2021 ACOI Annual Convention
And Scientific Sessions
October 27-30

Theranostic Nuclear Medicine Poised to Revolutionize Cancer Treatment

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Penn State Health (PSH), Hershey

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Disclosures

- I Love Nuclear Medicine … so expect some bias (i.e. passion) in my presentation
- I am not paid nor otherwise compensated by any commercial entity for this presentation
- I accepted no payments from commercial medical entities in the past 5 years
- I included discussion on Lu-177-PSMA-617 therapy that is not approved by the FDA (I have no financial relationship to the manufacturer nor am I the trial investigator)

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Learning Objectives

- Definitions
- What's Theranostic Nuclear Medicine (TNM)?
- First: Radioactive Iodine (RAI) in Graves' Disease
- Na ^{131}I (RAI) for Differentiated Thyroid Cancer (DTC)
- ^{177}Lu-DOTATATE for Neuroendocrine Tumors
- ^{177}Lu-PSMA for Metastatic Prostate Cancer
- Future Possibilities

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Thera(g)nostics – If we see it, we can treat it

What's in the Word?

- "Thera", from Greek "*therapeía*" = **healing**, e.g. therapy
- "gnostic" or "nostic" for short
- "Gnostic", from Greek ***gnos*** = **knowledge/know**, e.g. diagnostic

1. Using diagnostic RP we image to **know** where cancer is located, its extent, & avidity of the RP to cancer (reconnaissance mission!)
   a. Does the target tissue bind the diagnostic RP
   b. If it does, how much (dose) to give for therapy = Dosimetry
2. Then, using therapeutic RP we deliver the energy dose to destroy cancerous tissues (surgical strike!)

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Abbr.: RP = radiopharmaceutical

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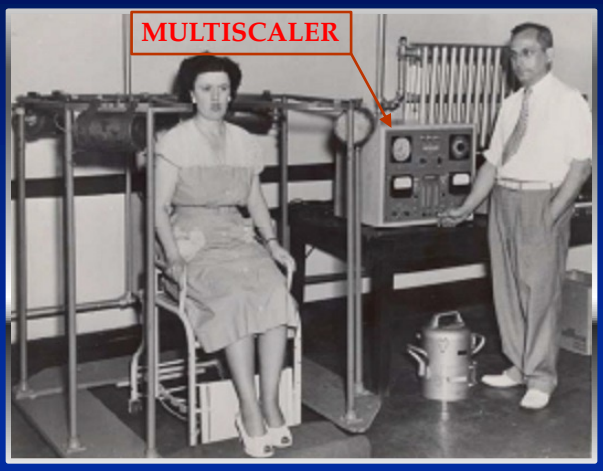
Radioactive Iodine (RAI) Administration for Graves' Disease: The Birthplace of Theranostic Nuclear Medicine



Saul Hertz, M.D.

(April 20, 1905 – July 28, 1950)

- The first to study RAI in an animal model of hyperthyroidism
- March 31st, 1941, at the age of 35, he treated the first Grave's disease patient with RAI
- He was the first to use RAI uptake to inform his treatment, i.e. developed and applied Theranostic Nuclear Medicine (TNM)

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Basic Principles Underlying the Radioactive Iodine Therapy (RAIT) of Graves' Disease

- RAI is taken up by Na^+ I^- symporter (NIS) on thyrocytes
- More active are NIS, the more RAI they uptake up
- We use Na ^{131}I to measure uptake at 24 hours
  - ✓ Used in calculation of how much to treat with
  - ✓ ^{131}I is trapped by NIS and incorporated into the hormones
- We use $^{99m}Tc^+ O_4^-$ to image the thyroid
  - ✓ Trapped by NIS & maps its distribution/function in thyroid
  - ✓ It is NOT incorporated into the hormones

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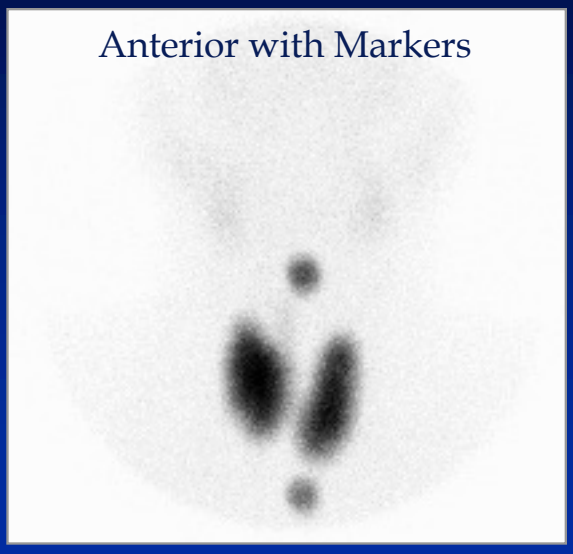
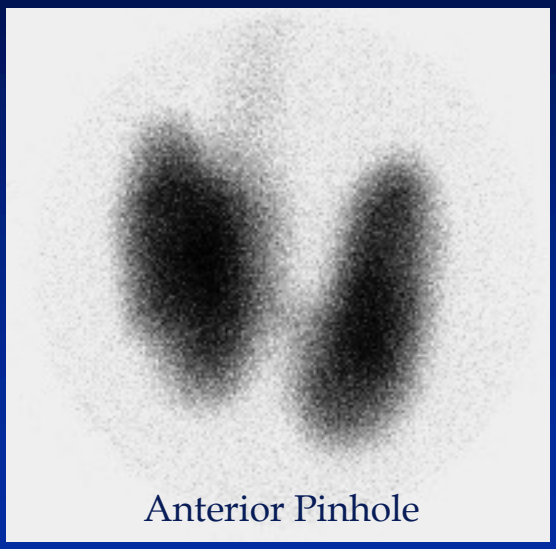
Graves' Disease (GD) – Diffuse Toxic Goiter
Exemplar of Productive Thyrotoxicosis = Hyperthyroidism





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RAIT of Graves' Disease
mCi/g of Thyroid, Corrected for 24-hr Uptake

- Most use ablation activity coefficient (AAC) of 0.12-0.20 mCi ^{131}I/g of thyroid, normalized to 24 hr. uptake
- Recommend at least 0.2 mCi/g => 93% cure (1)
- AAC at PSU is 0.24 mCi/g => 100% cure
- AA = (gland weight in g x 0.24 mCi/g) / 24 hr. uptake fraction (i.e. 50% uptake = 0.5 uptake fraction)
- Prep: 1-2 wks. of modest low iodine diet, stop ATD for 48 hrs. before start of 24-hr ^{131}I uptake study
- RAIT at the completion of 24 hrs. later

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1. Wong KK, et al. Efficacy of radioactive iodine treatment of Graves' hyperthyroidism using a single calculated ^{131}I dose. Clin Diabetes Endocrinol 2018;4:20. 10.1186/s40842-018-0071-6

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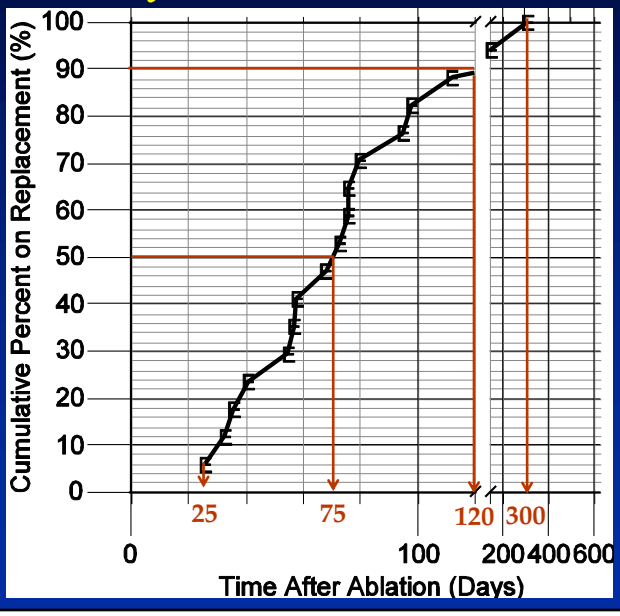
Response to ^{131}I Therapy in Graves' at PSH: Ablation Activity Coefficient of 0.24 mCi/gm



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Comparison of Mortality in Hyperthyroidism During Periods of Treatment With Thionamides and After Radioiodine

Kristien Boelaert, Patrick Maisonneuve, Barbara Torlinska, and Jayne A. Franklyn

Centre for Endocrinology, Diabetes, and Metabolism (K.B., B.T., J.A.F.), School of Clinical and Experimental Medicine, College of Medical and Dental Sciences, University of Birmingham, Birmingham B15 2TT, United Kingdom; and Division of Epidemiology and Biostatistics (P.M.), European Institute of Oncology, 20141 Milan, Italy

(*J Clin Endocrinol Metab* 98: 1869–1882, 2013)

Context: Hyperthyroidism is common, but opinions regarding optimal therapy with antithyroid drugs or radioiodine (131-I) differ. There are no randomized trials comparing these options in terms of mortality.

Objective: The aim of the study was to determine whether mortality associated with hyperthyroidism varies with treatment administered or other factors.

Design, Setting, and Patients: We conducted a prospective observational population-based study of 1036 subjects aged ≥ 40 years presenting to a single specialist clinic from 1989–2003 with a first episode of hyperthyroidism who were followed until June 2012.

Interventions: Antithyroid drugs or radioiodine (131-I) were administered.

Main Outcome Measures: We compared causes of death with age-, sex-, and period-specific mortality in England and Wales and used within-cohort analysis of influence of treatment modality, outcome, disease etiology, severity and control, and comorbidities.

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Comparison of Mortality in Hyperthyroidism During Periods of Treatment With Thionamides and After Radioiodine

Results: In 12 868 person-years of follow-up, 334 died vs 290.6 expected (standardized mortality ratio [SMR], 1.15 [95% confidence interval (CI),1.03–1.28]; $P = .01$). Increased all-cause mortality largely reflected increased circulatory deaths (SMR, 1.20 [95% CI, 1.01–1.43]; $P = .04$). All-cause mortality was increased for the person-years accumulated during thionamide treatment (SMR, 1.30 [95% CI, 1.05–1.61]; $P = .02$) and after 131-I not associated with hypothyroidism (SMR, 1.24 [95% CI, 1.04–1.46]; $P = .01$) but not during T_4 replacement for 131-I-induced hypothyroidism (SMR, 0.98 [95% CI, 0.82–1.18]; $P = .85$). Within-cohort analysis comparing mortality during thionamide treatment showed a similar hazard ratio (HR) for all-cause mortality when 131-I did not result in hypothyroidism (HR, 0.95 [95% CI, 0.70–1.29]), but reduced mortality with 131-I-induced hypothyroidism (HR, 0.70 [95% CI, 0.51–0.96]). Reduced mortality associated with hypothyroidism was seen only in those without significant comorbidities and not in those with other serious diseases. Atrial fibrillation at presentation ($P = .02$) and an increment of 10 pmol/L in serial free T_4 concentration during follow-up ($P = .009$) were independently associated with mortality.

Conclusions: Among hyperthyroid subjects aged 40 years or older, mortality was increased during periods of thionamide treatment and after radioiodine not resulting in hypothyroidism, but not during follow-up after radioiodine-induced hypothyroidism. Independent associations of mortality with atrial fibrillation and incomplete biochemical control during treatment indicate potential causative links with poor outcome. (*J Clin Endocrinol Metab* 98: 1869–1882, 2013)

i.e. ABLATION

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Brito JP, et al. Patterns of Use, Efficacy, and Safety of Treatment Options for Patients with Graves' Disease: A Nationwide Population-Based Study. Thyroid 2020;30(3):357-64. doi:10.1089/thy.2019.0132

Background: Considerable uncertainty remains about the pattern of use of treatment options for Graves' disease (GD) and their comparative effectiveness and safety.

Methods: Between 2005 and 2013, we identified patients with GD who received antithyroid drugs (ATDs), radioactive iodine (RAI) or surgery, and were represented in a large administrative data set in the United States (OptumLabs® Data Warehouse).

Results: We identified 4661 patients with GD: mean age 48 (SD ±14) years, white (63%), and female (80%). Patients received ATD, $n = 2817$ (60%), RAI, $n = 1549$ (33%), or surgery, $n = 295$ (6%). Success rates were 50% for ATD, 93% for RAI, and 99% for surgery. Median time to treatment failure was 6.8 months for ATD and 3 months for RAI and surgery. When patients were required to be on ATD for at least one year before assessing failure, the failure rate decreased to 25%. Adverse effects occurred in 12% of patients receiving ATD, 6% with RAI, and 24% with surgery. Factors associated with treatment success were age >55 years (for ATD) and female sex (for RAI). About 12% of patients receiving ATD continued this treatment for >24 months as initial therapy. When patients failed ATD therapy, the most common second-line therapy was reinitiation of ATD (65%), RAI (26%), and surgery (9%). Overall, 26% of patients remain on ATD therapy (combined first or second line).

Conclusions: ATD therapy was the most common GD therapy and demonstrated the lowest efficacy and infrequent significant adverse effect profile. With one fourth of patients remaining on ATD treatment (initial or second modality treatment), it becomes imperative to determine the long-term efficacy, safety, costs, and burdens of this modality of treatment.

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Table 3. Frequency of Adverse Effects (Brito *et al*. doi: 10.1089/thy.2019.0132)

Treatment	*Complications*	*No. of patients*	*% of patients*
Methimazole ($n=2443$)	Agranulocytosis	0	0
	Aplastic anemia	0	0
	Hepatitis, unspecified (includes drug induced)	31	1.3
	Rash and other nonspecific skin eruption	92	3.8
	New Graves' ophthalmopathy	177	7
	All methimazole complications[a]	299	12
Propylthiouracil ($n=374$)	Aplastic anemia	0	0
	Drug-induced cholestasis	0	0
	Rash and other nonspecific skin eruption	18	4.8
	ANCA vasculitis	0	0
	New Graves' ophthalmopathy	26	6.9
	All propylthiouracil complication[b]	46	12.3
RAI ($n=1549$)	Radiation-induced thyroiditis	13	0.84
	New Graves' ophthalmopathy	89	5.75
	All RAI complication	100	6.46
Total thyroidectomy ($n=177$)	Hypoparathyroidism	46	25.9
	All total thyroidectomy complications[c]	55	31
Partial surgery ($n=118$)	All partial surgery complications[d]	15	12.7

As of now, the evidence in Graves' disease is clear, RAIT has shown the most predictable success rates and the lowest complications rate compared to any other therapy

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CONCLUSIONS: TNM in Hyperthyroidism

- RAIT is the trailblazing Theranostic Nuclear Medicine agent
- The most common indication is Graves' disease
  - ✓ The most effective RAIT is 0.24 mCi/g of thyroid
  - ✓ Pretreat with ATDs if symptoms are moderate to severe
  - ✓ Mild-Moderate GO pretreat with steroids
- Real-world data shows
  - ✓ **Truth** - mortality & side-effects favor RAIT over ATD
  - ✓ **Fiction** - long-term use of ATDs is a safer option
  - ✓ Explanation for this discrepancy is **bias**
- A better standardization is needed for RAIT & follow-up
- Better studies/advocacy are needed for overcoming bias

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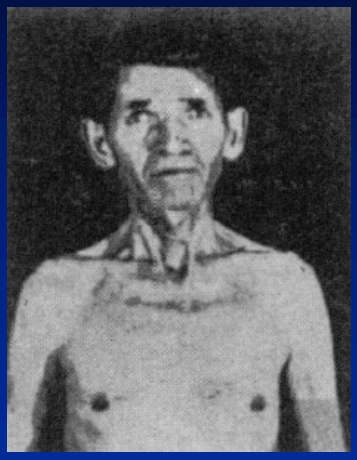
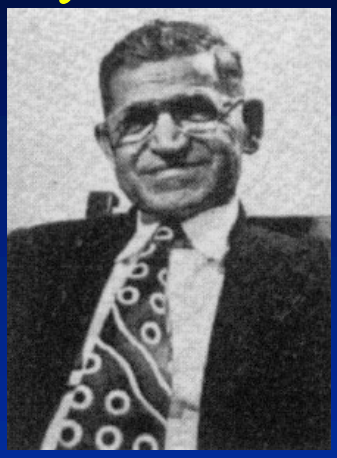
^{131}I for Differentiated Thyroid Cancer (DTC)





1943 1949

Before ^{131}I Treatment After ^{131}I Treatment

Seidlin et al. JAMA 1946

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The Most Important Nuclear Medicine Paper Ever Written*

RADIOACTIVE IODINE THERAPY

Effect on Functioning Metastases of Adenocarcinoma of the Thyroid

S. M. SEIDLIN, M.D.
L. D. MARINELLI, M.A.
and
ELEANOR OSHRY, B.S.
New York

Therapy of neoplastic disease usually consists of two phases: first, the treatment of the primary focus and, second, that of metastases. Specifically, in adenocar-

JAMA, Dec. 7, 1946

*according to Dr. Marshall Brucer

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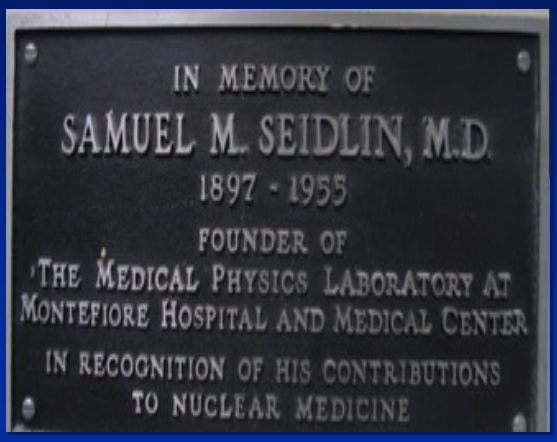
Samuel M. Seidlin, M.D.
First ^{131}I Therapy for Thyroid CA
Montefiore Medical Center, Bronx, NY



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37 y/o female with reactive airway developed "fullness in her throat"

- In December 2015 presented with above symptoms and got referred for thyroid US
- US showed 2 nodules, 1.6 and 1.2 cm in the right lobe
- She was sent for biopsy, 1.6 cm nodule showed follicular neoplasm, 1.2 cm nodule sample was insufficient for diagnosis
- Referred to a Surgeon for consult, Dr. S
- Lobectomy was recommended

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38 y/o female with "throat lump": Clinical-Pathological Characteristics

- Age 38, Female
- Focality/Size – Solitary, largest 1.5 cm
- Histology – PTC, Classical
- Margins – Involved
- Extrathyroidal Extension – Not Identified
- Tumor Capsule – None
- Lympho-Vascular Invasion – Not Identified
- LN – None sampled
- Extranodal Extension – Not Identified
- (1.2 cm nodule – adenoma)

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38 y/o female with "throat lump"

- Dr. S performed hemithyroidectomy 2/12/16, classical PTC 1.5 cm, positive posterior margin
- Dr. S offered either 1) active surveillance or 2) completion thyroidectomy
- Patient proceeded with completion-T 4/7/2016: encapsuled PTC, follicular variant. Foci measured 2 mm, 1 mm, and 1 mm and confined to the thyroid, without extrathyroidal extension. No evidence of perineural or angiolymphatic invasion. Margins negative.
- Endo consult:
  - ✓ Offered active surveillance vs. RAI
  - ✓ Later that month, Tg is 19.2, Ab 1, TSH 0.08
  - ✓ US suspicious LN, bx negative, referred to NM

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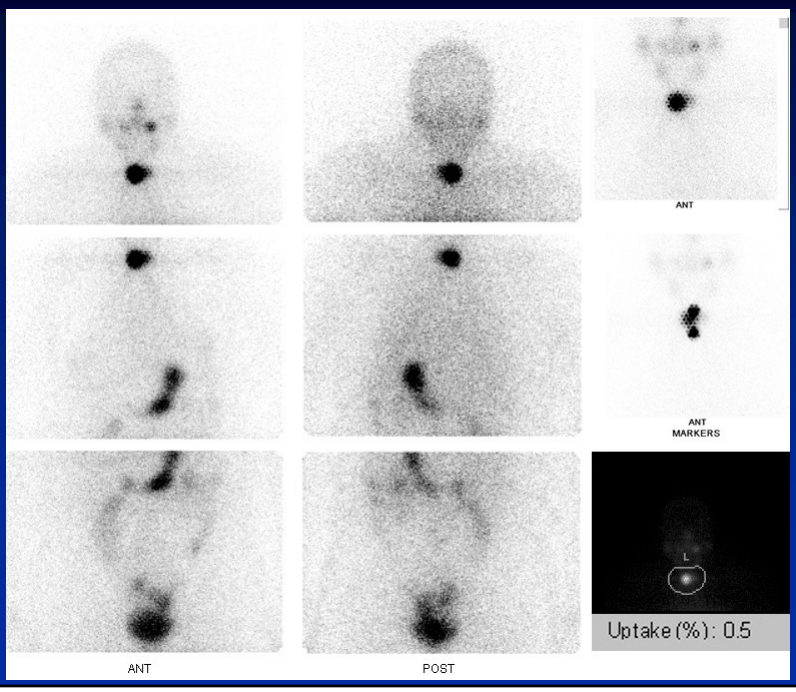
Pre-Treatment WBS 10/24/16



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38 y/o female with "Stage I"

- 24 hr. uptake in the neck = 1.5%
- 10/20/16 TSH 70.6, Tg 74, Ab 1
- RAI-WBS, remnant thyroid, no obvious mets
- Margin was involved at initial hemi-T
- Tg out of proportion to remnant thyroid tissue; hence, occult tumor present
- RAIT, ablative + adjuvant, activity 150 mCi
- Post-treatment RAI-WBS to follow

Case 2

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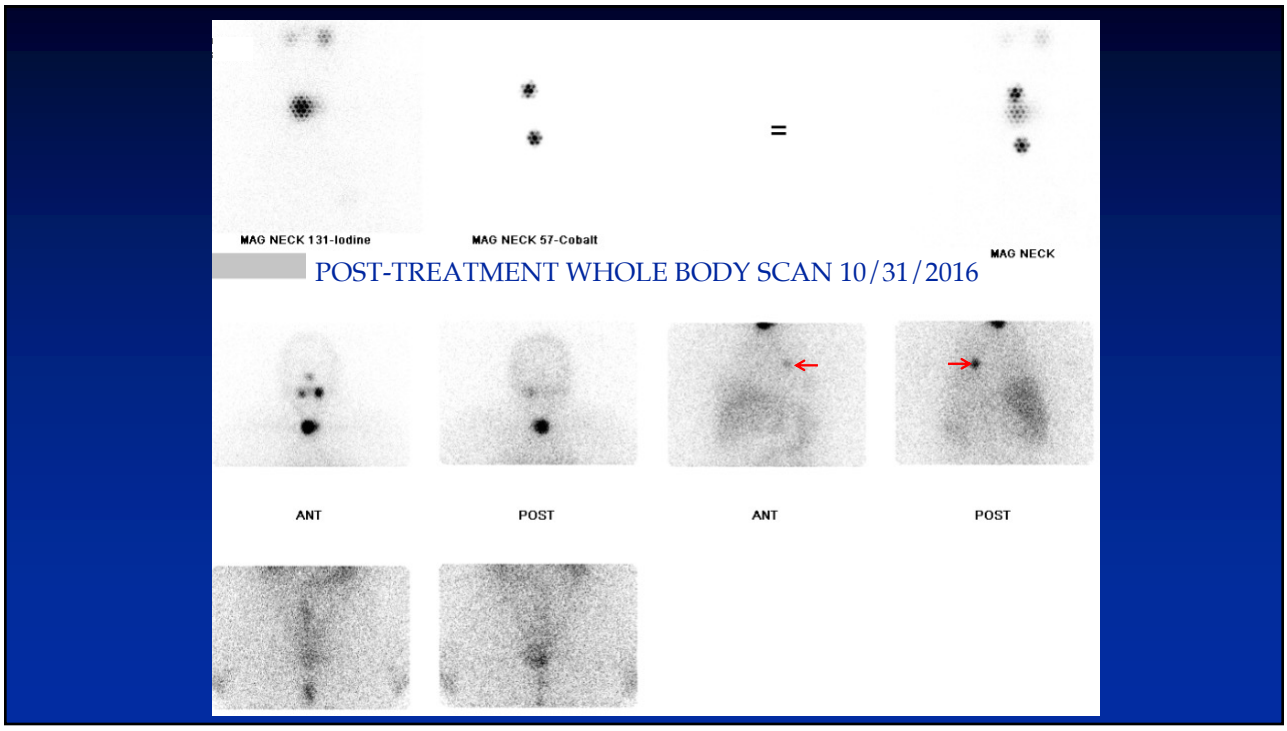
MAG NECK 131-Iodine
MAG NECK 57-Cobalt
=
MAG NECK
POST-TREATMENT WHOLE BODY SCAN 10/31/2016
ANT
POST
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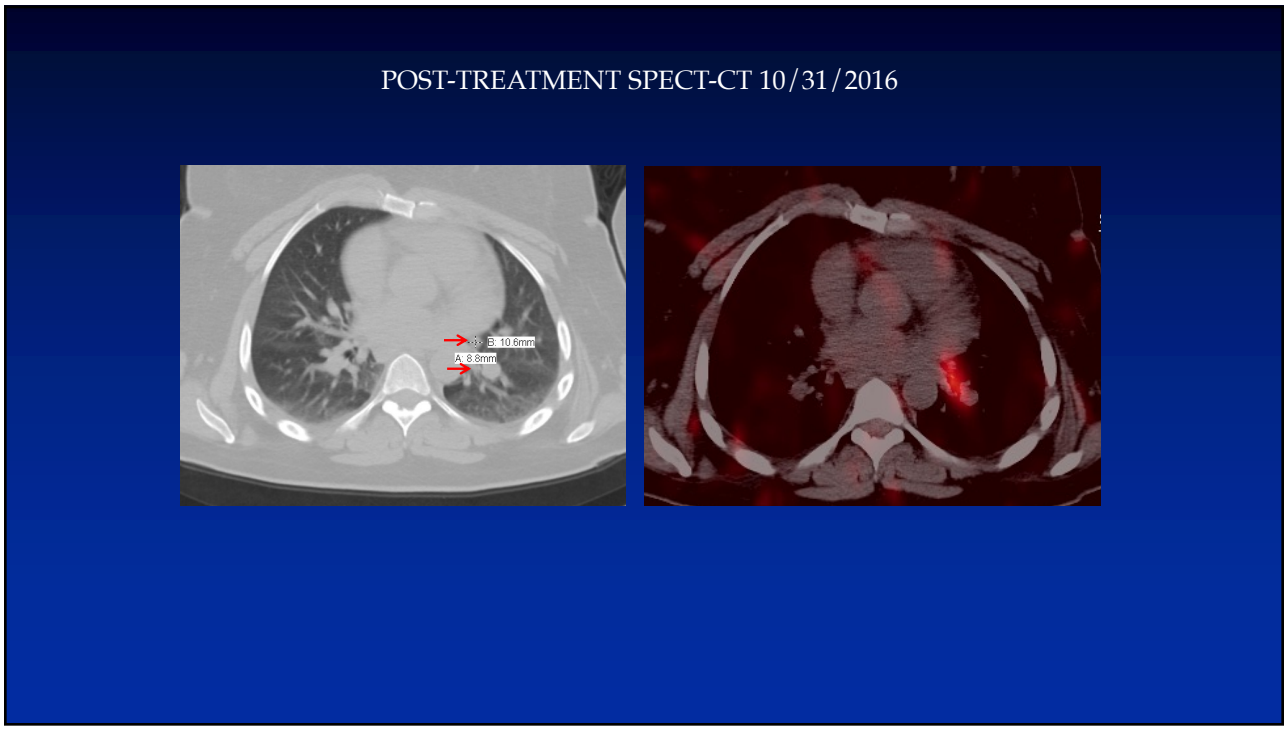
POST

23


POST-TREATMENT SPECT-CT 10/31/2016
B: 10.6mm
A: 8.8mm

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- Treat with ^{131}I those with ^{131}I scan evidence of functional NIS
- If below scan resolution, treat based on available evidence
- Incorporate pathology, labs, & imaging in decision-making

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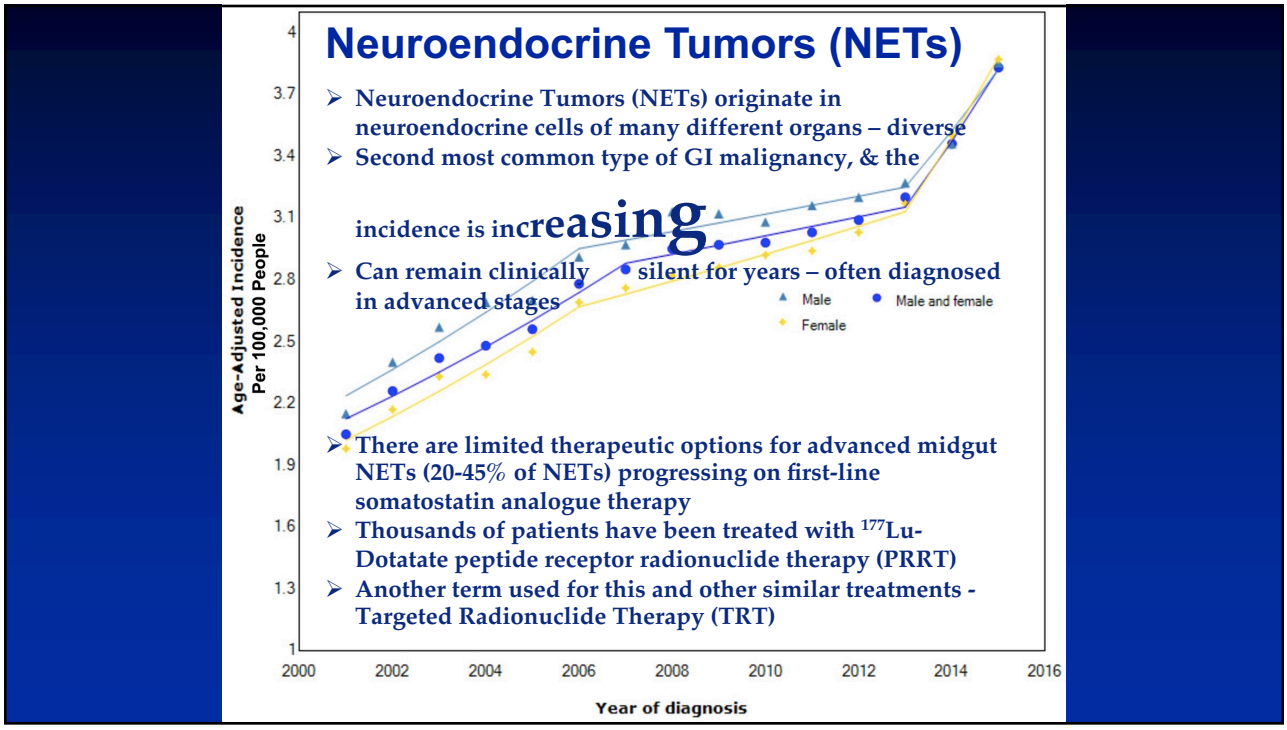

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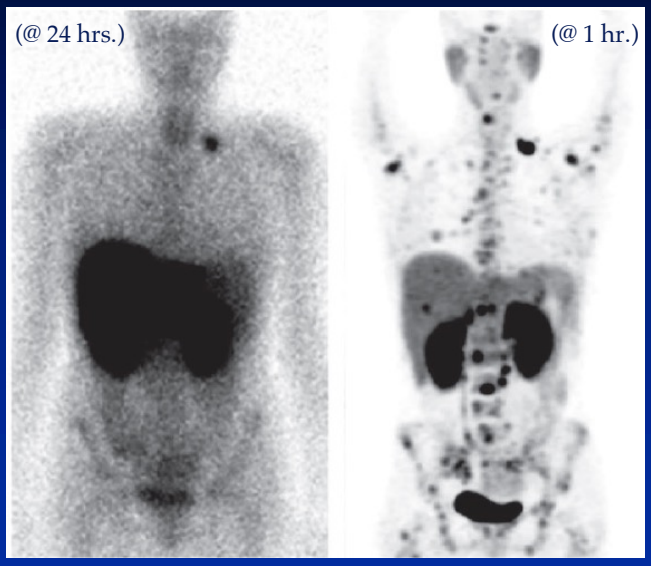
Good News – Nuclear Medicine Options Increasing/Improving

- NETs typically have abondance of somatostatin receptors
- Nuclear Medicine first developed radiolabeled stable somatostatin analogues to tag NETs for diagnosis
- Our technologies improved – planar scans to PET/CT 3-D imaging
- Our chemistry improved – better somatostatin analogues
- Our labeling improved – labeled therapeutic radioisotopes (^{177}Lu)



^{111}In-Octreotide Scan ^{68}Ga-Dotatate PET/CT

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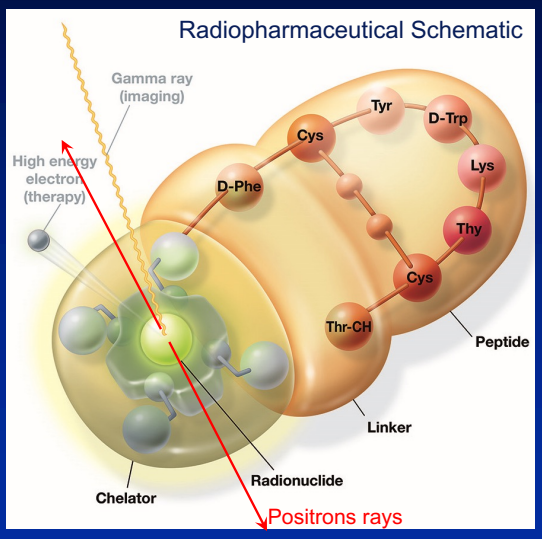
NMT for NETs: Current Status

- **Peptide** carrier designed with high affinity for somatostatin receptors (overexpressed in ~ 80% of all NETs) - DOTATATE
- Theranostic Nuclear Medicine Pair is now available & FDA-approved for PET/CT diagnosis (NETspot®) & for therapy (Lutathera®)
- Some call this therapy Peptide Receptor Radionuclide Therapy (PRRT)
- This represents the advancement of classic Theranostic Nuclear Medicine



Courtesy of Mark Tulchinsky, MD, FACNM, FSNMMI

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NETTER -1 Study Objectives and Design

Aim	Evaluate the efficacy and safety of ^{177}Lu-Dotatate plus Octreotide 30 mg compared to Novartis Octreotide LAR 60 mg (off-label use)[1] in patients with inoperable, somatostatin receptor positive, midgut NET, progressive under Octreotide LAR 30 mg (label use)
Design	International, multicenter, randomized, comparator-controlled, parallel-group Phase III study conducted in 51 centers with 230 patients

Treatment and Assessments
Progression free survival (RECIST criteria) every 12 weeks

Dose 1 Dose 2 Dose 3 Dose 4

Baseline and Randomization

- n = 115 — 4 administrations of 7.4 GBq of ^{177}Lu-Dotatate every 8 weeks + Octreotide 30 mg
- n = 115 — Octreotide LAR 60 mg every 4 weeks

5 Years follow up

1. FDA and EMA recommendation

Courtesy of Mark Tulchinsky, MD, FACNM, FSNMMI

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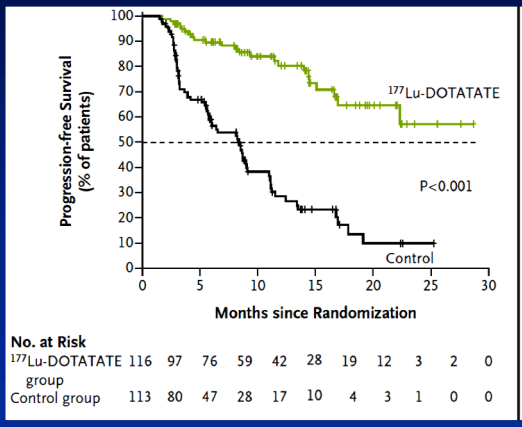
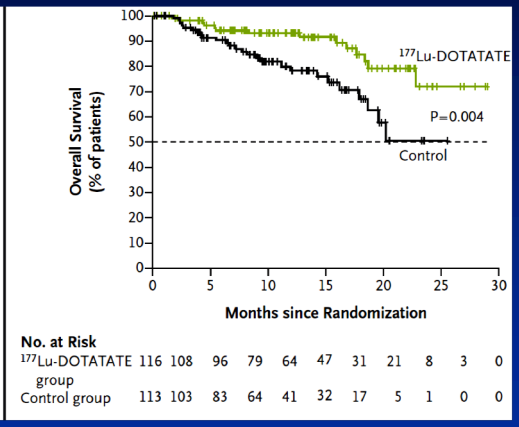
Progression Free Survival



Overall Survival



79% Risk Reduction for disease progression/death

Median PFS in DOTATATE arm: 40 Mos

Courtesy of Mark Tulchinsky, MD, FACNM, FSNMMI

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^{177}Lu-Dotatate Treatment – Out-patient Infusion Room Model

Courtesy of Mark Tulchinsky, MD, FACNM, FSNMMI

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TNM for NETs: Conclusions

- ^{177}Lu-Dotatate therapy (and 68Ga-Dotatate PET/CT) – generally well tolerated and offers patients with indolent but terminal disease much increased progression free survival w/o disabling side-effects
- The administration takes 6-7 hours of visiting an infusion room, repeated 4 times (cycles), 8 weeks between the cycles
- This is the first of many advanced theranostic agents in the process of being approved by the FDA
- The next, expected this year, will be theranostic pair for better imaging & treatment of prostate cancer!

Courtesy of Mark Tulchinsky, MD, FACNM, FSNMMI

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TNM for Prostate Cancer

- Target – Prostate Specific Membrane Antigen (PSMA)
- Intelligence Agent – PSMA labeled with ^{68}Ga using PET/CT
  - ✓ FDA approved 1st radiotracer in Dec. 1, 2020, 2nd May 27, 2021
  - ✓ Available Now: ^{68}Ga-PSMA-11 & ^{18}F-piflufolastat (Pylarify®)
- "Silver Bullet" – PSMA labeled with ^{177}Lu
  - ✓ Phase 3 trial published in the New England Journal of Medicine, 9/16/2021 (1)
  - ✓ Under consideration for approval by the FDA – Not Approved

https://www.nejm.org/doi/full/10.1056/nejmoa2107322 (September 16, 2021)

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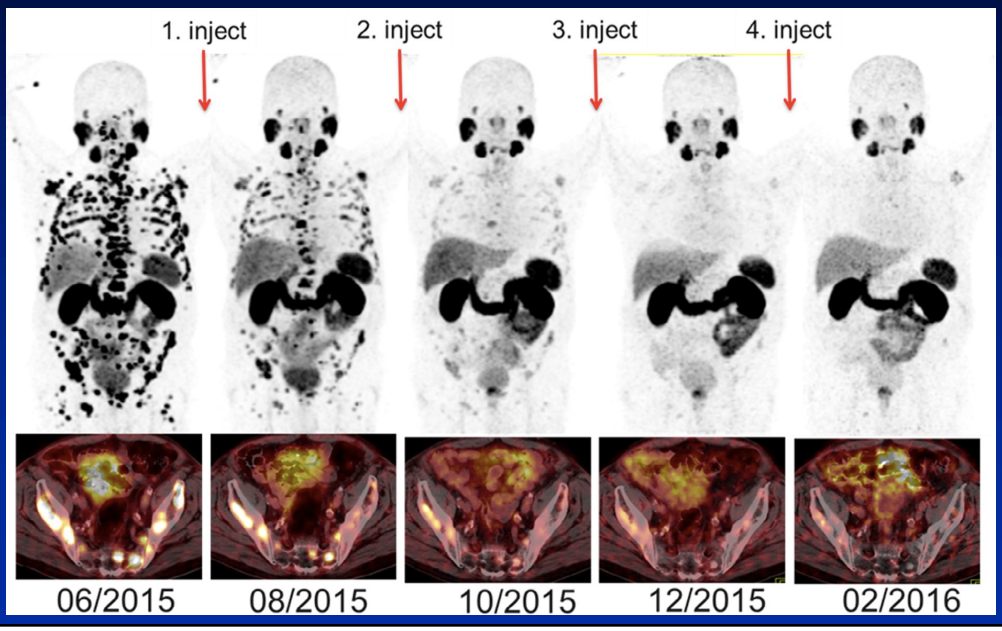
^{68}Ga-PSMA PET/CT imaging in a patient with metastatic castration resistant prostate cancer prior, during and after 4 cycles of ^{177}Lu-PSMA



Susanne Lüthe, et al. PSMA ligands in prostate cancer – Probe optimization and theranostic applications Methods 130 (2017) 42–50

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer

O. Sartor, J. de Bono, K.N. Chi, K. Fizazi, K. Herrmann, K. Rahbar, S.T. Tagawa, L.T. Nordquist, N. Vaishampayan, G. El-Haddad, C.H. Park, T.M. Beer, A. Armour, W.J. Pérez-Contreras, M. DeSilvio, E. Kpamegan, G. Gericke, R.A. Messmann, M.J. Morris, and B.J. Krause, for the VISION Investigators*

N ENGL J MED 385;12 NEJM.ORG SEPTEMBER 16, 2021

ABSTRACT

BACKGROUND

Metastatic castration-resistant prostate cancer remains fatal despite recent advances. Prostate-specific membrane antigen (PSMA) is highly expressed in metastatic castration-resistant prostate cancer. Lutetium-177 (^{177}Lu)–PSMA-617 is a radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells and the surrounding microenvironment.

CONCLUSIONS

Radioligand therapy with ^{177}Lu-PSMA-617 prolonged imaging-based progression-free survival and overall survival when added to standard care in patients with advanced PSMA-positive metastatic castration-resistant prostate cancer. (Funded by Endocyte, a Novartis company; VISION ClinicalTrials.gov number, NCT03511664.)

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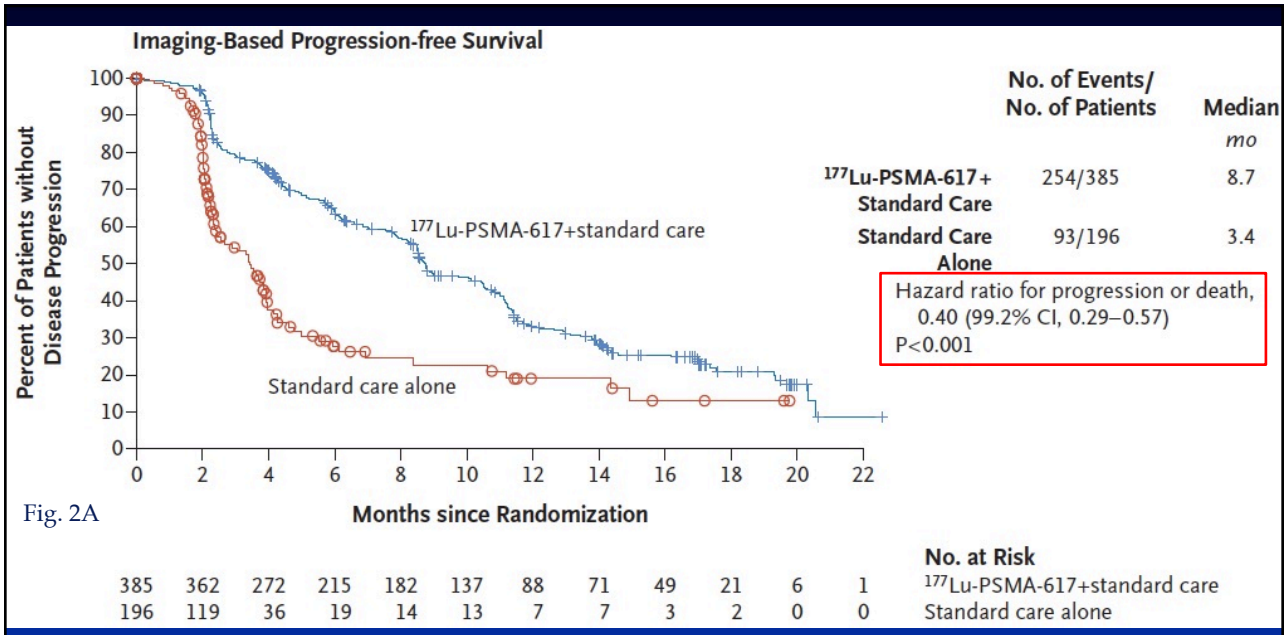

Fig. 2A

Drs. Sartor, Morris, and Krause, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. NEJM 2021;385:1091-103.

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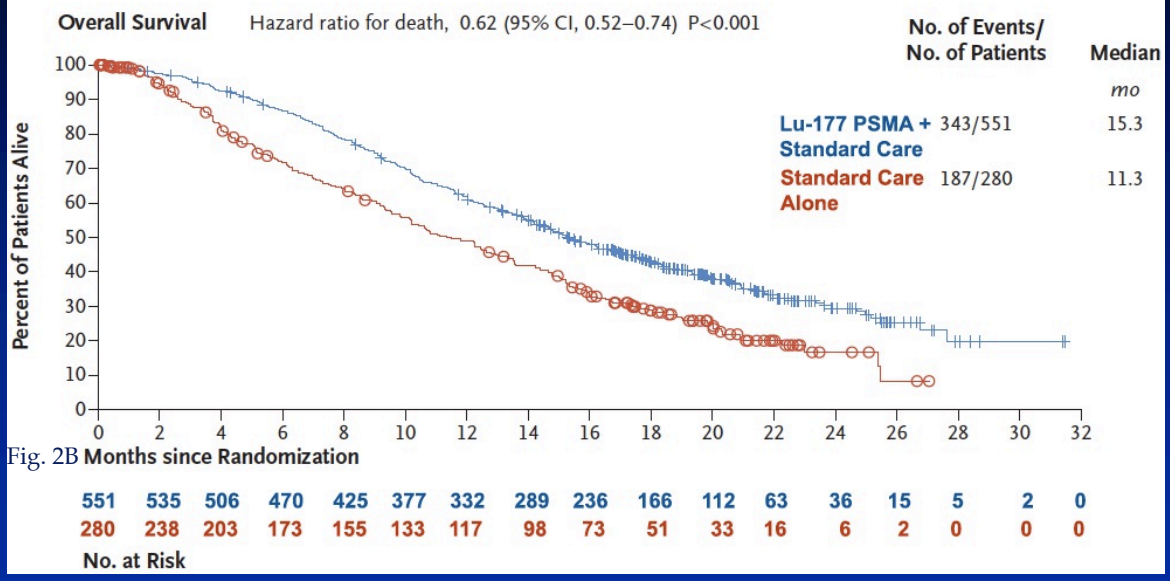

Fig. 2B

Drs. Sartor, Morris, and Krause, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. NEJM 2021;385:1091-103.

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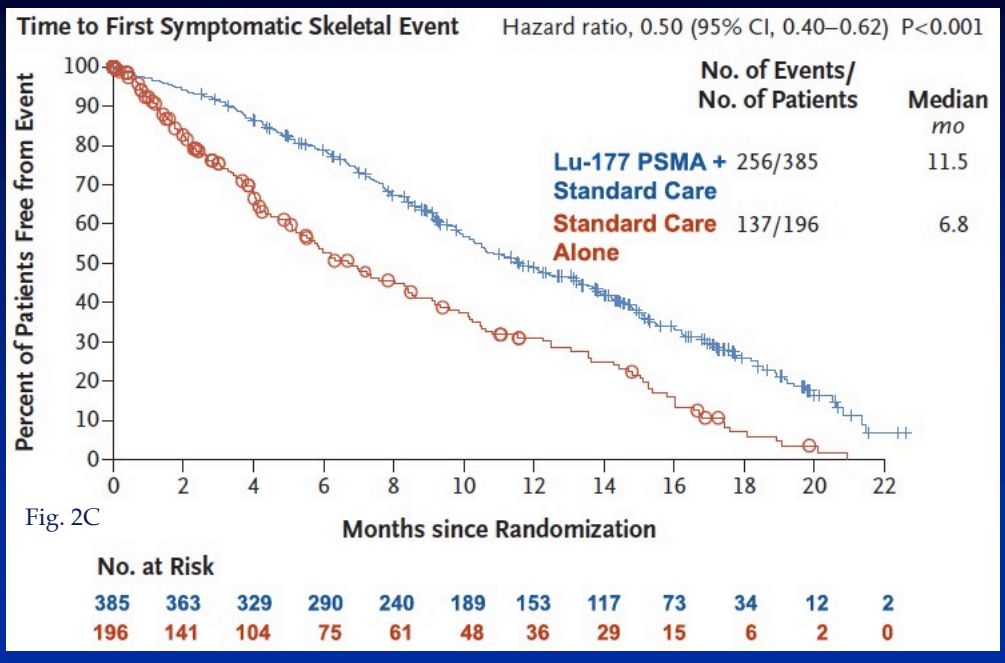

Fig. 2C

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TNM for Prostate Cancer … and Beyond!

- TNM with ^{177}Lu PSMA-617 is the most effective therapy for metastatic CRPC
- This treatment option is just around the corner, coming soon to the TNM Clinic near you
- This treatment is likely only the beginning of TNM revolution – treatments in early disease states is to follow
- You may want to get to know your Nuclear Medicine colleagues – you will likely collaborate more often
- Science and discovery are only accelerating in discovery of new targets on cancer cells and possibly certain cellular promoters in other diseases

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