Radioiodio e Terapia Radiorecettoriale

Annibale Versari

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Arcispedale S. Maria Nuova

Istituto in tecnologie avanzate e modelli assistenziali in oncologia
Istituto di Ricovero e Cura a Carattere Scientifico

Bari,
7-10 novembre 2013

- *Dichiaro di non avere alcun conflitto di interesse in merito agli argomenti trattati*
- *in questa presentazione*

Bari,
7-10 novembre 2013

Eur J Nucl Med Mol Imaging (2008) 35:1941–1959
DOI 10.1007/s00259-008-0883-1

GUIDELINES

Guidelines for radioiodine therapy of differentiated thyroid cancer

M. Luster · S. E. Clarke · M. Dietlein · M. Lassmann ·
P. Lind · W. J. G. Oyen · J. Tennvall · E. Bombardieri

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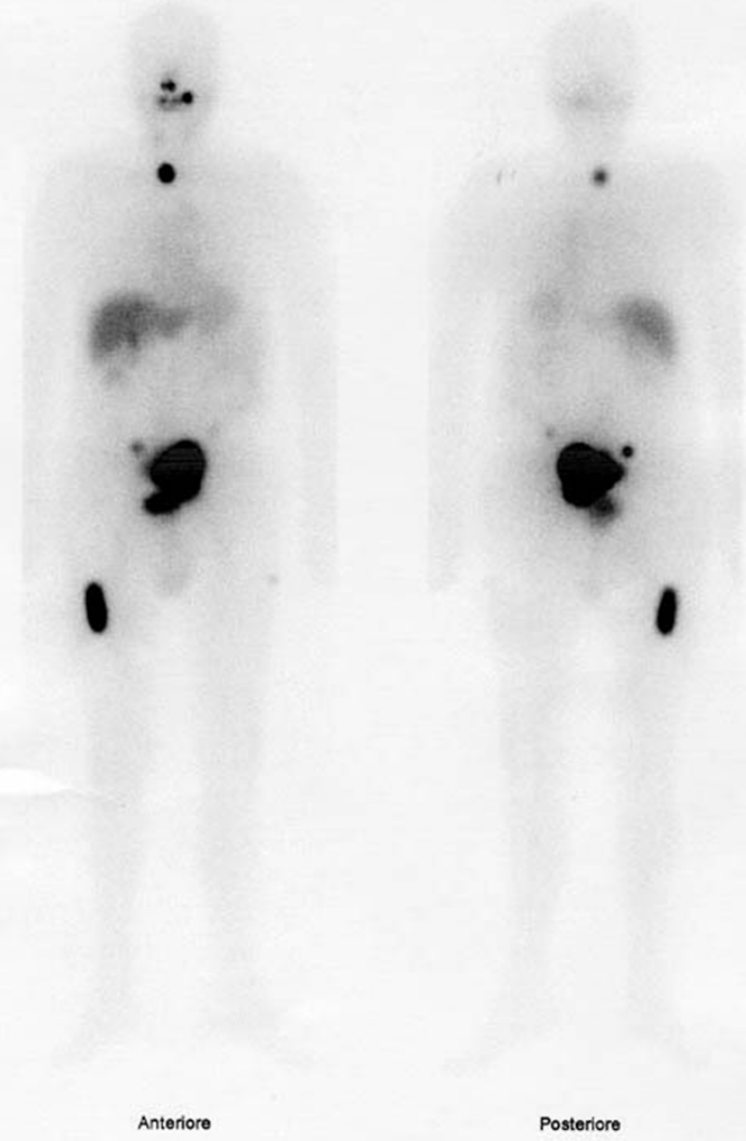
A. Definite indications

1. Unresectable iodine-avid lymph node metastases where one or more of the following is true:
   - morphological imaging does not reveal location
   - surgery is high-risk or contraindicated
   - distant involvement is present that would indicate RAIT anyways
2. Iodine-avid pulmonary micrometastases, especially before they become visible on CT
3. Non-resectable or partially resectable iodine-avid pulmonary macrometastases
4. Non-resectable or partially resectable iodine-avid soft tissue metastases

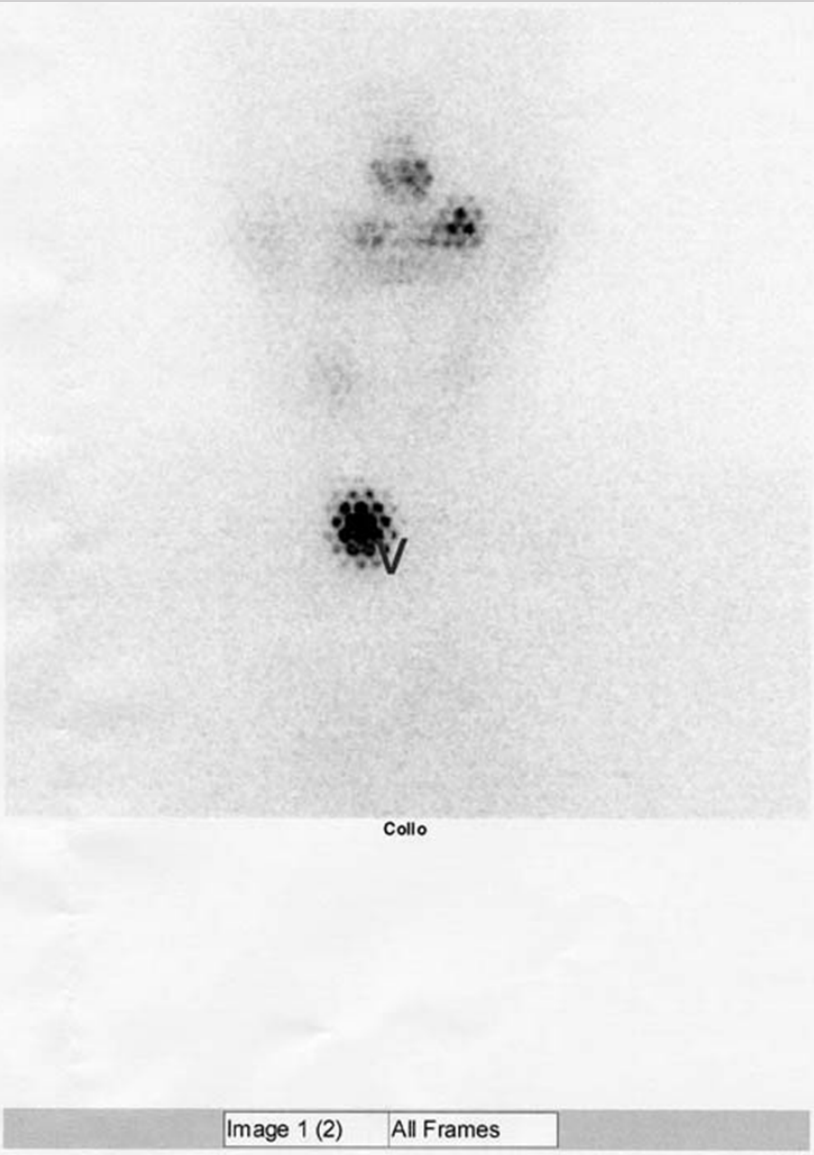
^{131}I WBS
DTC plurimetastatico

^{131}I WBS
DTC plurimetastatico



Anteriore

Posteriore



Collo

DTC plurimetastatico

^{131}I SPECT/CT

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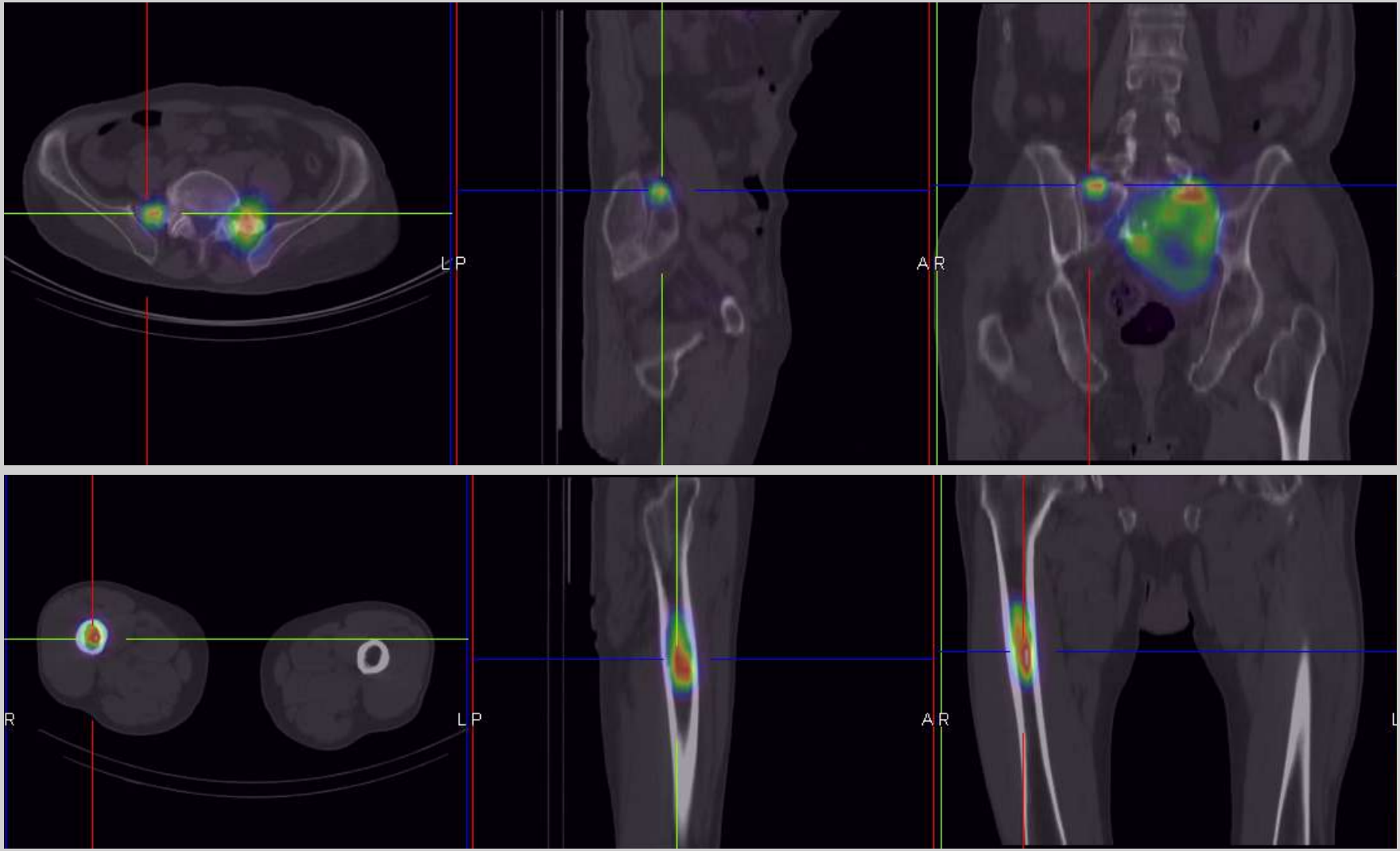

Incremental Value of ^{131}I SPECT/CT in the Management of Patients with Differentiated Thyroid Carcinoma

Libo Chen[1], Quanyong Luo[1], Yan Shen[2], Yongli Yu[1], Zhibin Yuan[1], Hankui Lu[1], and Ruisen Zhu[1]

[1]*Department of Nuclear Medicine, Shanghai Sixth People's Hospital, Shanghai Jiao Tong University, Shanghai, China; and*
[2]*Department of Radiology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China*

Bari,
7-10 novembre 2013

J Nucl Med 2008; 49:1952–1957
DOI: 10.2967/jnumed.108.052399

CONCLUSION

^{131}I SPECT/CT after planar imaging represents a new imaging modality for DTC patients who have received an oral therapeutic dose of ^{131}I. In this study, the fusion of SPECT and CT images was of incremental value over WBS in increasing diagnostic accuracy, reducing pitfalls, and modifying therapeutic strategies in 73.9% of DTC patients through precise localization and characterization of ^{131}I-avid foci. As SPECT/CT techniques emerge, ^{131}I SPECT/CT may demonstrate higher value than WBS in the management of DTC.

^{131}I WBS

DTC plurimetastatico

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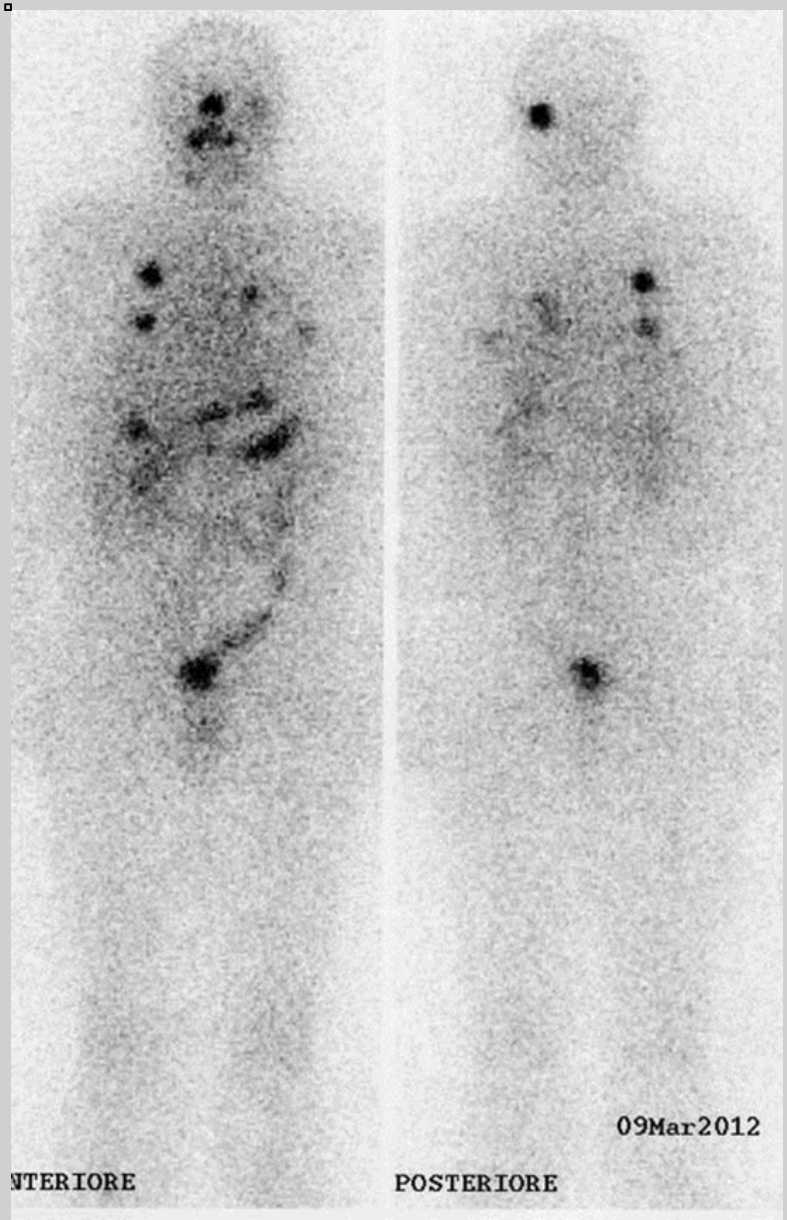
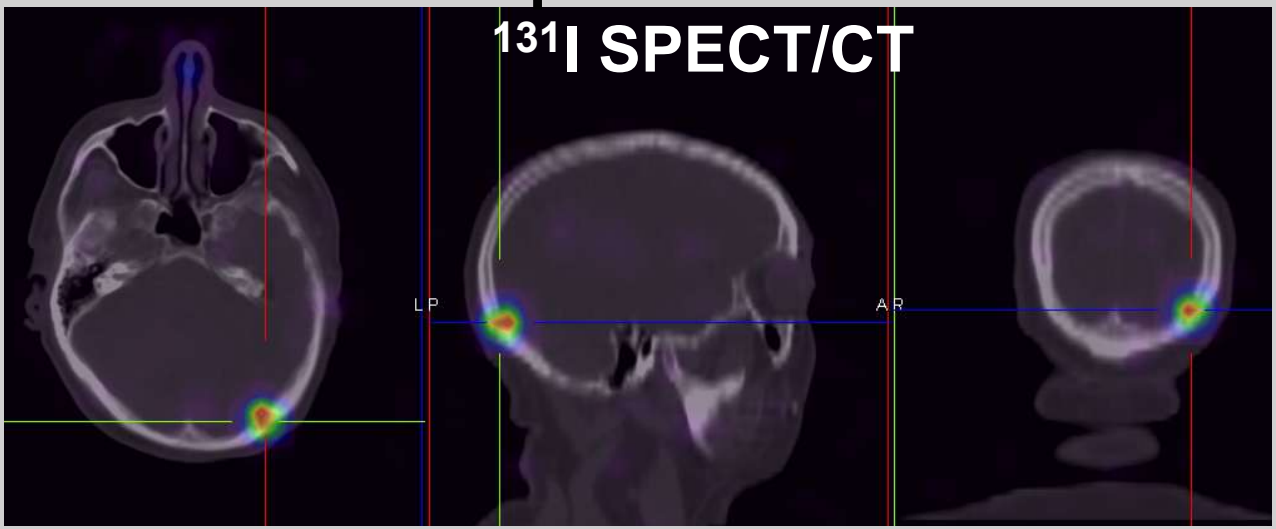
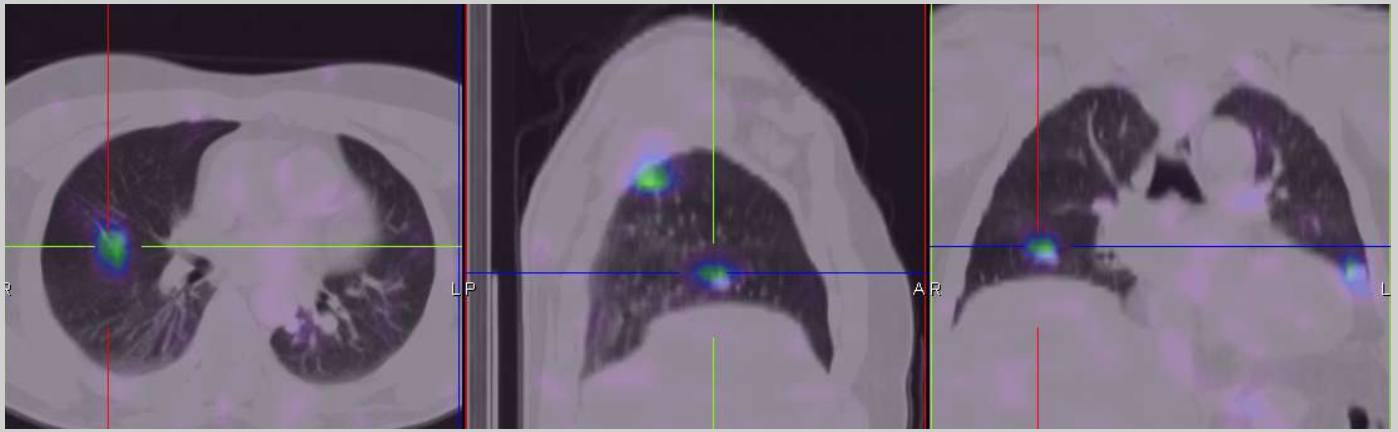
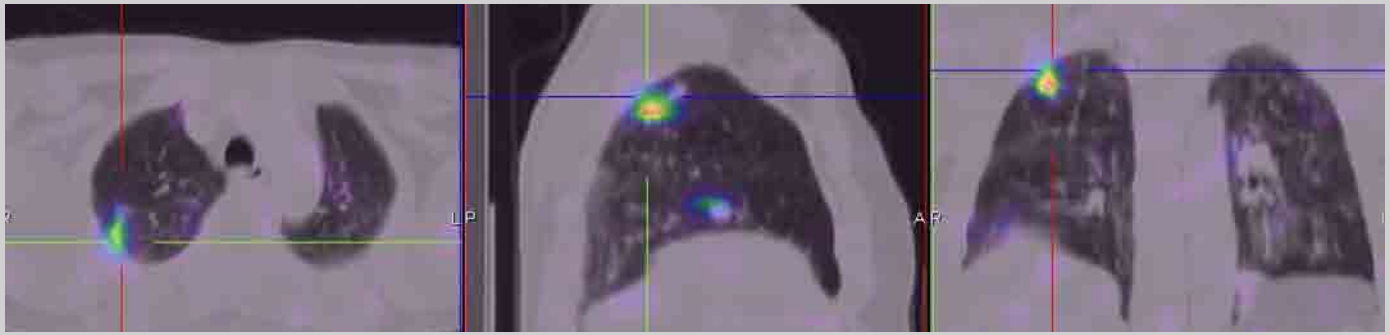


DTC plurimetastatico

^{131}I SPECT/CT







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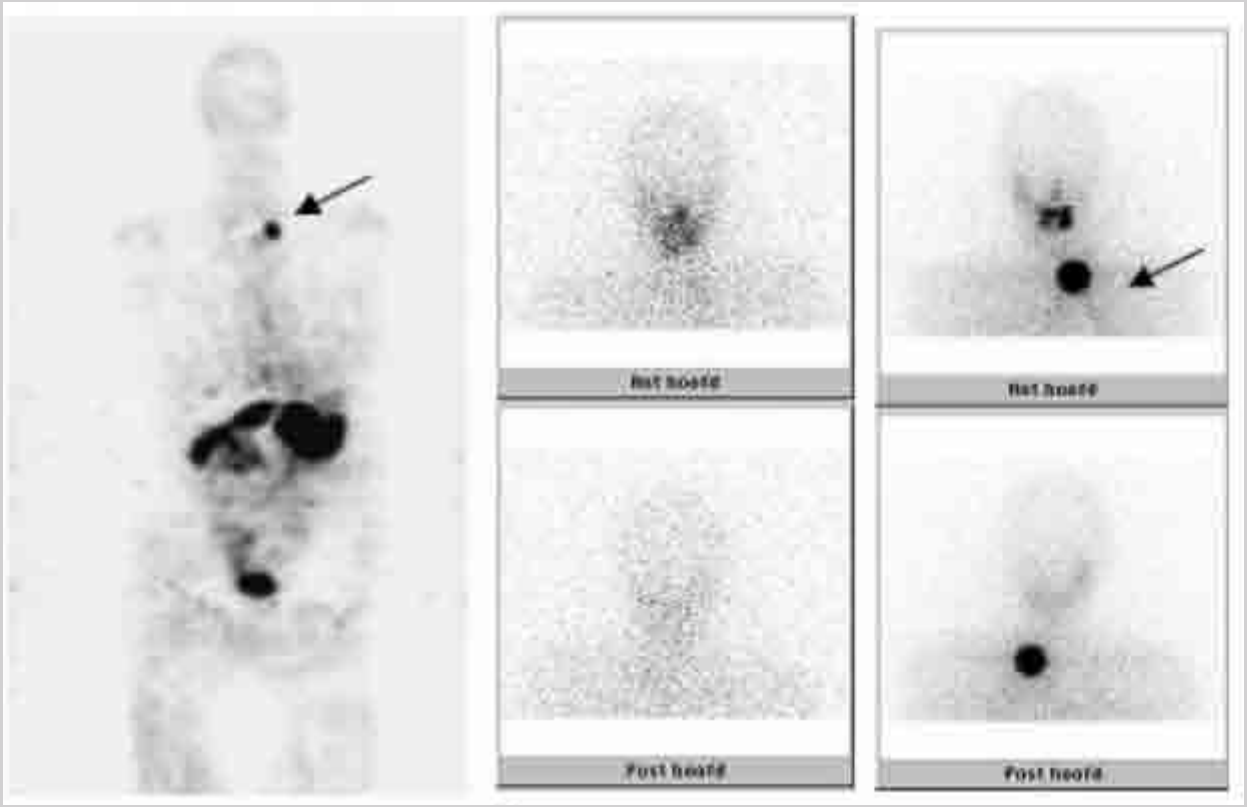
Eur J Nucl Med Mol Imaging (2008) 35:958–965
DOI 10.1007/s00259-007-0660-6

ORIGINAL ARTICLE

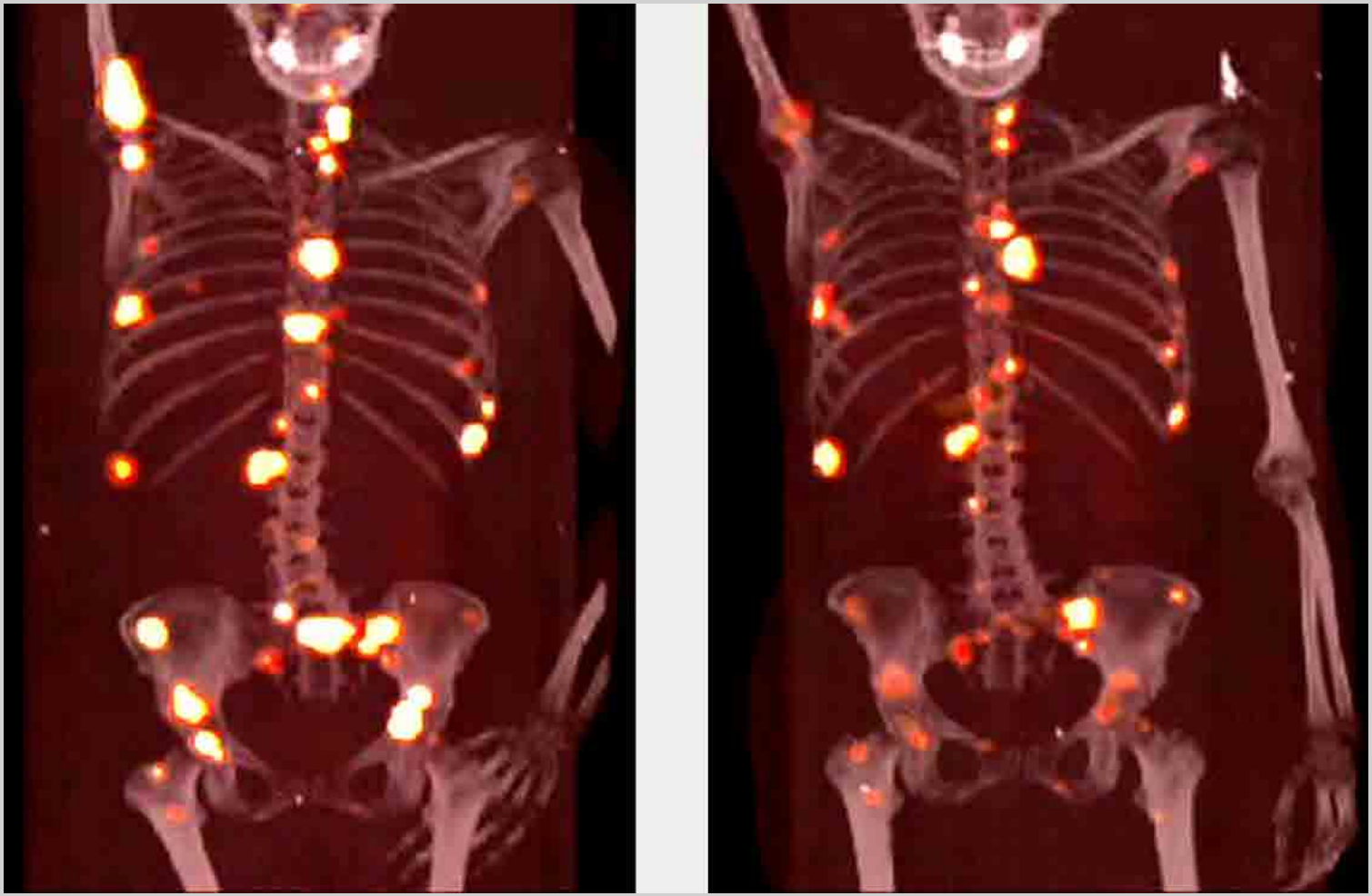
Ha T. T. Phan · Pieter L. Jager · Anne M. J. Paans · John T. M. Plukker · M. G. G. Sturkenboom · W. J. Sluiter · Bruce H. R. Wolffenbuttel · Rudi A. J. O. Dierckx · Thera P. Links

The diagnostic value of ^{124}I-PET in patients with differentiated thyroid cancer

124I PET | 131 WBS diagn | 131 WBS post ter



^{124}I PET/CT



Pre ^{131}I-therapy Post

Terapia con ^{131}I per metastasi

- Dose elevata:
- **200 mCi**
  - metastasi polmonari
- **300 mCi**
  - metastasi ossee

  (consigliata successiva radioterapia esterna se lesione unica o critica)
- Le secondarietà linfonodali loco regionali, ove possibile, vanno trattate chirurgicamente

Tossicità da ^{131}I

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- acuta
  - nausea, epigastralgia, vomito
  - scialoadenite
  - xerostomia, disgeusia
- cronica
  - gonadica
  - genetica
  - carcinogenesi

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Rischio di seconda neoplasia in pazienti con carcinoma tiroideo

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- I pazienti con carcinoma tiroideo hanno un aumentato rischio di seconda neoplasia rispetto alla popolazione generale
- ciò soprattutto per tumori di mammella, colon-retto, sistema nervoso centrale, rene, leucemia, linfoma non-Hodgkin, prostata (Subramarian S et al, Thyroid 17: 1277-1288, 2007)
- l'aumento del rischio assoluto tuttavia è modesto:
  - **7% in 8.6 anni** sec. Brown AP et al., JCEM 93: 504-515, 2008
  - **8% in 13 anni** sec. Rubino C et al., Br J Cancer 89: 1638-1644, 2003

…. e l'ambiente?

Minimizzazione dei rischi ambientali

Bari,
7-10 novembre 2013

- Degenze protette con vasche di contenimento e scarichi controllati
- Raccolta in appositi locali dei rifiuti solidi e della biancheria, inviati alle loro destinazioni dopo decadimento

Minimizzazione dei rischi ambientali

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- Dimissione solo dopo l'eliminazione di gran parte dello ^{131}I ed il raggiungimento dei limiti di legge (**16 mCi** ritenuti = limite per i trattamenti ambulatoriali)
- Rigorose norme comportamentali alla dimissione per contenere la contaminazione ambientale e l'irradiazione dei conviventi

^{131}I WBS DTC plurimetastatico ^{18}F-FDG PET

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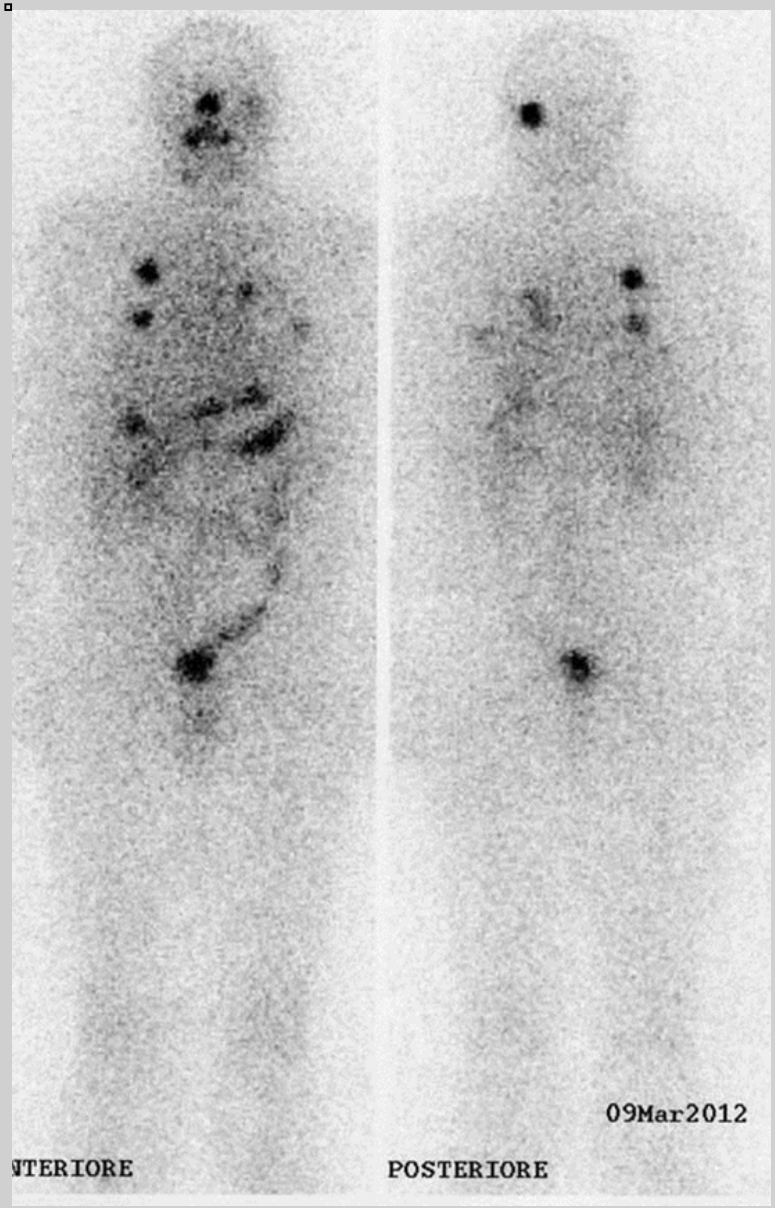
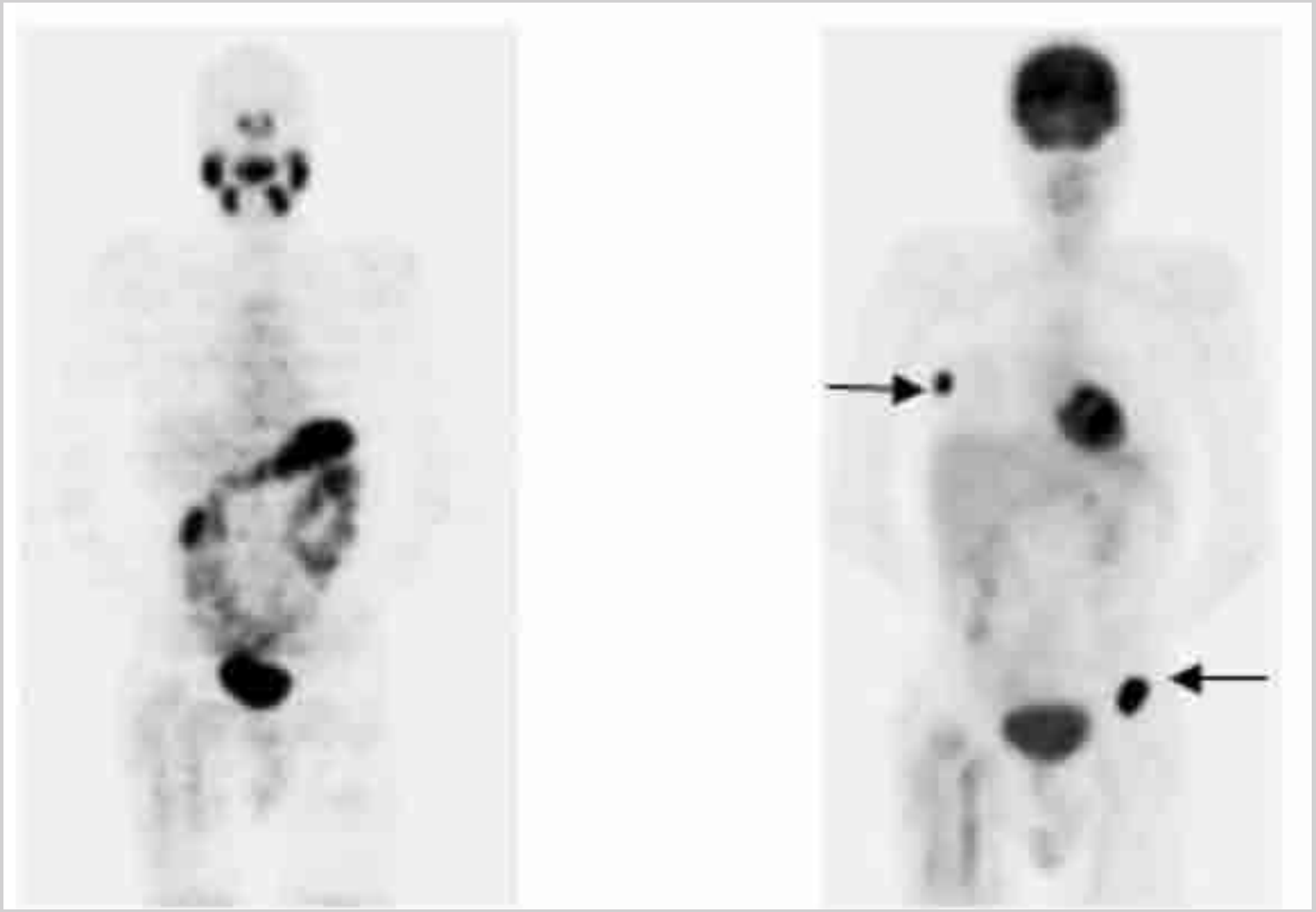


124I PET 18F-FDG



- Metastases from differentiated thyroid carcinoma (DTC) can lose in time the capacity to concentrate radioiodine and the possibility to have a specific treatment.

Presupposti per l'impiego della PRRT nel DTC

Authors	Thyroid tumours evaluated	Methods	Somatostatin receptors detected
Pazaitou-Panayiotou et al 2012[5]	47 (38 PCs, 4 FCs, 2 ACs, 3 HCCs)	Immunohistochemisty for all SSTRs subtypes	SSTR 2 and 3 were expressed in all non-medullary thyroid carcinomas, SSTR 1 and 5 in 75% and SSTR 4 in 38%. The expression of SSTRs subtypes in normal thyroid tissue was low or absent.
Müssig et al 2012[7]	93 (67 PCs, 26 FCs)	Immunohistochemisty for all SSTRs subtypes	SSTR 1 to 5 were detected in 15% to almost 30% of thyroid tumours.
Sancak et al 2010[6]	17 PCs	Immunohistochemisty for SSTR 2	SSTR subtype 2 was expressed in PCs.
Klagge et al 2010[8]	45 (20 PCs, 20 FCs, 5 ACs)	mRNA expression for SSTRs	Thyroid tumours showed a predominant expression of SSTR 2 and SSTR 5, and a weak expression of SSTR 1 and SSTR 3.
Druckenthaner et al 2007[9]	17	mRNA expression for SSTRs correlated with immunochemistry for SSTR2	Thyroid tumours expressed SSTR 2, and less predominantly SSTR 3 and 5.
Forssell-Aronsson et al 2000[10]	9 PCs and 2 HCCs	mRNA expression	All thyroid tumours regularly expressed SSTR 1, 3, 4, and 5. SSTR 2 was not detected in PCs and was irregularly expressed in HCCs.
Ain et al 1997[11]	Cell lines derived from 2 PCs, 2 FCs and 4 ACs	mRNA expression for SSTRs in thyroid cancer cell lines	Most thyroid cancer cell lines expressed SSTR 3 and 5.

Treglia G, et al. Hormones (Athens). 2012;11:230-232.

Nuclear Medicine Imaging

Scintigraphy, SPECT, SPECT/CT

- ^{111}In-Octreoscan

PET/CT

- ^{68}Ga-DOTATOC
- ^{68}Ga-DOTANOC
- ^{68}Ga-DOTATATE

Presupposti per l'impiego della PRRT nel DTC

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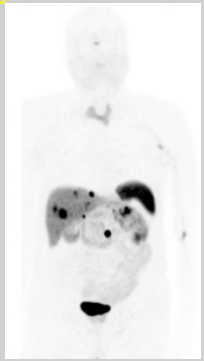

Riferimento	Numero pts	Detection rate
Baudin et al. 1996	25	70%
Postema et al. 1996	8	70%
Garin et al. 1998	16	30%
Valli et al. 1999	15	30%
Giammarile et al. 2004	43	51%
Rodrigues et al. 2005	18	83%
Middendorp et al. 2010	12	49%
Ocak et al. 2013	13	62%
Kroiss et al. 2013	21	na
Mittal et al. 2013	5	100%

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Peptide Receptor Radionuclide Therapy for Non–Radioiodine-Avid Differentiated Thyroid Carcinoma

J Nucl Med 2005; 46:107S–114S

Jaap J.M. Teunissen, MD[1]; Dik J. Kwekkeboom, PhD[1]; Peter P.M. Kooij, MSc[1]; Willem H. Bakker, PhD[1]; and Eric P. Krenning, PhD[1,2]

[1]*Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; and* [2]*Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands*

TABLE 3
Peptide Receptor Radionuclide Therapy in 58 Patients With Differentiated Thyroid Carcinoma

References	Tumor classification	Radiopharmaceutical			Cumulative dose	Response (TTP [mo])	Criteria*
		Radionuclide	Chelator	Peptide			
Gorges et al., 2001 (*14*)	3 × HCTC	^{90}Y	DOTA		1.7–9.6 GBq	1 × SD (21), 2 × PD	NA
Waldherr et al., 2001 (*15*)	3 × FTC; 4 × PTC; 1 × ATC	^{90}Y	DOTA		1.7–14.8 GBq	2 × SD (8,6); 6 × PD	WHO
Virgolini et al., 2002 (*16*)	25 × TC	^{90}Y	DOTA	Lanreotide	0.9–7.0 GBq	3 × RD (NA), 11 × SD (NA), 11 × PD	WHO
Valkema et al., 2002 (*17*)	1 × FTC; 4 × PTC	^{111}In	DTPA	Octreotide	3.0–8.3 GBq	4 × PD; 1 × SD	SWOG
Chinol et al., 2002 (*21*)	2 × PTC	^{90}Y	DOTA		>7.4 GBq		SWOG
Christian et al., 2003 (*12*)	1 × HCTC	^{90}Y	DOTA				NA
Gabriel et al., 2004 (*24*)	4 × FTC; 1 × PTC	^{90}Y	DOTA		5.6–7.4 GBq	5 × SD (5)	NA
Stokkel et al., 2004 (*23*)	4 × FTC; 5 × PTC	^{111}In	DTPA	Octreotide	14.3–33.1 GBq	4 × SD; 5 × PD	NA

*WHO = World Health Organization criteria: regressive disease = >25% reduction in tumor size; SD = <25% reduction or increase in tumor size; PD = >25% increase in tumor size. SWOG = Southwest Oncology Group criteria of tumor response: PR = >50% reduction in tumor size; SD = ±25% reduction or increase in tumor size; PD = >25% increase in tumor size.

TC = undefined thyroid cancer; ATC = anaplastic thyroid carcinoma; NA = not available.

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7-10 novembre 2013

Peptide Receptor Radionuclide Therapy for Non–Radioiodine-Avid Differentiated Thyroid Carcinoma

J Nucl Med 2005; 46:107S–114S

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Results

TABLE 2
Results of ^{177}Lu-DOTATATE Therapy

Patient	Tumor uptake score*		Best response after therapy†		TTP (mo)‡
	Pretherapy ^{111}In-octreotide	Post ^{177}Lu-octreotate therapy	Tumor volume	Tg	
1	2	1	SD	Increase	18
2	2	3	PD	Increase	4
3	3	3	MRe	Decrease	43
4	2	2	SD	Decrease	24+
5	1	3	PR	Decrease	22+

*Tumor uptake score according to SSTR scintigraphy visual scoring system as described previously (*19*).

†SD = <25% reduction or increase in tumor size; PD = >25% increase in tumor size; MRe = between 25% and 50% reduction in tumor size; PR = >50% reduction in tumor size.

‡TTP = number of months since start of therapy.

PRRT nel DTC

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[^{90}Yttrium-DOTA]-TOC Response Is Associated With Survival Benefit in Iodine-Refractory Thyroid Cancer

Long-term Results of a Phase 2 Clinical Trial

Fabienne Iten, MD[1,2], Beat Muller, MD[2], Christian Schindler, MD[3], Helmut Rasch, MD[1], Christoph Rochlitz, MD[4], Daniel Oertli, MD[5], Helmut R. Maecke, PhD[6], Jan Muller-Brand, MD[1], and Martin A. Walter, MD[1,2]

Institute criteria. Survival analyses were performed by using multiple regression models. **RESULTS:** A total of 24 patients were enrolled. A median cumulative activity of 13.0 GBq (range, 1.7-30.3 GBq) was administered. Response was found in 7 (29.2%) patients. Eight (33.3%) patients developed hematologic toxicity

[^{90}Y-DOTA]-TOC treatment. Response to treatment was associated with longer survival from time of diagnosis (hazard ratio [HR], 0.17; 95% confidence interval [CI], 0.03-0.92; $P = .04$) and from time of first [^{90}Y-DOTA]-TOC therapy (HR, 0.20; 95% CI, 0.04-0.94; $P = .04$). The visual grade of scintigraphic tumor

Iten F, et al. Cancer 2009;115:2052–62.

^{68}Ga DOTATOC PET/CT

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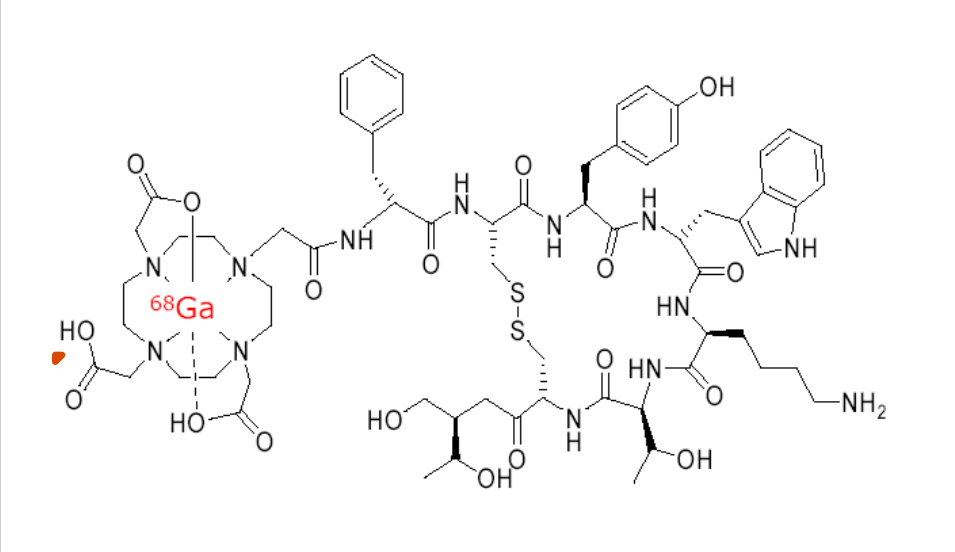
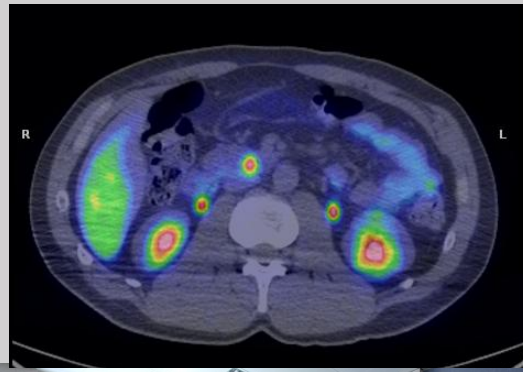
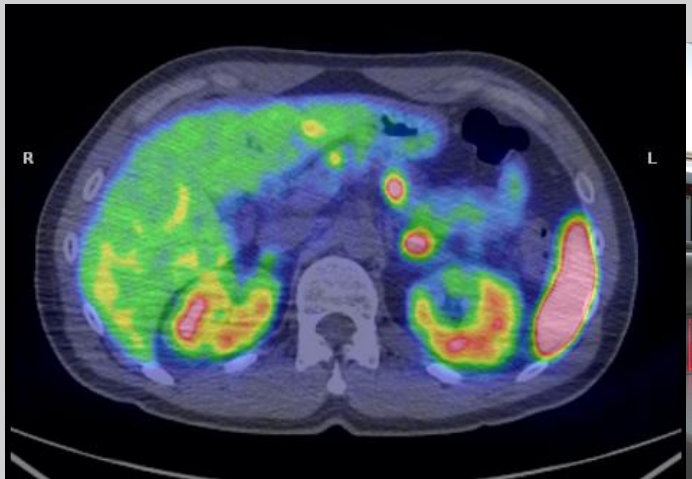
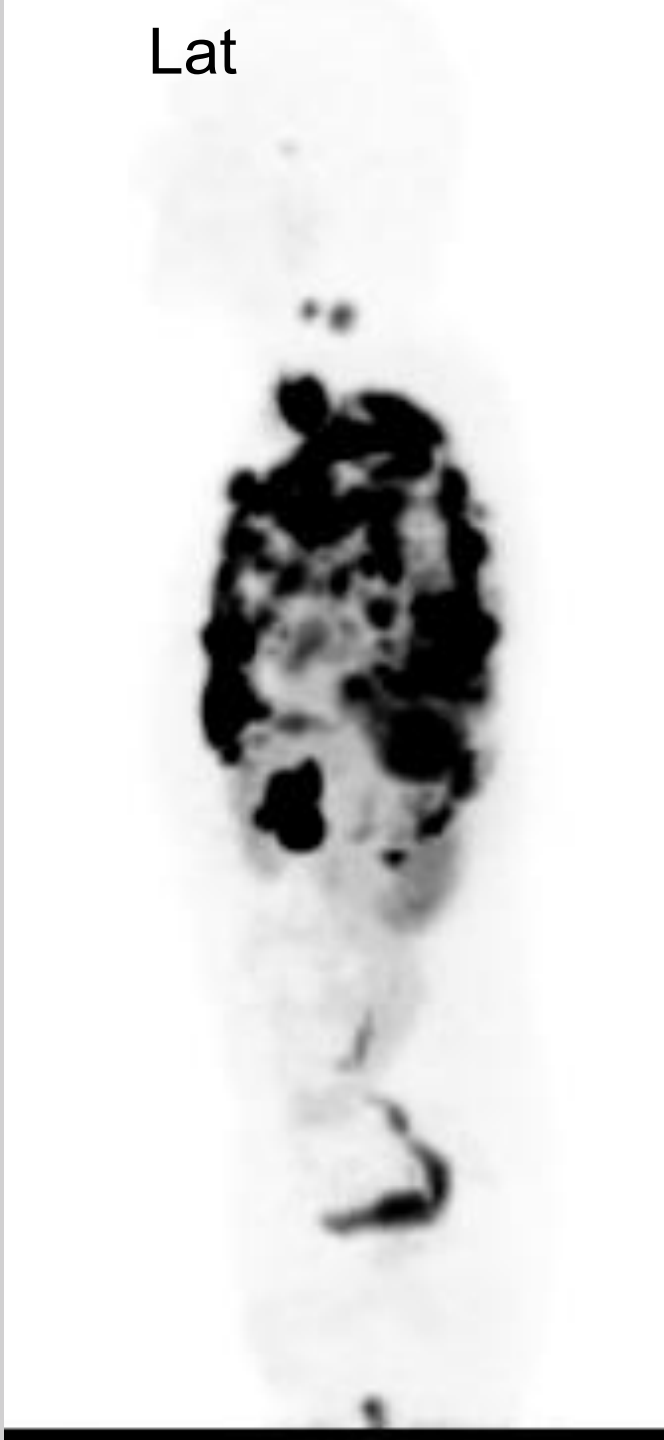




68Ge/68Ga Generator



68Ga-DOTATOC PET/CT



Metastatic differentiated thyroid cancer negative at radioiodine scan

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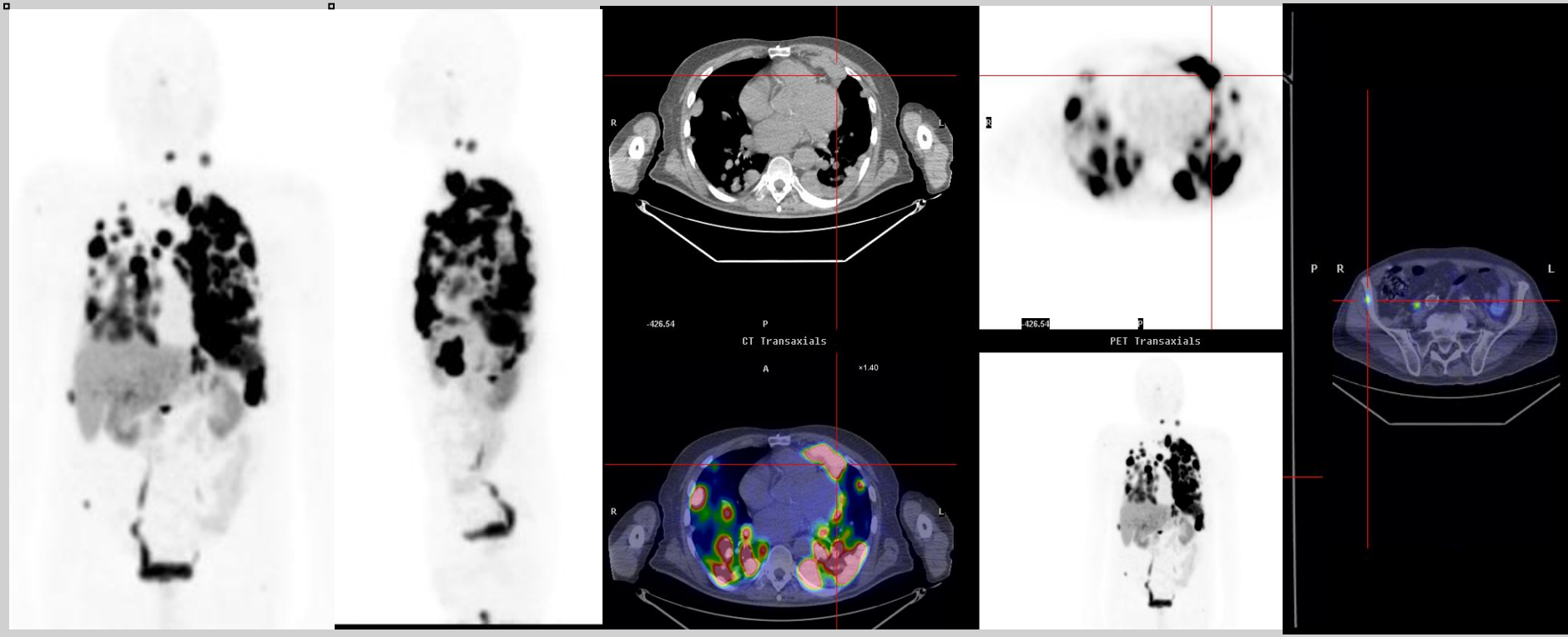
B.M. male, 75 year old ^{68}Ga-DOTATOC PET/CT: Diffuse lung metastases (+ bone and lymph node mts)



68Ga-DOTATOC PET/CT

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Metastatic differentiated thyroid cancer negative at radioiodine scan

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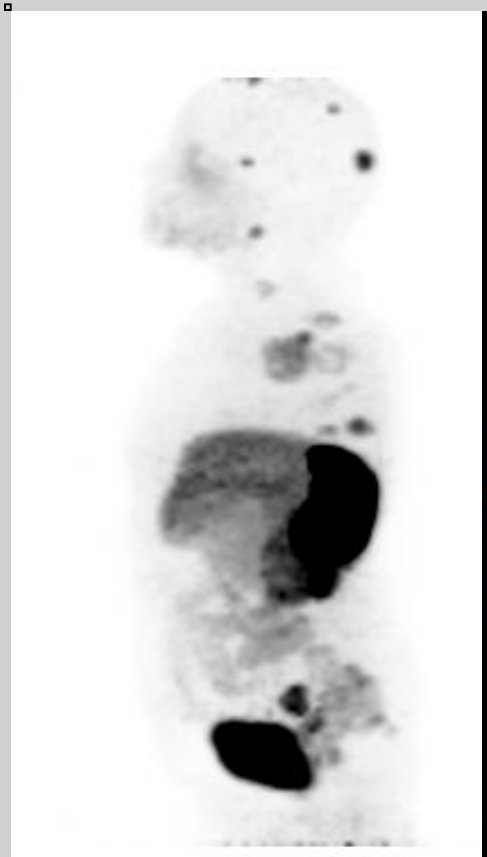
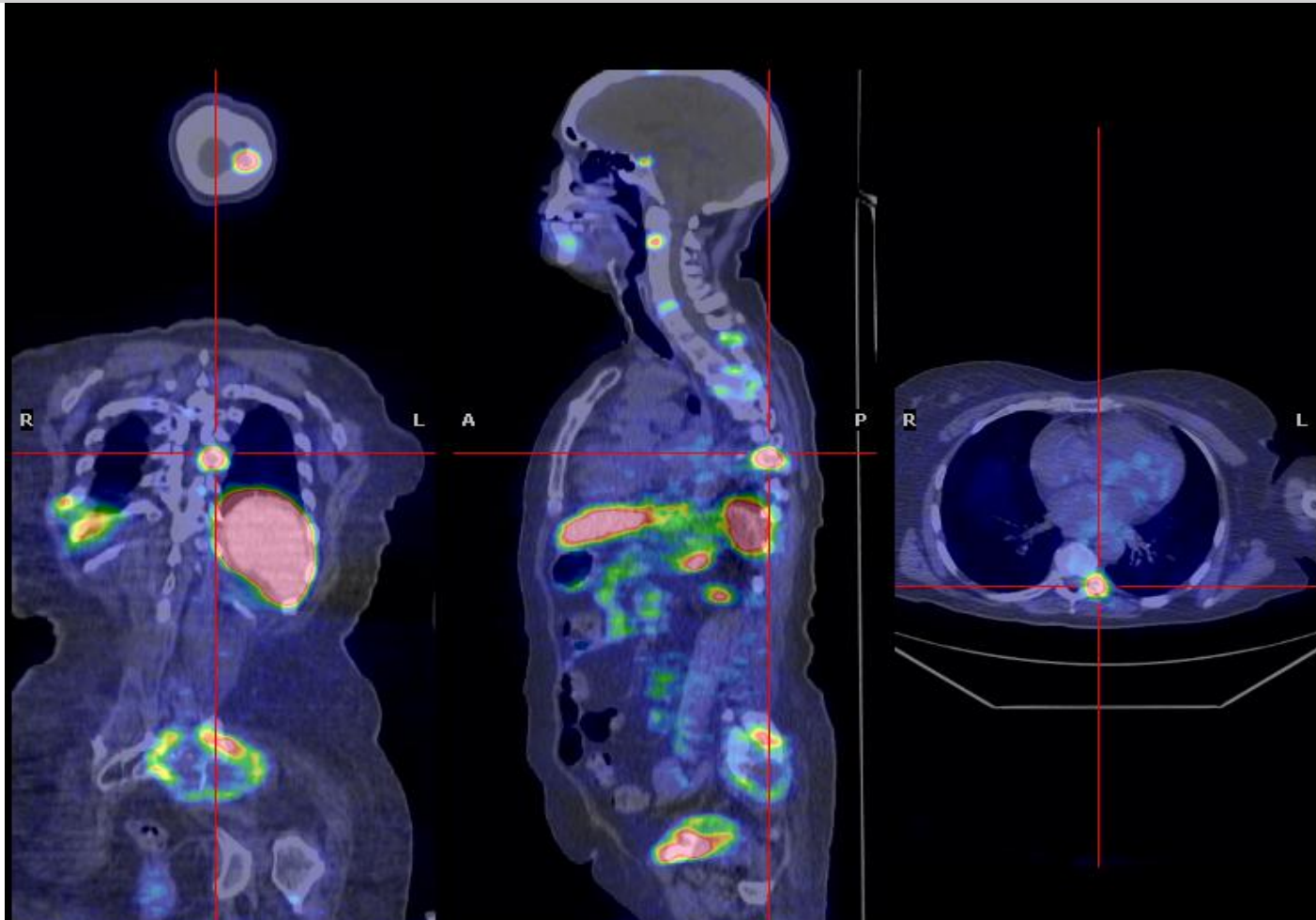
7-10 novembre 2013

P.M. female, 61 year old
^{68}Ga-DOTATOC PET/CT: multiple bone metastases





PRRT nel DTC: la nostra esperienza

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Differentiated thyroid cancer: a new perspective with radiolabeled somatostatin analogues for imaging and treatment of patients

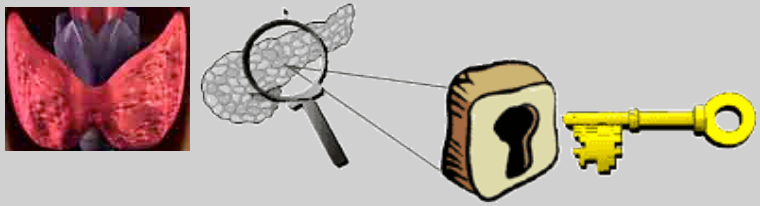
Obiettivo: valutare la risposta alla PRRT in pazienti con "*progressive radioiodine negative DTC*"

Versari A, et al. Thyroid. In Press

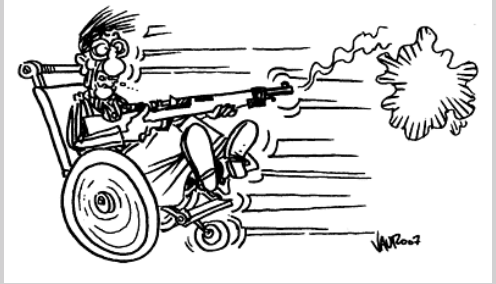
From Diagnosis to Treatment

Diagnosis

^{68}Ga



DOTATOC



Treatment

^{90}Y / ^{177}Lu

Physics properties

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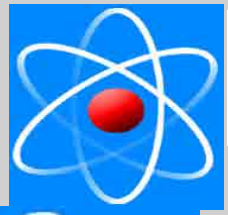
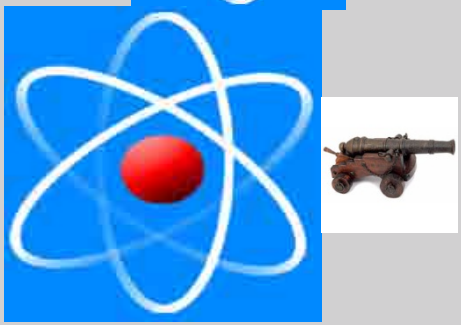
	β- (Mev)	γ (Kev)	T1/2 (days)
^{177}Lu	0.49	110-210	6.7
^{90}Y	2.27		2.7

mean range in body tissue

^{177}Lu  ▸ **0.5-2mm**

^{90}Y  ▸ **3-11 mm**

Pazienti e metodi

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- ✓ **41 pazienti arruolati** (M:F=17:24; età media=53.9 aa)
  - Ca papillare n=31
  - Ca follicolare n=4
  - Ca insulare n=4
  - Ca a cellule di Hürtle n=2
- ✓ **24 paz. con ^{68}Ga-DOTATOC PET/CT positiva** (58%)
- ✓ 13 pazienti eleggibili per la PRRT: **11 pazienti trattati**
- ✓ 44 sm di ^{90}Y-DOTATOC (2-6 sm/paziente) a 70±24.6 giorni (range 45-140) con una mediana di attività iniettata cumulativa di 3.5 GBq (range 1.5-3.7 GBq).

Versari A, et al. Thyroid. In Press

Risultati

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Response criteria		RECIST criteria		
		PR	SD	PD
Patients (n=10*)		2	4	4
Tumor lesions	Thyroid lodge (n=4)	1	2	1
	Lymph-nodes (n=19)	1	12	6
	Lung (n=18)	1	12	5

*1/11 patients not evaluated by RECIST criteria since this patient presented only bone metastasis

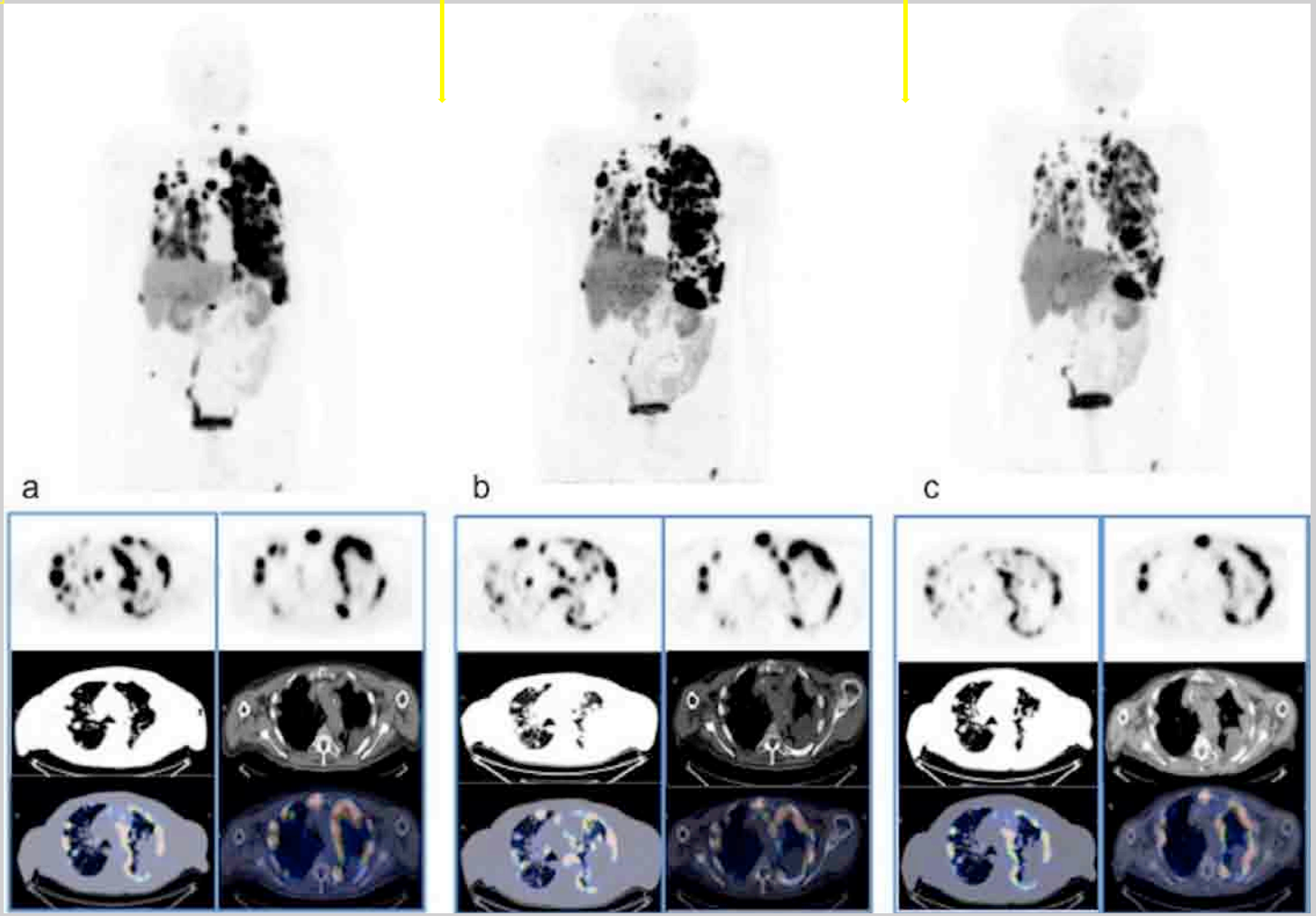
Response criteria	EORCT criteria		
	PR	SD	PD
Patients (n=11)	2	5	4
Bone lesions (n=38)	10	7	21

Versari A, et al. Thyroid. In Press

Ca a cellule di Hürtle

^{90}Y-DOTATOC (3.4 GBq)

^{90}Y-DOTATOC (11.7 GBq)



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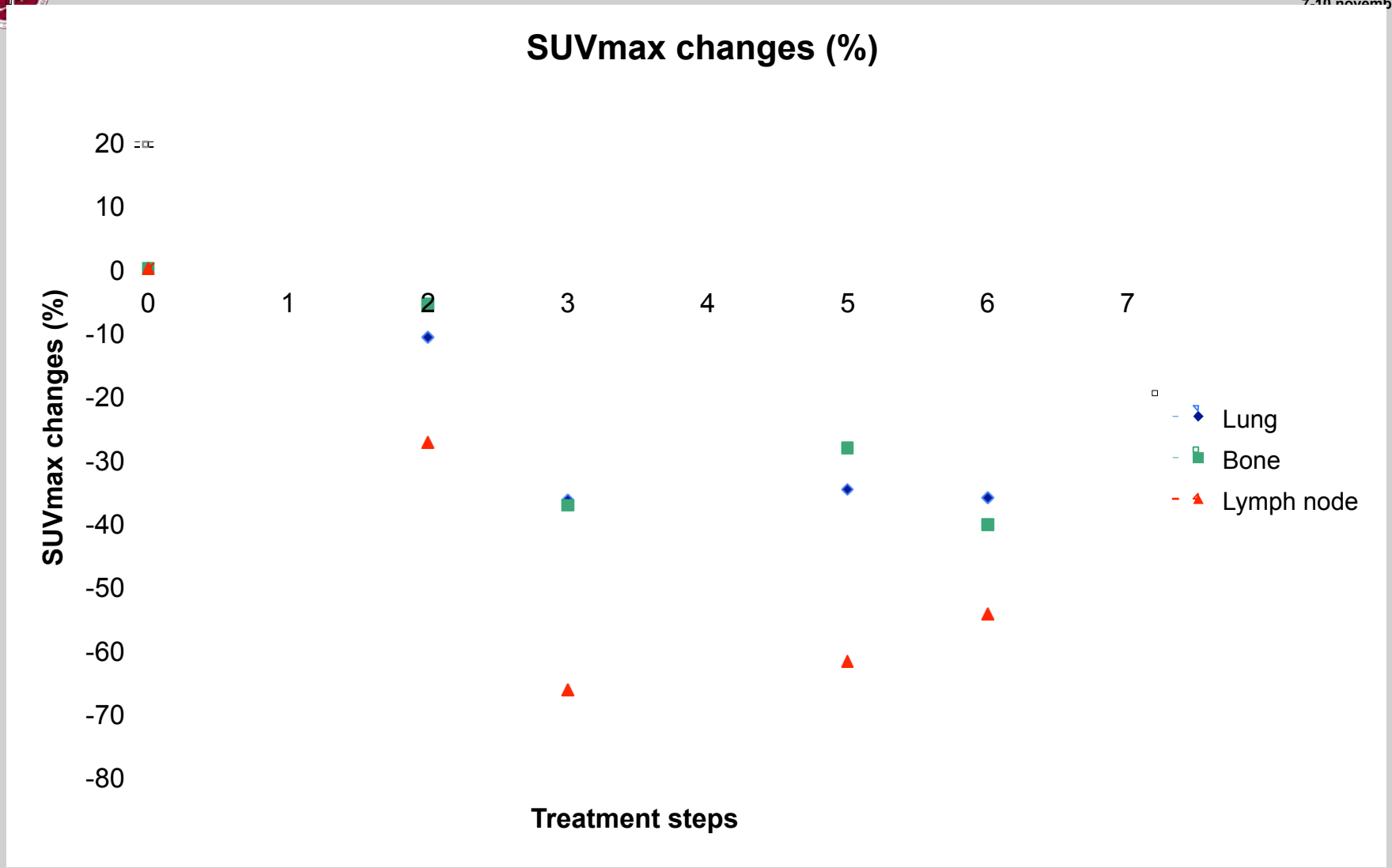

B.M. male, 75 year old

PD in un paziente con Ca insulare della tiroide

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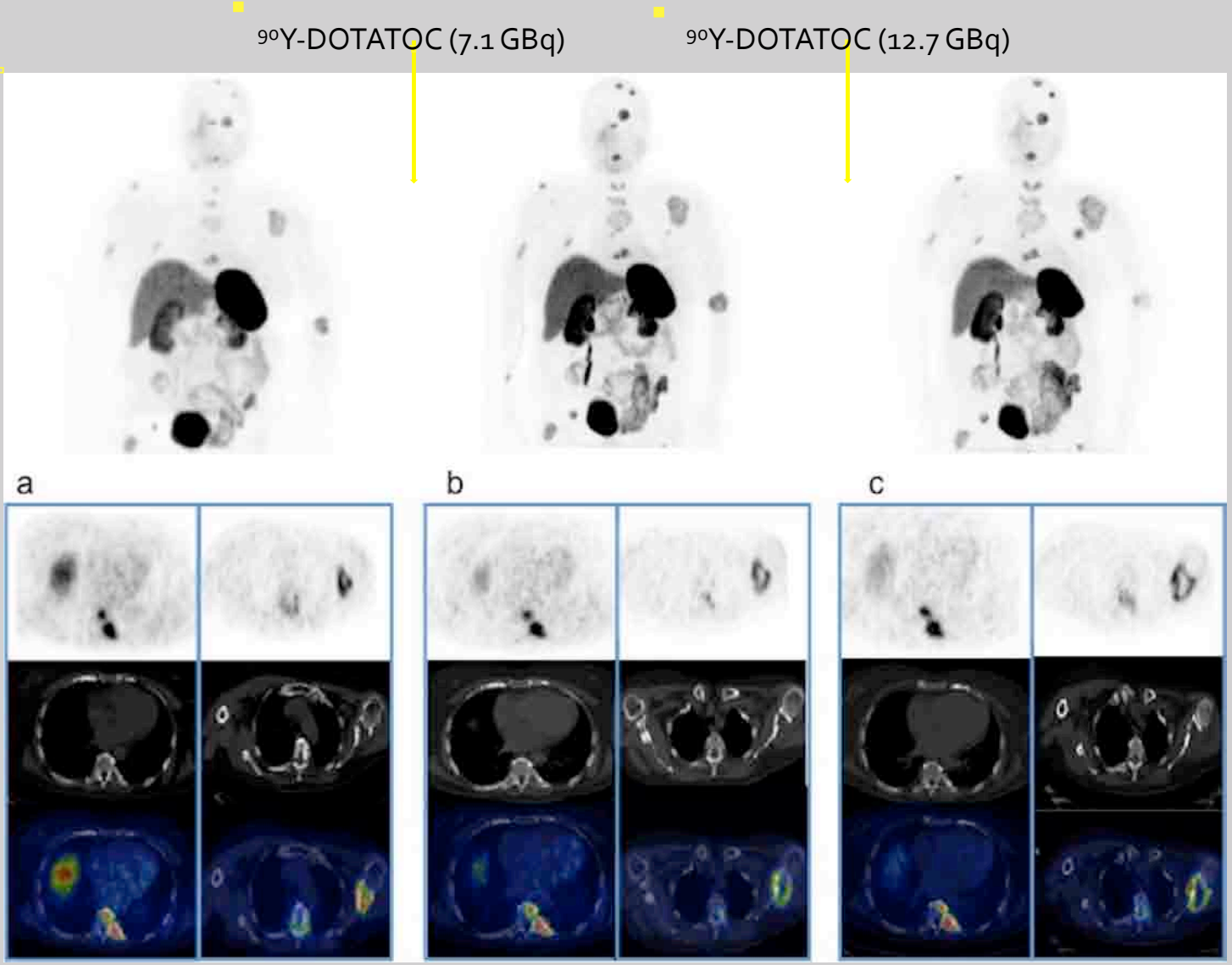
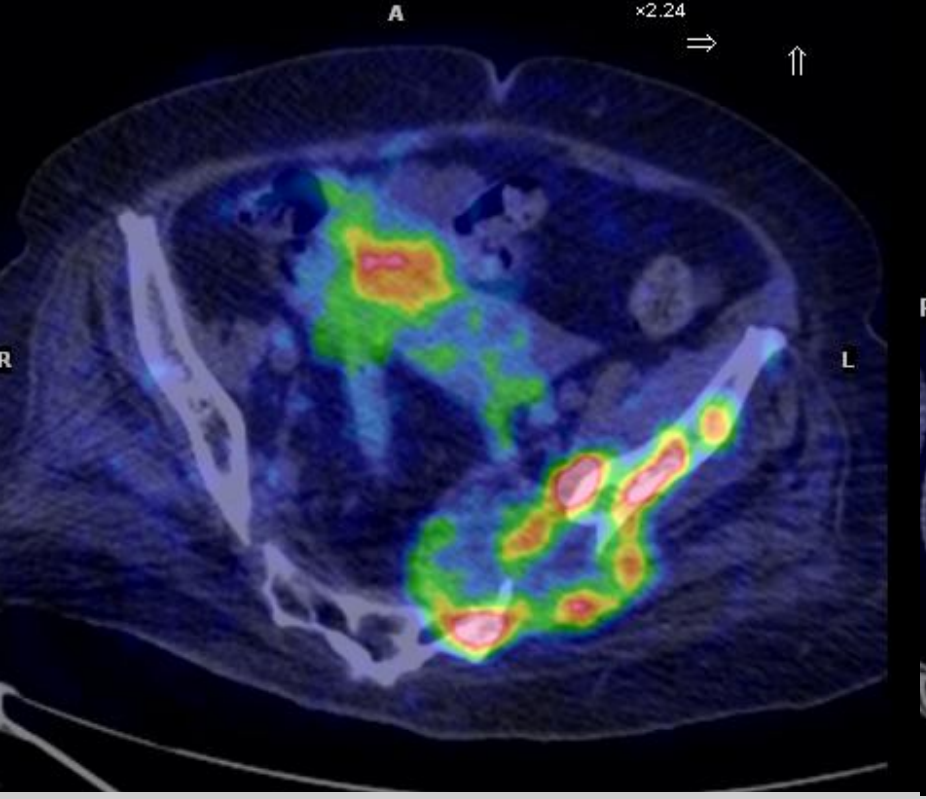
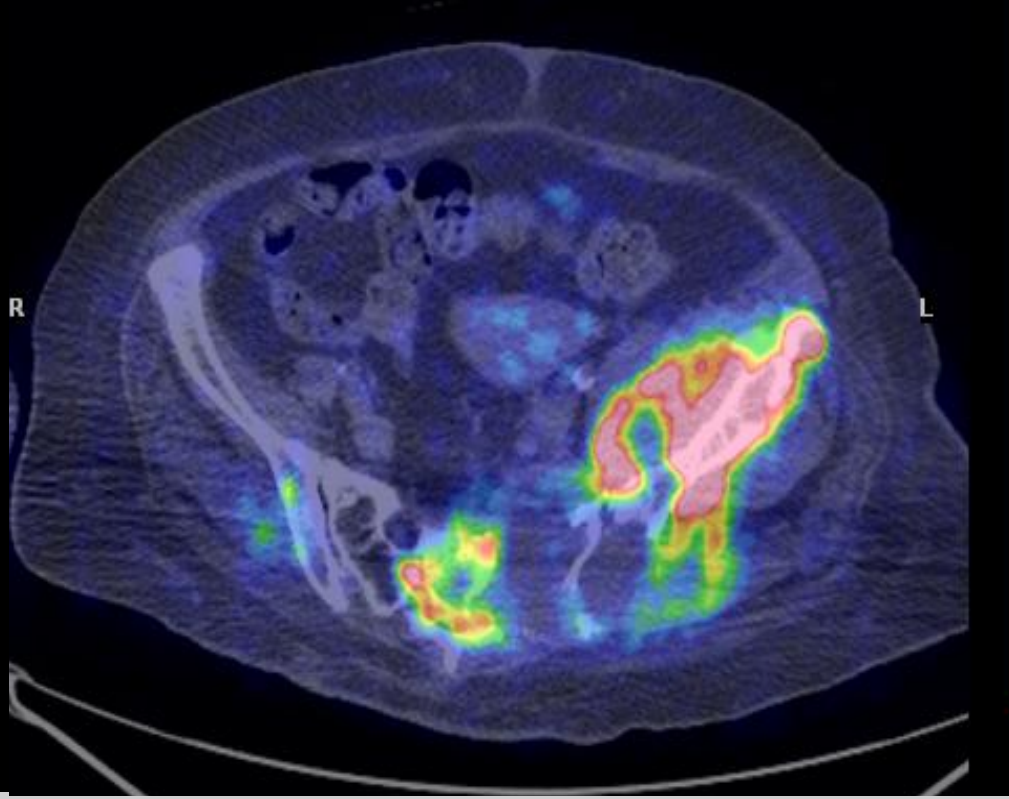
7-10 novembre 2013



Versari A, et al. Thyroid. In Press





Pre-therapy

Post-therapy

P.M. female, 61 year old

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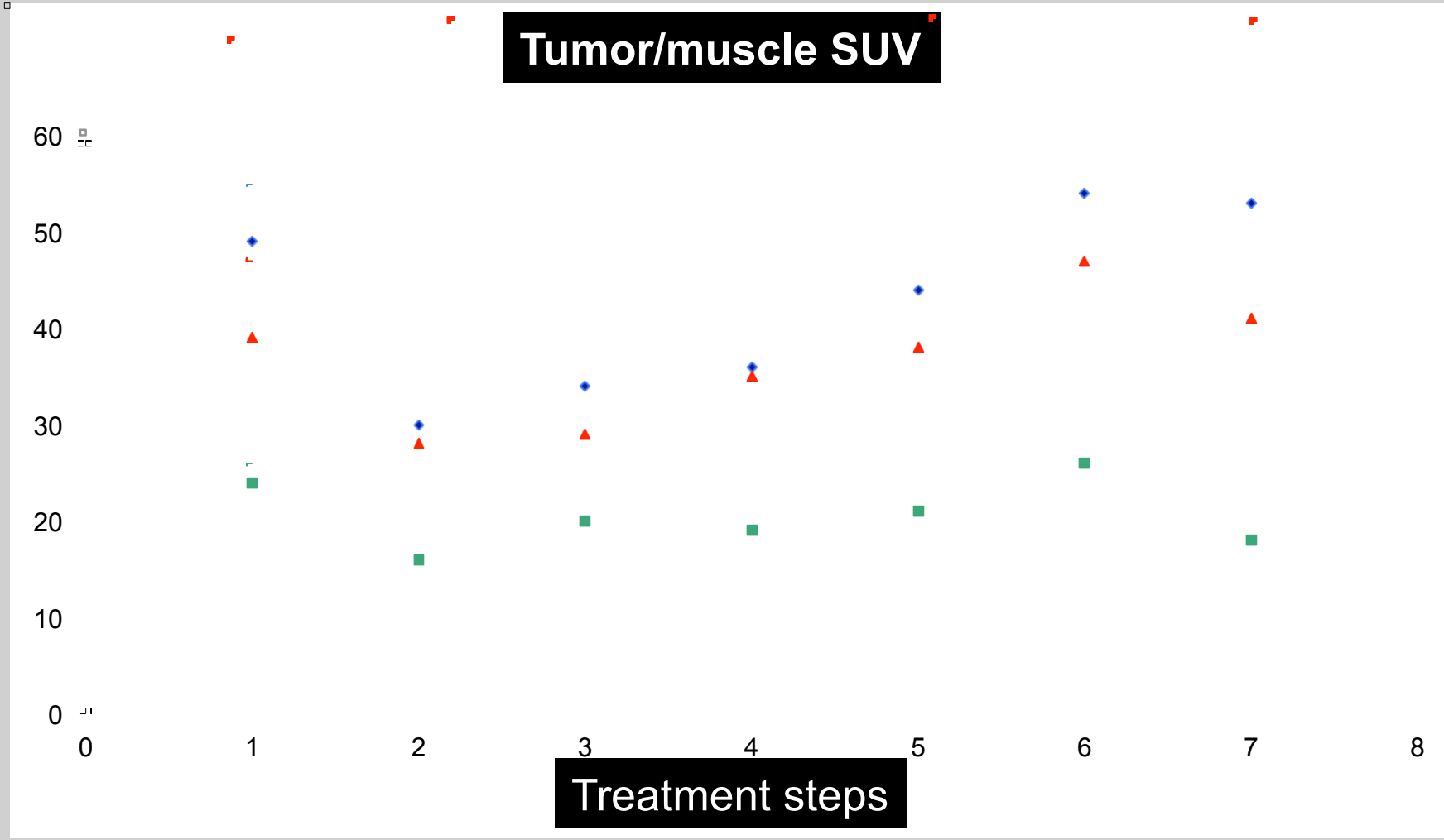
pain no pain no pain pain



P.M. female, 61 year old

Risultati

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Tossicità:

- ✓Nausea (G1) n=4/11
- ✓Astenia (G1) n=2/11
- ✓Leucopenia (G3-G4) n=2/11
- ✓Anemia (G3-G4) n=2/11
- ✓IRC (G2 16 mesi dopo la PRRT) n=1/11
- ✓Aumento transitorio transaminasi (G1) n=1/11

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Conclusions

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Radioiodine is an established treatment for pts with

- **progressive** iodine-avid Differentiated Thyroid Cancer

- **non-resectable** or partially-resectable lesions (lymph nodes, lung, bone, …)

Conclusions

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- **Radiolabelled somatostatin analogs** are very interesting for pts with progressive radioiodine-negative Differentiated Thyroid Cancer for

- **Diagnosis**

(about 50% of these pts are positive at ^{68}Ga-DOTATOC PET/CT)

- **Therapy (PRRT)**

(more than 50% of positive response in eligible pts)

- The possibility to use the same peptide for therapy in PET positive pts is promising but needs further confirmation in larger number of pts.

Grazie per l'attenzione

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Reggio Emilia