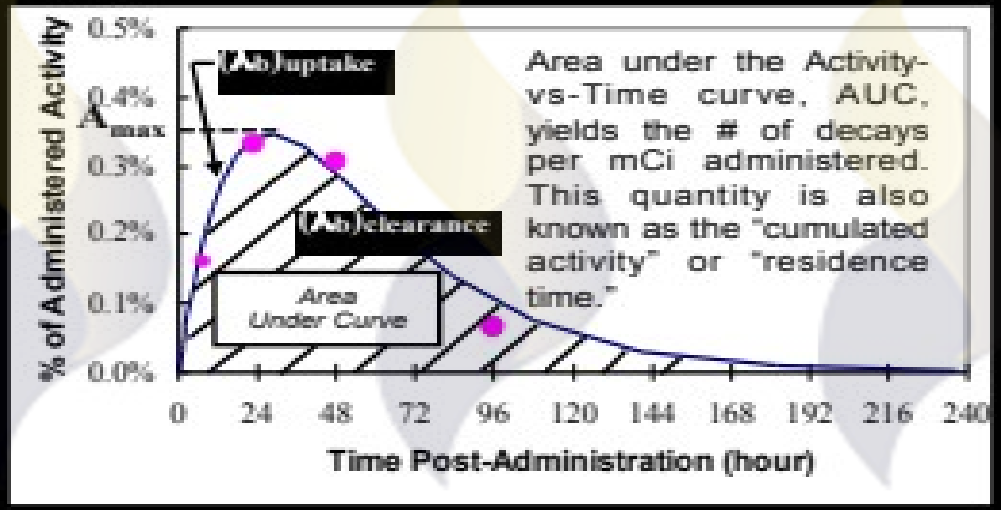
Re-induction Therapy for RAIR

Sharpen Dose-Response for RAI

“Sooth-sayer” an Imaging based Dosimetry Biomarker of Known Precision (SUV @ 48 hours)

- AUC = area under time activity curve for time actiivty curve of 4 time ponts : 24, 48, 72, 96 hours after 6 mCi NaI -^{124}I
- Dose in rads(cGy) for each lesion is AUC*$D_{I\text{-}131}$ (gm-rad/uCi-hr)
- Choose time near uptake equilibrium (clearance relatively slow)
- Regression Statistics for SUV and uCi/cc @48 hours
- Validation procedures include “leave one out” Crossvalidation

Calculating radiation absorbed dose (rads) to individual lesions thyroid Ca



Serial measurements fit to the following function:

$$\%\,AA = A_{max}\,[1 - e^{-(\lambda_b)_{uptake}}]\;e^{-(\lambda_b)_{clearance}}$$

$(\lambda_b)_{uptake}$, $(\lambda_b)_{clearance}$: biological (b) uptake and clearance constants (corrected for radioactive decay).

λ_p: physical (p) decay constant.

Total radioactive decays per mCi (aka cumulated activity, residence time), $\tilde{A}$ (in μCi-h/mCi):

Calculating Radiation Absorbed dose in Rads (cGy) requires equilibrium dose constant (Δ) for ^{131}I (in gm-rad/μCi-h/mCi) =0.405

$$\tilde{A} = A_{max}\left[\frac{1}{(\lambda_b)_{clearance} + \lambda_p} - \frac{1}{(\lambda_b)_{uptake} + (\lambda_b)_{clearance} + \lambda_p}\right] \bullet 10$$

$\tilde{A}$ * (Δ) * Total Dose (mCi) = Rads to lesion

SUV

$$\frac{\text{Activity per unit volume}}{\text{Injected Activity/Body Wt*}}$$

*also, lean body mass, BSA, etc

Concept

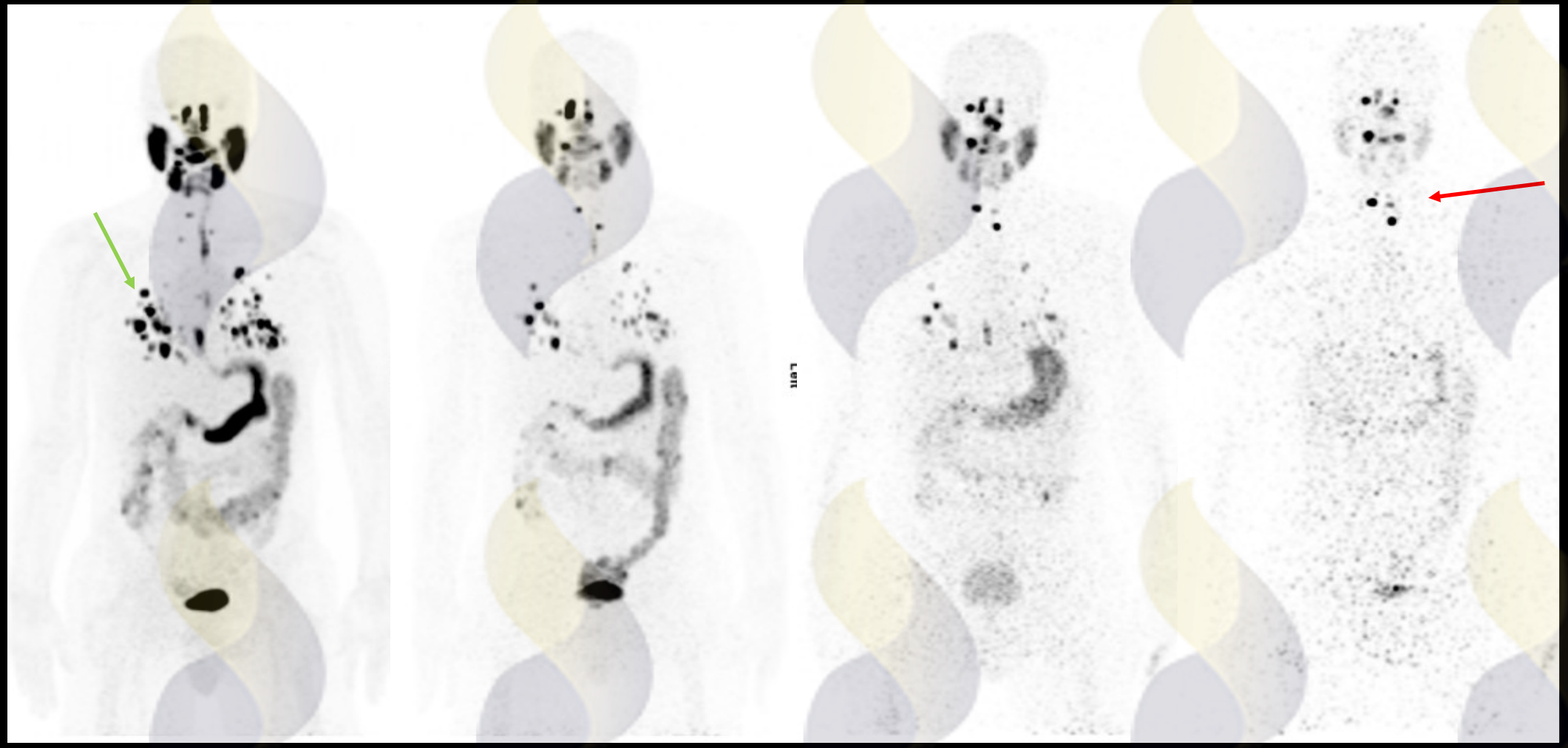
Based on a single PET quantitative imaging time point, (SUV, micro-curies/gram,) at 48 hours, assess correlation expressed as a prediction interval for integrated AUC (uCi-hour) Proportional to dose cGy.

Study Population and Plan

- 21 patients (208 lesions with advanced WDTC for consideration of RAI therapy
- 6.0 mCi PO ^{124}I Na at time zero, followed by 4 -PET whole body images at 24,48, 72 and 96 hours
- Determine optimal time point for single image correlation, 24, 48, 72
- Compare 1 and 2 images minimizing mean errors squared
- Determine algorithm based on correlation with 208 lesions AUC as a surrogate for dose, and individual quantitative parameters(e.g. SUV)
- 48 hours SUV optimal predictor, and correlation with integrated AUC validated with “leave one patient out “ approach

124 I-NaI Lesion Dosimetry

24 hours | 48 hours | 72 hours | 96 hours



Site	Mean size	Lesion Dose per mCi	T1/2 eff	AUC	SUV	Activity (mCi)	Dose (cGy)	Dose (cGy)
	cm	cGy	days	uCi.hr	at 48h	to deliver 20 Gy	patient received	at MTA
R. parietal skull	4.03	41.92	8.02	79.28	25.58	48	17063	22345
L. scapula	3.63	27.73	8.02	50.87	17.31	72	11285	14778
R. ant. 2 rib	4.10	21.18	8.02	40.22	13.85	94	8622	11291
L. lateral 7 rib	3.17	25.72	8.02	44.73	14.65	78	10469	13711
L. post elements T3	1.07	8.89	2.33	6.17	3.57	225	3618	4739
spinous process T4	0.77	51.74	8.02	22.52	7.68	39	21056	27575
T7 vertebral body	0.60	71.05	5.24	19.66	8.03	28	28917	37869
L2 vertebral body	0.40	100.03	4.90	17.63	8.26	20	40710	53314
L. post. Acetabulum	4.27	10.16	6.30	19.46	6.87	197	4134	5414
L. post. 5 rib	1.90	3.59	8.02	4.51	1.24	556	1463	1916
L3 vertebral body	0.87	3.34	2.21	1.76	1.35	600	1357	1778
Ant. Aspect of thyroid cartilage	2.00	234.88	8.02	306.97	127.01	9	95597	125193
L. thyroid bed	0.93	32.00	6.75	18.57	7.70	63	13023	17054

Algorithm for predictor vs dosimetry

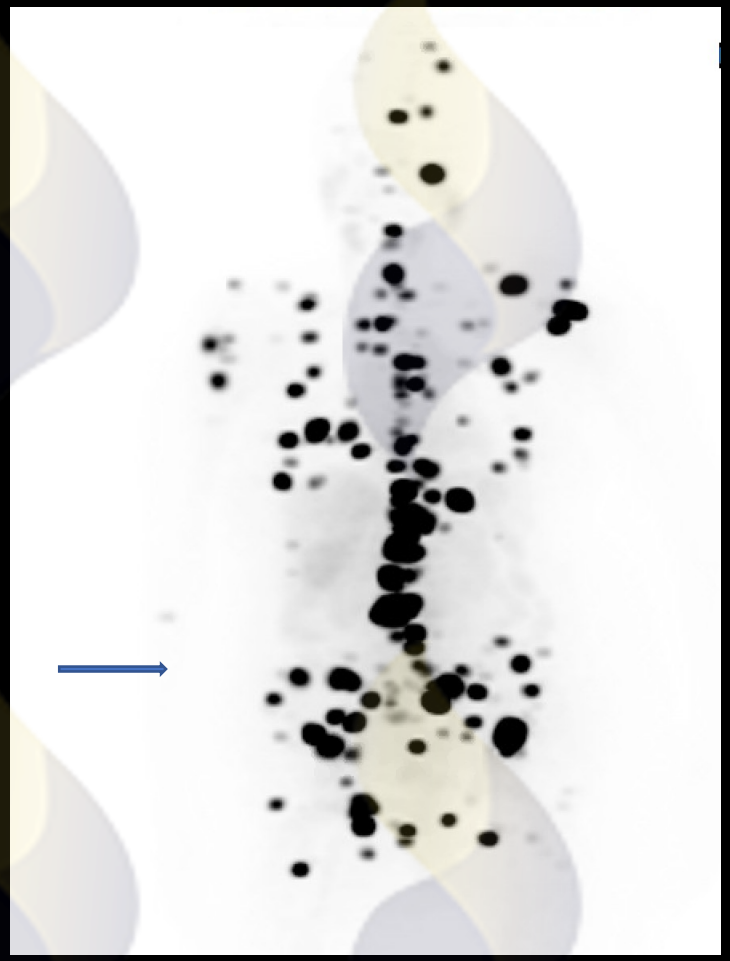
Estimate the linear relationship between the dosimetry as summarized by the Area Under the Curve based on 4 measured timepoints and the activity measured at one timepoint, called predictor (eg, SUV at 48h), For this estimation, the unit is the lesion, and a Generalized Estimating Equation(GEE) approach is used to estimate the parameters (intercept, slope and robust variance matrix) accounting for the correlation between the lesions in a same patient. Log-transformed values of the uptake and doses are used to ensure the data are normally distributed. The linear model is as follows, where the errors are correlated, is the logarithm of the AUC value is the uptake measured at one time-point, eg the logarithm of 48h SUV measured on and for the lesion j from patient i.:

Second, using the estimations for and the covariance matrix, a prediction interval (PI) is calculated. A PI differs from a confidence interval, as it aims to predict with 95% confidence where future measurements will fall in. In our case, if we observed the same value of SUV at 48h for 100 new lesions, what is the range in which 95 of the AUC value of those lesions will be. As difficulties arose to analytically construct the PI, the PIs are calculated using simulated prediction following the steps detailed in Gelman and Hill (2007) [ref Gelman and Hill book] and summarized in Appendix A.

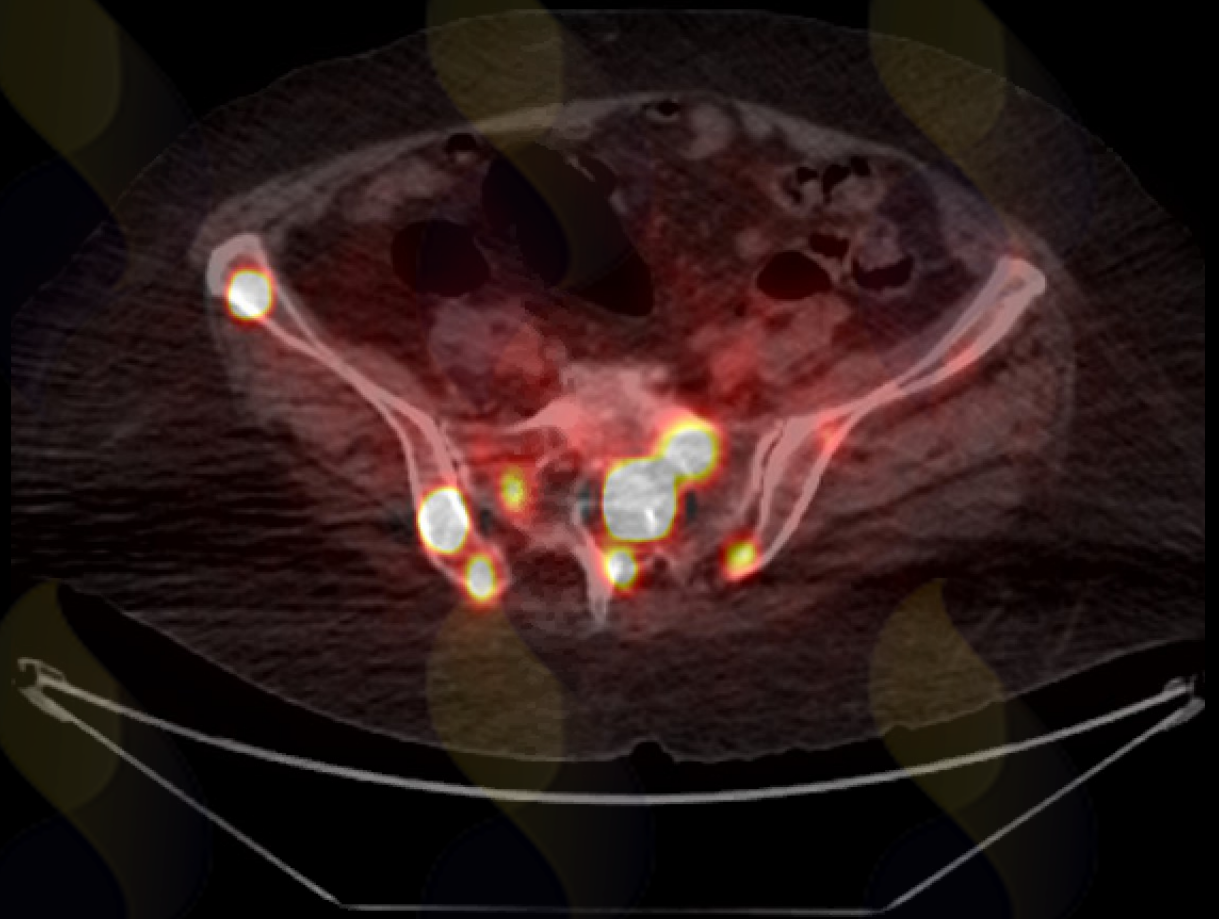
Gelman, Andrew, and Jennifer Hill. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. Cambridge University Press, 2007.

^{124}I NaI Day 2 DTC Dosimetry Study

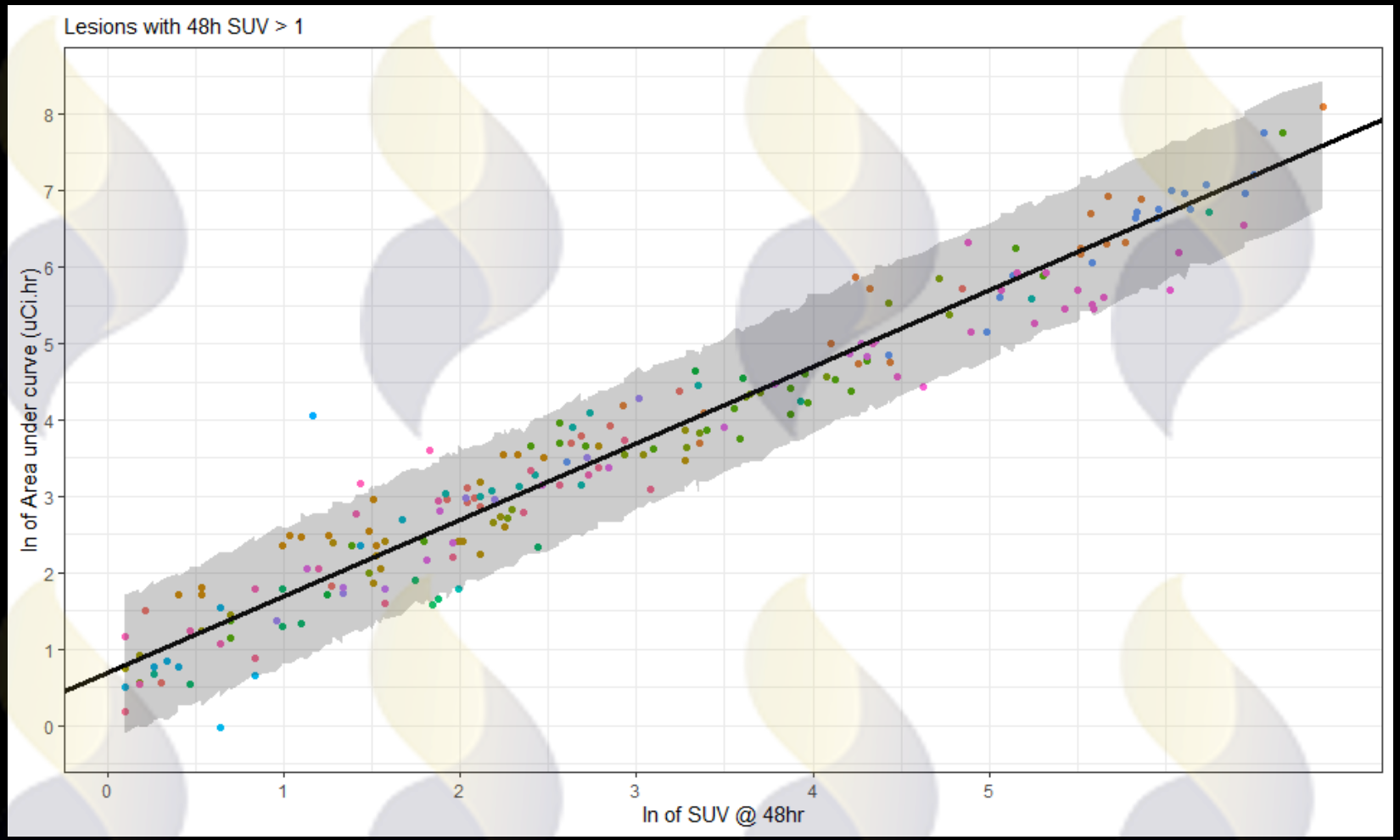
MIP



PET/CT Fusion Image



Twenty-one patients with 208 lesions >SUV 1.0: estimated regression line (black); coefficient (slope) is 1.002 (robust se = 0.024; 95% prediction interval(grey zone) : 0.954 to 1.049; p < 0.0001). The full predicted value of AUC based on the 48h uptake can be calculated as: .



SU 2 5 8 10 20 40 50 100 200

Estimate of the linear regression parameters, prediction error and cross-validated prediction error, for different predictors using 1 timepoint. What is most precise predictor?

Predictor	N	Slope	Robust se	Squared Error	CV Squared Error
uCi 24h	231	1.018	0.050	0.615	0.665
uCi 48h	231	0.934	0.043	0.443	0.484
uCi 72h	231	0.859	0.051	0.679	0.761
SUV 24h	217	1.057	0.045	0.436	0.472
SUV 48h	**208**	**1.002**	**0.024**	**0.204**	**0.223**
SUV 72h	193	0.963	0.039	0.292	0.327
SUL 24h	211	1.062	0.046	0.403	0.434
SUL 48h	**200**	**1.013**	**0.028**	**0.207**	**0.225**
SUL 72h	186	0.955	0.044	0.301	0.338

Estimate of the linear regression parameters, prediction error and cross-validated prediction errorfor different predictors using an early and late timepoint. **What is most precise combination of predictors**? Is it better than a single predictor

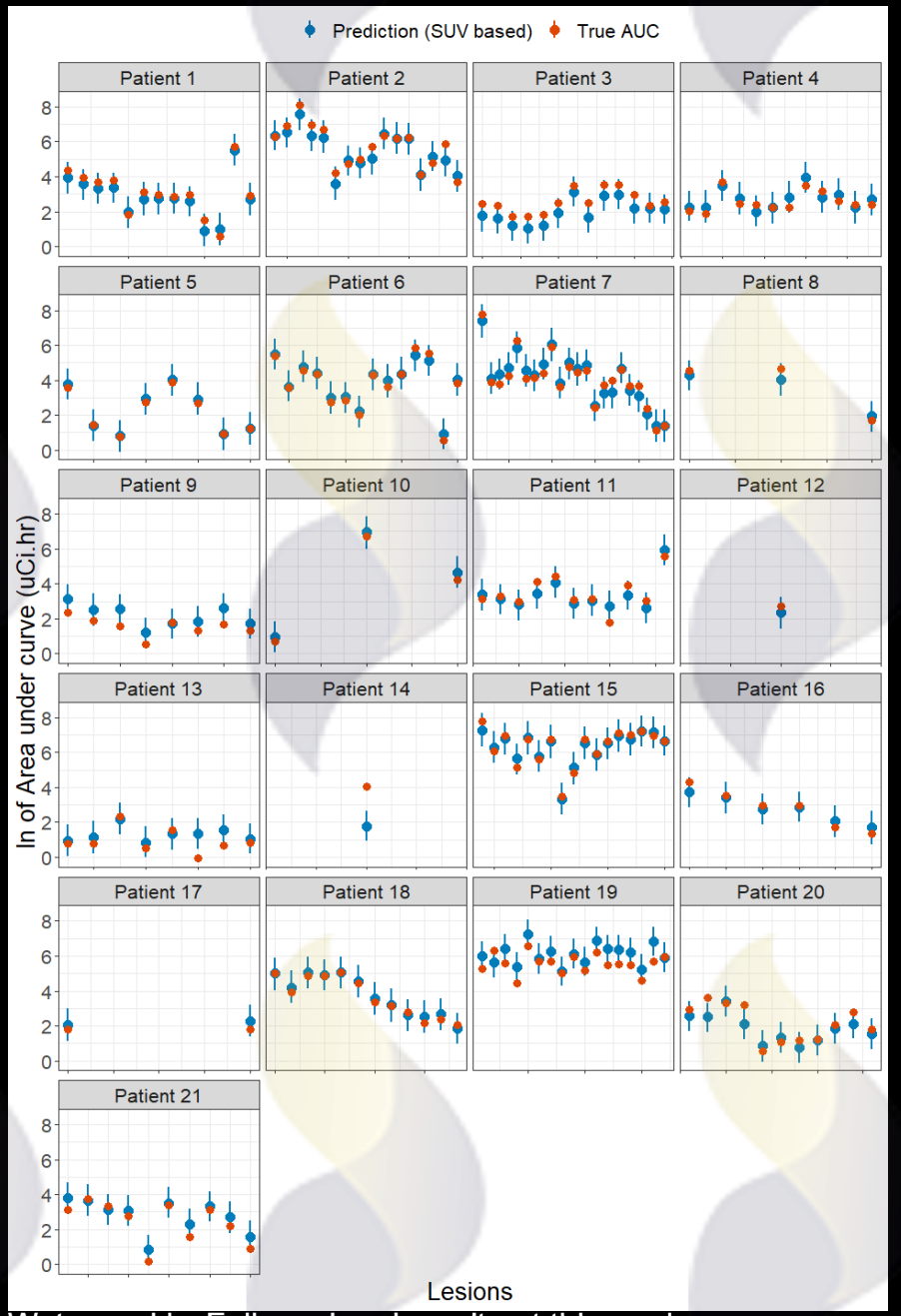
Timepoint	N	Squared Error	CV Squared Error
uCi 48h and uCi 72h	231	0.449	0.514
uCi 48h and ratio 72/48	231	0.449	0.515
SUV 48h and SUV 72h	208	0.226	0.298
SUV 48h and ratio 72/48	208	0.226	0.299
SUL 48h and SUL 72h	**200**	**0.224**	**0.296**
SUL 48h and ratio 72/48	200	0.224	0.297

Activity (^{131}I mCi) Dose to deliver 2000 cGy, based on single time point imaging at 48 hours

	AUC (microcuric-Hr/gm (cGy) per mCI		Activity in mCi to achieve 2000 cGy			
SUV @ 48 Hr.s	**Mean Estimate**	**95% PI**	**Mean Estimate**	**95% PI (97.5% upper bound)**	**95% upper bound**	**90% upper bound**
10	20.2 (8.18 cGy)	8.6 - 48.4	244.8	102.1 - 576.6	517.0	431.4
15	30.3 (12.27 cGy)	11.9 – 71.0	163.1	69.6 - 416.2	355.5	292.3
20	40.4(16.35) cGy)	16.1 - 97.1	122.2	50.9 - 306.9	254.8	217.6
30	60.6((24.5cGy)	24.3 - 147.4	81.4	33.5 - 202.9	179.1	153.1
50	101.2 ((40.99 5cGy)	40.8 - 252.9	48.8	19.5 - 121.1	102.7	87.9
100	202.6(81 cGy)	82.3 - 479.6	24.4	10.3 – 60.0	53.1	45.3
200	405.8 (164 cGy)	164.2 - 951.2	12.2	5.2 - 30.1	26.0	21.5
300	609.2 ((243.5cGy)	257.8 - 1476.2	8.1	3.3 - 19.2	16.7	14.5

Validation Testing of Soothsayer , single time point PET predictor for Mearured AUC in RAI dosimetry .

1. To show agreement with prediction interval for actual measured AUC vs predition interval (blue) of individual lesions (*94% agreement)
2. To show use in “leave on patient out validation , so that each patient at a time for all 21 patients is left out and the variance of lesions measured and compared to original 21. minimal change. Noted.



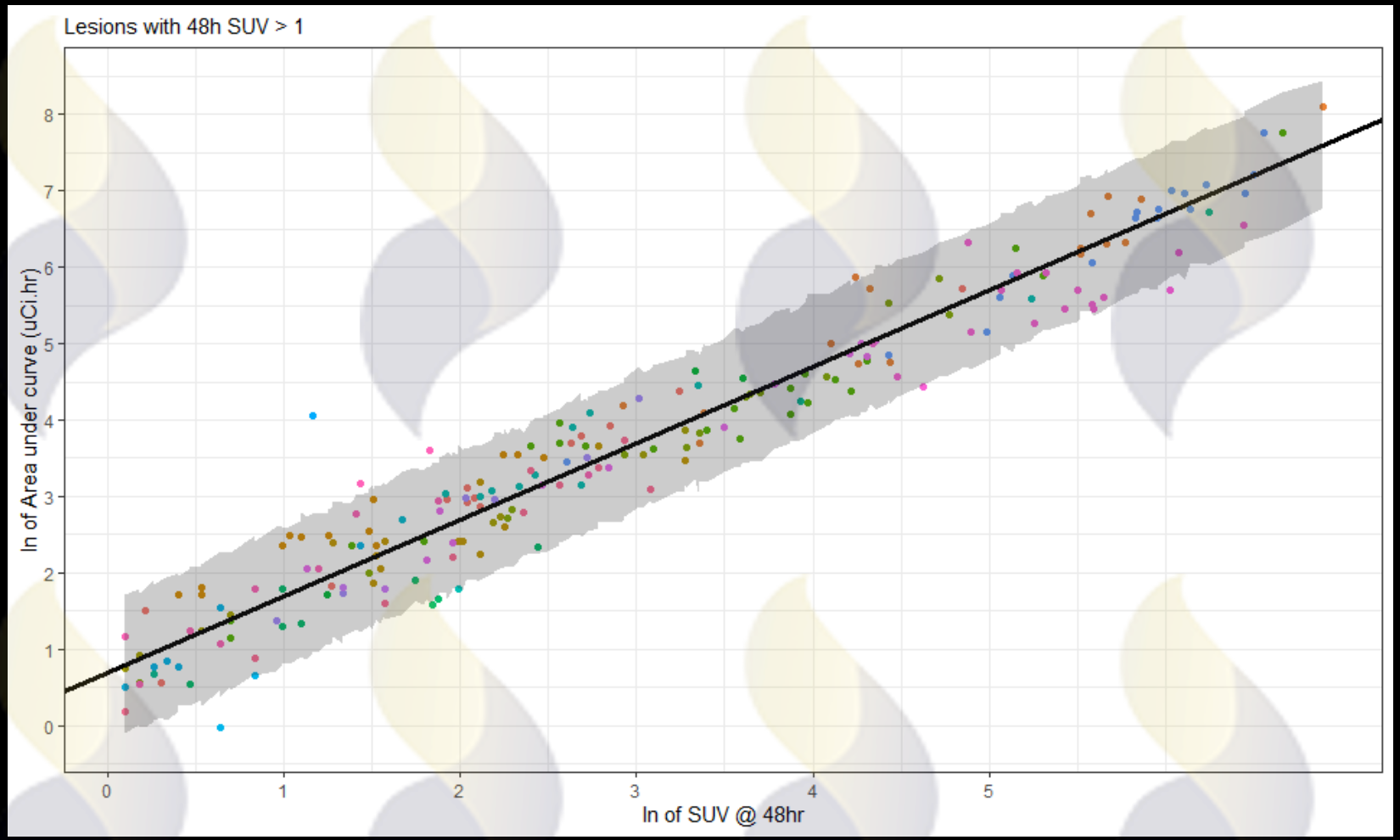
Simulation studies of optimized precision

- Below is a simulation of N patients having the characteristics close to our 15 patients. The simulations study:
- 1-simulate a total of N similar patients, with between 3 and 23 lesions
- 2- simulate their 48h time point values, and a corresponding AUC
- 3- reproduce the prediction approach based on this simulated data
- 4- estimate the average half-width of the prediction interval (= precision)

Simulation Prediction of AUC

		Normal scale		Log scale	
N patients	**Average predicted AUC**	**Precision based on low boundary**	**Precision based on high boundary**	**Precision based on low boundary**	**Precision based on high boundary**
15	65	56.6	275.5	1.56	1.56
60	33	28.0	120.5	1.45	1.45

Twenty-one patients with 208 lesions >SUV 1.0: estimated regression line (black); coefficient (slope) is 1.002 (robust se = 0.024; 95% prediction interval(grey zone) : 0.954 to 1.049; p < 0.0001). The full predicted value of AUC based on the 48h uptake can be calculated as: .



SU 2 5 8 10 20 40 50 100 200

Study Output parameters and findings

- 15 patients treated with RAI (from 21 patients with 4 point dosimetry), 96% of lesions had > 2000 cGy (Maxon threshold for response in majority of tumors). **Validates mCi RAI prediction**
- **mCi Dose** to achieve > 2000 cGy for 95% of lesions Maximum total mCi dose (aka MTA) according to MSKCD normal tissue dosimetry
- **Inidivdiual lesion mean rad dose(cGy) and 95% Prediction interval** at a given SUV .
- In test of algorithm for 48 hour predictor SUV, 95% of 208 lesions within prediction interval in ”leave patient out: comparison corroborates algorithm

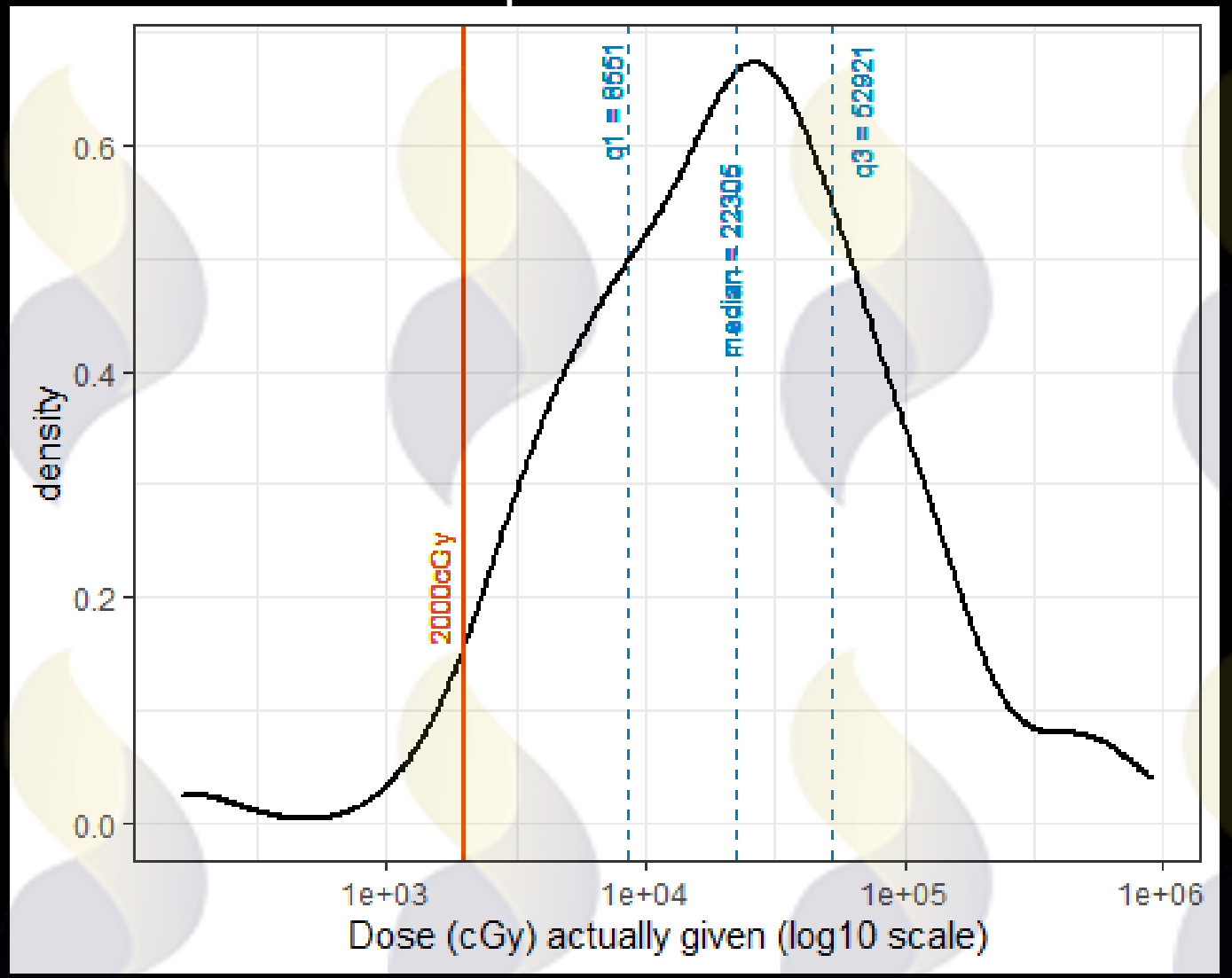
Concept

Calculating Radiation Absorbed dose in Rads (cGy) requires equilibrium dose constant (**Δ**) for ^{131}I (in gm-rad/**μCi-h/mCi**) =0.405

$\tilde{A}$ * (Δ) * Total Dose (mCi) = Rads to lesion

“Gold Std” Doses (cGy) of individual lesions

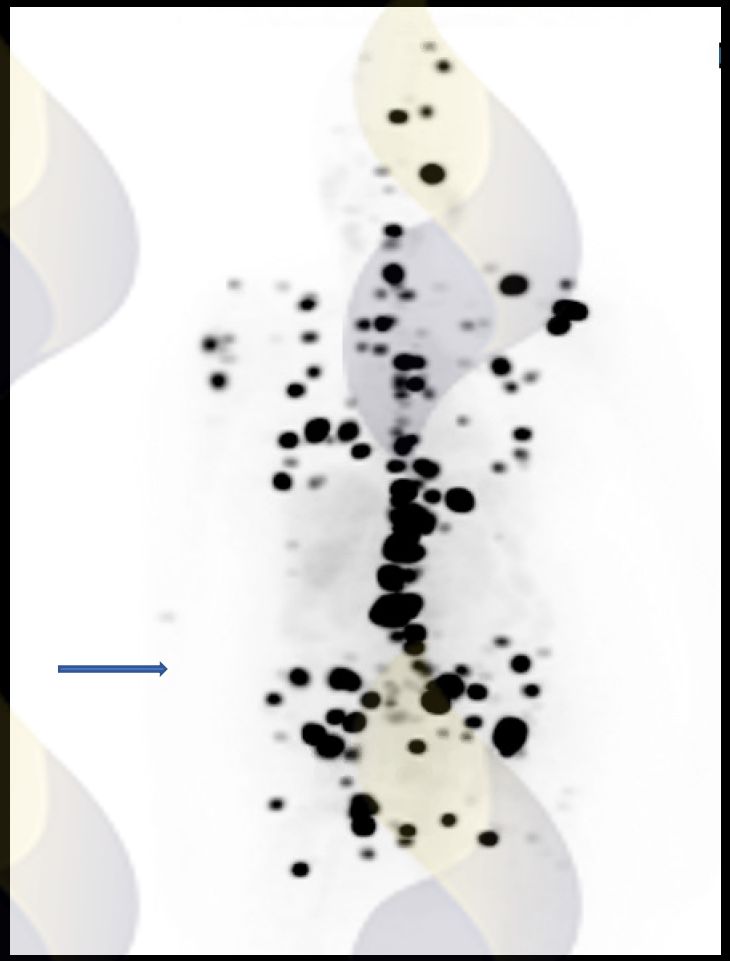
N=169 ^{124}I via 4-time point AUC * Δ in 15 treated patients



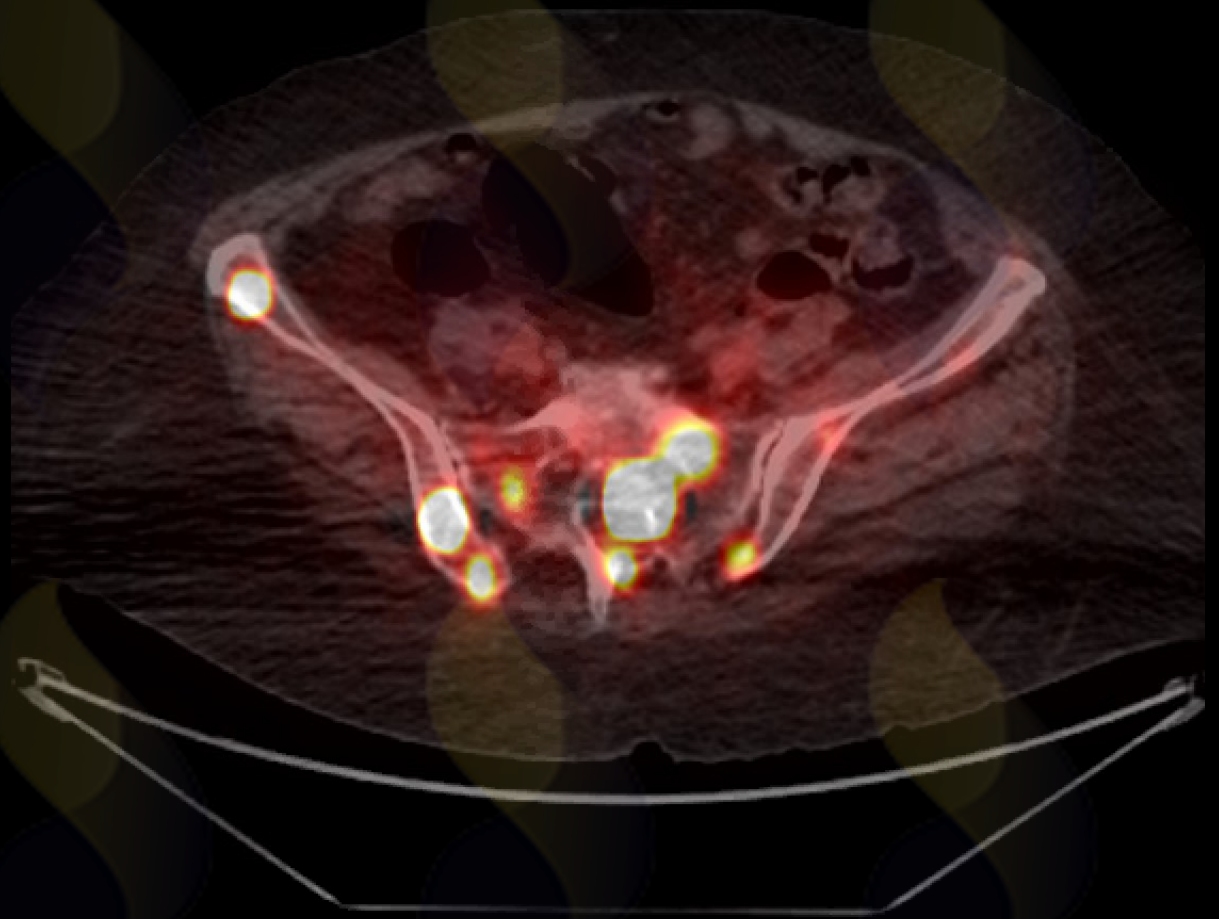
25% = 8551 cGy
50%= 22305 cGy
75% =52921 cGy
96% of 169 lesions estimated to have >2000 cGy

^{124}I NaI Day 2 DTC Dosimetry Study

MIP



PET/CT Fusion Image



MSKCC Largest Safe Treatment Dose*

- Dosimetry measurements based on total and blood clearances 200 rads to blood
- Body retention less 120 mCi in 48 hrs, 80 mCi in diffuse lung diseases
- No limit of single dose
  - Usually under 0.5 Ci
  - Less than 300 mCi if salivary complication is concern

*Benua , Sonenberg, Rawson et al: American J Roentgenology Radium Therapy and Nuclear Medicine 1962; 87 (1): 171-182.

“Sooth-sayer” an Imaging based Dosimetry Biomarker of Known Precision (SUV @ 48 hours)

- AUC = area under time activity curve for time actiivty curve of 4 time ponts : 24, 48, 72, 96 hours after 6 mCi NaI -^{124}I
- Dose in rads(cGy) for each lesion is AUC*Δ_{I-131} (gm-rad/uCi-hr)
- Choose time near uptake equilibrium (clearance relatively slow)
- Regression Statistics for SUV and uCi/cc @48 hours
  - AUC = exp(1.002 + 0.991 * ln (t48; SUV)) n=158 lesions
  - The estimated regression coefficient (slope) is 1.007 (robust se = 0.022; 95% confidence interval: 0.963 to 1.051; p < 0.0001).
- Validation procedures include “leave one out” Crossvalidation

Special Features of Soothsayer

- Development Based on “Gold Standard” of 4-point dosimetry and measured AUC
- A generalized estimating equation (GEE) model is fitted on the log-transformed values, AUC being the outcome variable. Robust standard-error estimates are obtained, accounting for the correlation between the observations from similar patients .
- Dose Estimates (cGy) of Known precision
- Because multiple sources of variation impact correlation, a simulation approach was used to predict sample size effects on precision: 95% confidence internal reduced by ½ for 4 X sample size.
- Applicable to normal organ dose ie Bone Marrow; salivary glands
- Data driven and applicable to other TRT agents for both individual lesion dose and organ dose e.g. Lutathera (NET); PSMA-617 (Prostate); DOTA and SADA PRIT

Clinical Thyroid Therapy in MITS (Nuc Med)






5R01 CA201250-4 124I-NaI PET: Building block for precision medicine in metastatic thyroid cancer 2016-present

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I choose a block of marble and chop off whatever I don't need. ..Rodin

On Invention and Development