Integrazione delle metodiche nella ricerca clinica precoce in Oncologia

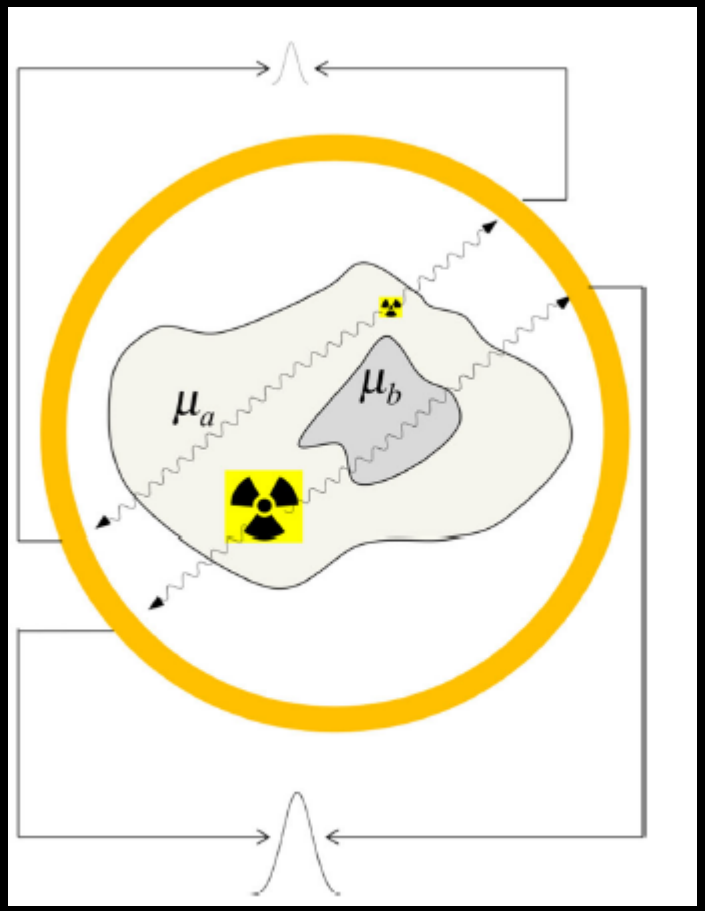
Metodica SPECT-CT nella ricerca clinica precoce.

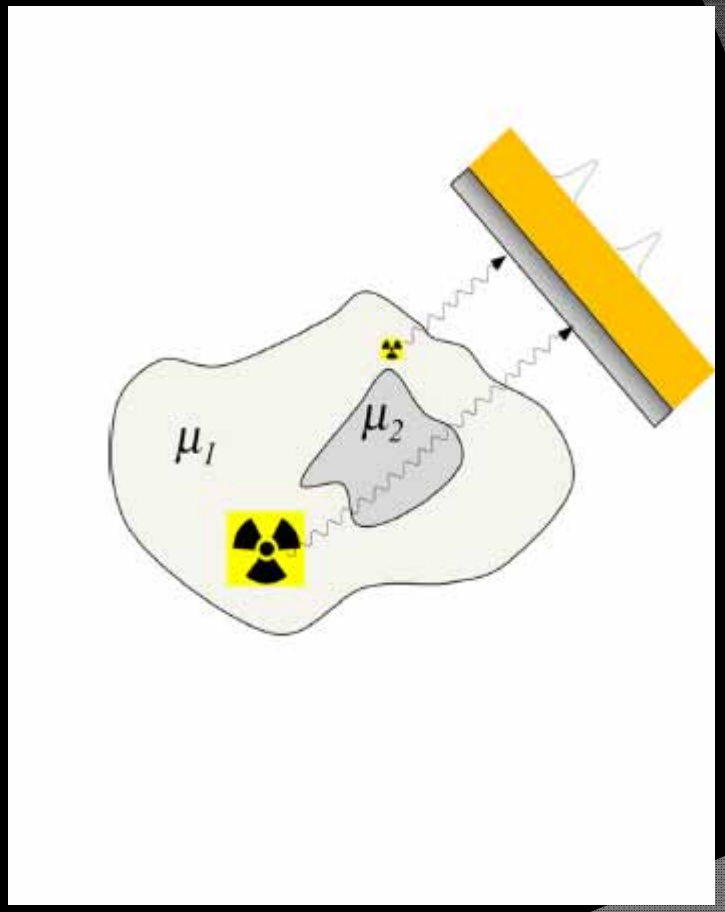
Grassi Elisa

S.C. Fisica Medica

ASMN-IRCCS Reggio Emilia

PET versus SPECT





They are non-invasive imaging methods, so several valuable imaging measurements are feasible to quantitatively measure tumour growth, to assess tumour status and to predict treatment response.

Eur J Nuc Med Mol Imaging (2014)41 (Suppl 1): S17-S25

Quantitative Imaging

- Quantitative imaging from different integrated and calibrated modalities may be used to achieve insights of practical predictive quantities.
- Data from PET and SPECT are affected by poor spatial resolution (only appreciable size tumours)
- Many traditional medical imaging techniques (CT, MRI, US) have been routinely used to monitor therapeutic effects of cancer intervention for the last decades.
- Hybrid rechnology shows that much can be translated from research into clinics.

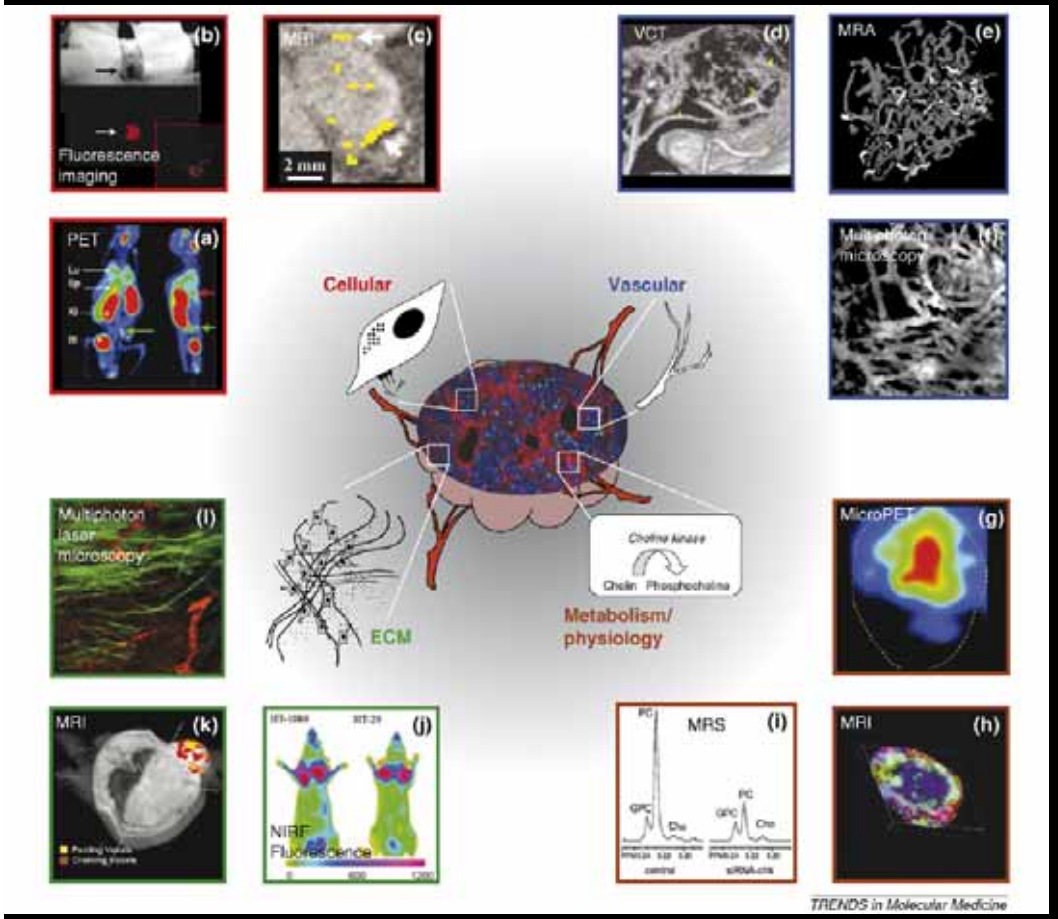
- Molecular radiotherapy (MRT – also known as nuclear medicine therapy) uses radioactive pharmaceuticals administered to patients to treat some types of cancer and other non-cancer diseases.

- The origins of MRT are multidisciplinary, since the treatments arise from the collaboration of radiochemists, immunologists, physicists, endocrinolgists, nuclear medicine physicins, oncologists and radiation oncologists.

Phys Med Biol (2010) 55 (9): 2429-2449
J Nuc Med (2008) 49: 113S-128S

Eur Journal of Cancer (2014) 50: 2360-2363

Molecular-functional imaging



- Molecular imaging has the capabilities to image gene expression, receptors, signaling pathways, apoptosis, multidrug resistance and extracellular matrix.
- Functional imaging has the capabilities to assess angiogenesis, hypoxia and metabolism.

Molecular-functional imaging

Objective: to track specific molecular pathways and tissue/cell function for an individualized cancer treatment

Table 2. MFI of important molecular targets and functional parameters in cancer as discussed in this review article

Functional MFI applications	Functional parameters/probes in cancer	Cancer characteristics/pathways	Molecular/cellular targets in cancer	Molecular MFI applications
NA	NA	Oncogenesis pathways	p53	Bioluminescence, PET
			myc	Bioluminescence
NA	NA	Multidrug resistance	P-glycoprotein	PET, SPECT
NA	NA	Apoptosis	Phosphatidyl serine externalization	PET, SPECT, MRI, Optical (Annexin V)
NA	NA	Cell surface receptors	EGFR	PET, SPECT, NIR fluorescence
			HER-2/neu	T_1-MRI, T_2-MRI, PET, SPECT, fluorescence
			PSMA	PET, SPECT, fluorescence
NA	NA	Proliferation/differentiation	Thymidine kinase	PET (^{18}F-FLT)
			Telomerase	PET
Contrast enhanced MRI, CT, PET, fluorescence	Blood flow, vascular volume, permeability, interstitial fluid pressure	Angiogenesis/lymph-angiogenesis	VEGF	PET, SPECT, MRI, fluorescence
			$\alpha_v\beta_3$	Fluorescence, PET, SPECT, MRI
PET, SPECT, fluorescence	^{18}F-MISO, Cu-ATSM, HRE-GFP	Hypoxia	HIF-1	PET, fluorescence
MRS, PET (^{18}FDG)	Glucose, choline	Metabolism	NA	NA
Optical techniques (DIC, reflection, SHG, IR, AFM)	Collagen I fibers, ECM structure	ECM degradation	Cathepsin D	NIR fluorescence
			Cathepsin B	NIR fluorescence
			Matrix	NIR fluorescence
			Lysosomes	Fluorescence
NA	NA	Invasion and metastasis	Cell labeling with fluorescent proteins	Fluorescence

TRENDS in Molecular Medicine 2007; vol. 13, no. 7

Table 1. Sensitivity, spatial resolution and clinical translation of molecular-functional imaging modalities

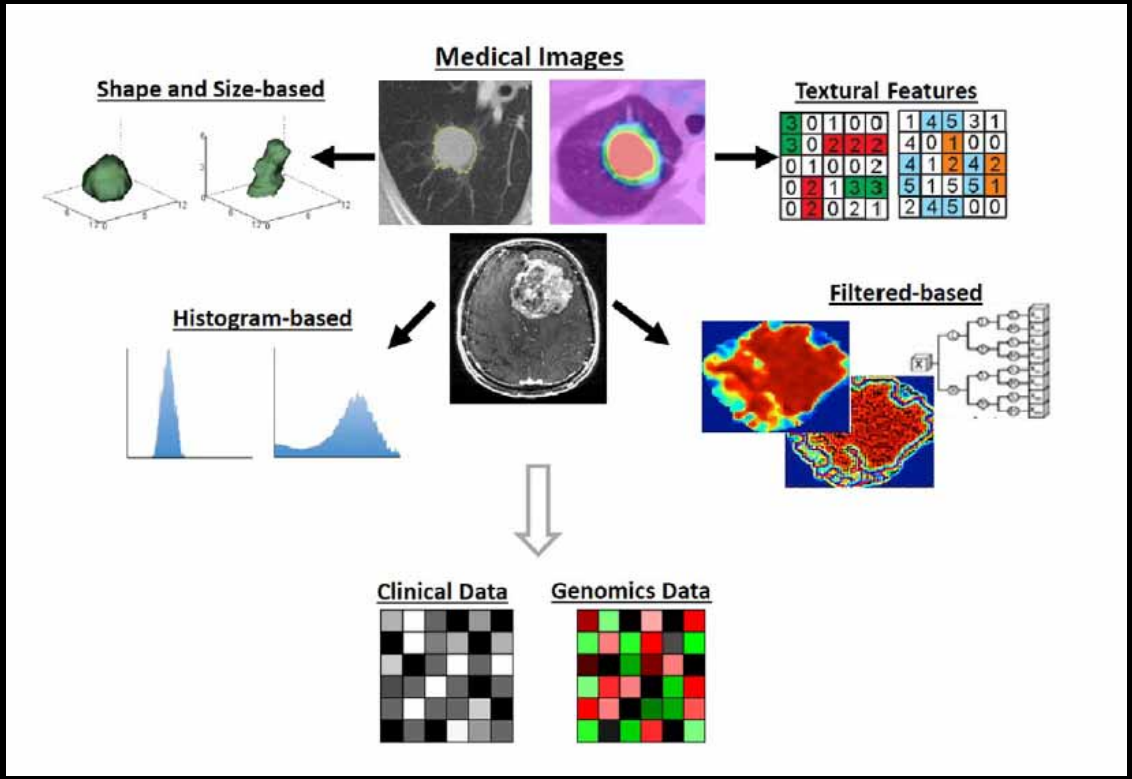
Imaging	Sensitivity of detection in MFI	Spatial resolution *in vivo*	Advantages	Disadvantages
CT	500 micromolar (Gd-DTPA)–low millimolar (Iodine) range	>10 μm	High spatial resolution	Patients are exposed to radiation
MRI	T_2-contrast, iron oxide nano-particles: nanomolar–micromolar range	4 μm (experimental MRI), 250 μm in plane (clinical MRI)	High spatial resolution	Particle size is often large, which restricts *in vivo* delivery
	T_1-contrast, multilabeled targeted Gd-DTPA macromolecules: >10 μM	4 μm (experimental MRI), 250 μm in plane (clinical MRI)	High spatial resolution	Particle size of contrast agent or reporters is relatively large
MRS	Millimolar range (^{1}H at 4.7–11 Tesla)	≥0.5 cm (3 Tesla), 0.7 cm (1.5 Tesla)	Detection of endogenous metabolites	Low sensitivity results in low spatial resolution
Optical	Nanomolar range: ≥50 cells (fluorescence); ≥1000 cells (bioluminescence)	>25 μm, intravital microscopy: 1–15 μm	High sensitivity, high spatial resolution	Restricted depth detection
PET	Picomolar range	≥1 mm (microPET), ~4–5 mm (clinical PET)	High sensitivity, short-lived isotopes	Low spatial resolution, cyclotron required for generating some isotopes
SPECT	Picomolar range	>1 mm (microSPECT), ≥3 mm (clinical SPECT)	High sensitivity	Low spatial resolution, long-lived isotopes
Ultrasound	>10^6 microbubbles per ml blood	>40 μm	High spatial resolution, cost effective	Few probes available

- Early diagnosis: combined molecular-functional–anatomical approach provides high benefit for high sensitivity and specificity and for the purpose to go beyond the relative weakness and strenght of each modality.
- Successful treatment: it is the ultimate goal of several molecular targeted therapies many of which are still under cinical trial.

TRENDS in Molecular Medicine 2007; vol. 13, no. 7

Radiomics

- Tumour characteristics at cellular and genetic level are reflected in the phenotypic patterns that can be captured with medical images



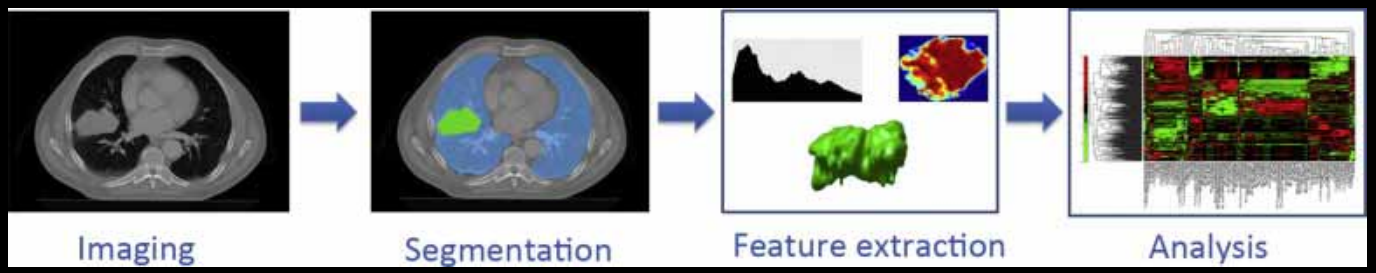
Aim: obectively and reproducibility to quantify various imaging features that may reveal the underlying biology of the tumour

Phy Med Biol 61 (2015) R150-166

Radiomics in oncology

- Prediction
- Staging
- Tissue identification
- Assessment of cancer genetics

Some issues in radiomics' steps related to nuclear medicine imaging:



accurate tumour delineation, reproducibility between scans, image resampling schema, respiratory motion, tumour size and intratumoral heterogenity

Strong need for standardization and harmonization

Radiomics and imaging

- Radiomics is the extraction of large amount of features from radiographic images.
- Images have a central role in clinical oncology in the context of individualised medicine
- Images contain complementary and interchangable information compared to other sources.
  - CT: anatomical imaging
  - PET, MRI: functional imaging
  - Molecular imaging: molecular markers

such as those for hypoxia, the labelled antibodies to assess the level of expression of the tumour receptors,…

Eur J Cancer 2012 48(4): 441-446

Medical Imaging evolution

- Four distinct ways:
  - Innovation in medical devices
  - Innovation in imaging agents
  - Standardised protocols for quantitative imaging
  - Innovation in imaging analysis → RADIOMICS

An accurate standardised quantitative imaging is good, but a smart automatic software is required to extract reliable information from image-based features.

Steps of radiomics enterprise (and challenges) :

- Image acquisition and reconstruction (harmonization)
- Image segmentation and rendering (robustness; automated)
- Feature extraction and qualification (robustness)
- Databases and data sharing (to be generated)
- Informatic analysis (optimization of statistical analysis)

AIM: to build descriptive and predictive models relating to image features and gene-protein signatures

Initial application of radiomics to:

- Image acquisition and reconstruction (PET-CT, MRI)
- Image segmentation and rendering (PET-CT, MRI)
- Feature extraction and qualification (PET: lung, H&N, esophageal cancer)
- Databases and data sharing (????)
- Informatic analysis (initial work)

Poor population of works about application of radiomics to SPECT imaging.

WHY?

SPECT in steps of radiomics

- Image acquisition and reconstruction (harmonization)
- Image segmentation and rendering (robustness and automated to be achieved)
- Feature extraction and qualification (robustness)….. Few works

Application of texture analysis to DAT SPECT imaging: Relationship to

PubMed ▾ spect texture analysis

Create RSS Create alert Advanced

Format: Summary ▾ Sort by: Most Recent ▾ Send to

Search results

Items: 3 Selected: 1

Filters activated: published in the last 5 years. Clear all to show 14 items.

1. Texture analysis of (125)I-A5B7 anti-CEA antibody SPECT differentiates metastatic colorectal cancer model phenotypes and anti-vascular therapy response.
Rajkumar V, Goh V, Siddique M, Robson M, Boxer G, Pedley RB, Cook GJ.
Br J Cancer. 2015 Jun 9;112(12):1882-7. doi: 10.1038/bjc.2015.166.
PMID: 25989271 Free PMC Article
Similar articles

clear

linder[e], Ivan S. Klyuzhin[f], Gwenn S. Smith[g],

rget, Advance Publications 2016

g radionuclide therapy
ptor heterogeneity

, Takahiro Higuchi[1], Andreas
ank Bengel[3], Imke Schatka[4],
bias Große-Ophoff[8], Markus

Program International Symposium - Quantification and Standardisation in Medical and Preclinical Imaging: state of the art and future developments.

University Medical Center Groningen, Groningen,

Tuesday 20th September State of the art in quantitative medical imaging technology		
9:00-10:30	Registration + coffee & tea	
10:30-11:00	Welcome R.A. Dierckx, chairman Medical Imaging Center Opening R. Boellaard, symposium president	
11:00-12:30	**State of the art in quantitative CT imaging**	
	Physics of quantitative CT imaging	*M. Greuter (Groningen)*
	Dual energy CT imaging	*L. Jacobi-Postma (Maastricht)*
	Application of quantitative CT imaging	*M. Oudkerk (Groningen)*
12:30-14:00	Lunch & exhibition	
14:00-15:00	**State of the art in quantitative PET and SPECT imaging**	
	Physics of quantitative SPECT	*H.W.A.M. de Jong (Utrecht)*
	Quantitative image reconstruction	*J. Nuyts (Leuven)*
15:00-15:30	**Vaalburg lecture:** Quantitative molecular imaging	*A.A. Lammertsma (Amsterdam)*
15:30-16:00	Coffee, tea & exhibition	
16:00-17:00	**State of the art in MR and PET/MR imaging**	
	Quantitative MR	*R.H. J. Borra (Groningen)*
	Quantitative PET/MR	*H. Zaidi (Geneva)*
17:00-18:00	Poster, exhibition & drinks	*(Fonteinpatio)*

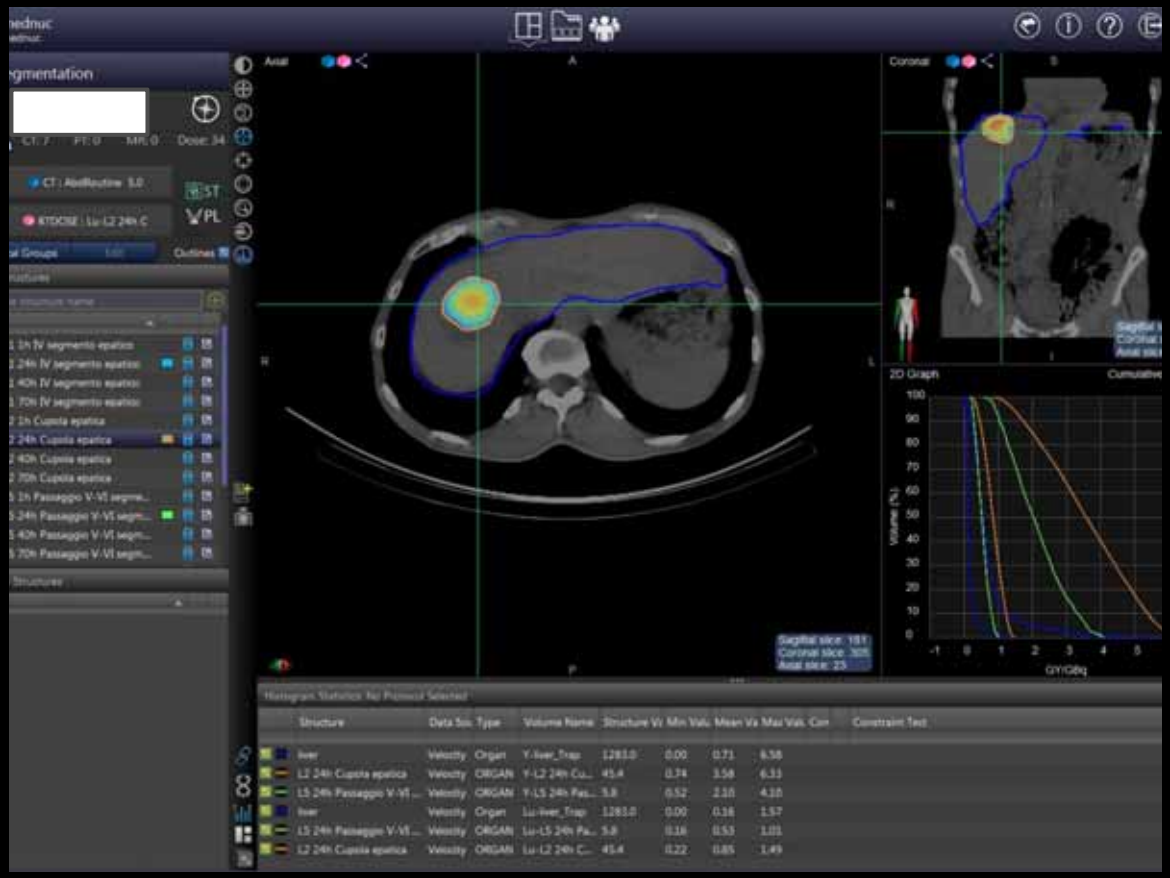
Wednesday 21th September Clinical applications of quantitative imaging		
8:30-9:30	Registration + coffee & tea	
9:30-11:00	**Quantitative imaging in oncology**	
	Quantitative molecular Imaging of Mabs	*E.G.E. de Vries (Groningen)*
	Application and state of the art in optical imaging	*W.B. Nagengast (Groningen)*
	Quantitative MRI in breast oncology	*M.D. Dorrius (Groningen)*
	Quantification & standardisation in onco PET	*R. Boellaard (Groningen)*
11:00-11:30	Coffee, tea & exhibition	
11:30-13:00	**Quantitative imaging in Cardiology/vascular**	
	Quantitative CT/MRI cardiovascular imaging	*N.H.J. Prakken (Groningen)*
	Quantitative PET perfusion imaging	*P. Knaapen (Amsterdam)*
	Quantitative molecular imaging cardiology	*J. Knuuti (Turku)*
	Quantitative vascular imaging	*F. Bengel (Hannover)*
13:00-14:00	Lunch & exhibition	
14:00-15:00	**Quantitative imaging in Neurology/brain**	
	PET and MR imaging in Alzheimer's disease	*B. N.M. van Berckel (Amsterdam)*
	Response evaluation in neuro oncology	*P.J. van Laar (Groningen)*
	Glucose Imaging in Parkinsonian syndromes	*K.L. Leenders (Groningen)*
15:00-15:30	Coffee, tea & exhibition	
15:30-17:00	**Quantitative imaging in infection and inflammation**	
	Quantitative imaging in infection	*A. Signore (Roma)*
	Quantitative imaging in inflammation	*J. Beukinga (Groningen)*
	Bone imaging/bone densitometry	*M. Punda (Zagreb)*
17:00-17:15	**Poster awards**	
17:15-18:00	Walking/transfer to conference dinner	*(Ni Hao Groningen)*
18:00- 21:00	Conference dinner	

SPECT-CT in MRT (PRRT, antibodies,...)

- SPECT-CT plays an important role in dosimetry at organ and at voxel level.
- Image acquisition and reconstruction: scanner calibration, optimization of acq&recon protocols.
  Harmonization and standardization may reduce the total uncertainties
- Quantification: definition of a calibration factor, partial volume effect correction
- Image segmentation: manual contouring, CT or SPECT guided (organs at risk and lesions respectively)
- Dose calculation: organ level (routinely) and voxel level (will be routine) with S-voxel value convolution or with Monte Carlo simulations.

Planning of the personalized treatment and study of the dose-response correlation

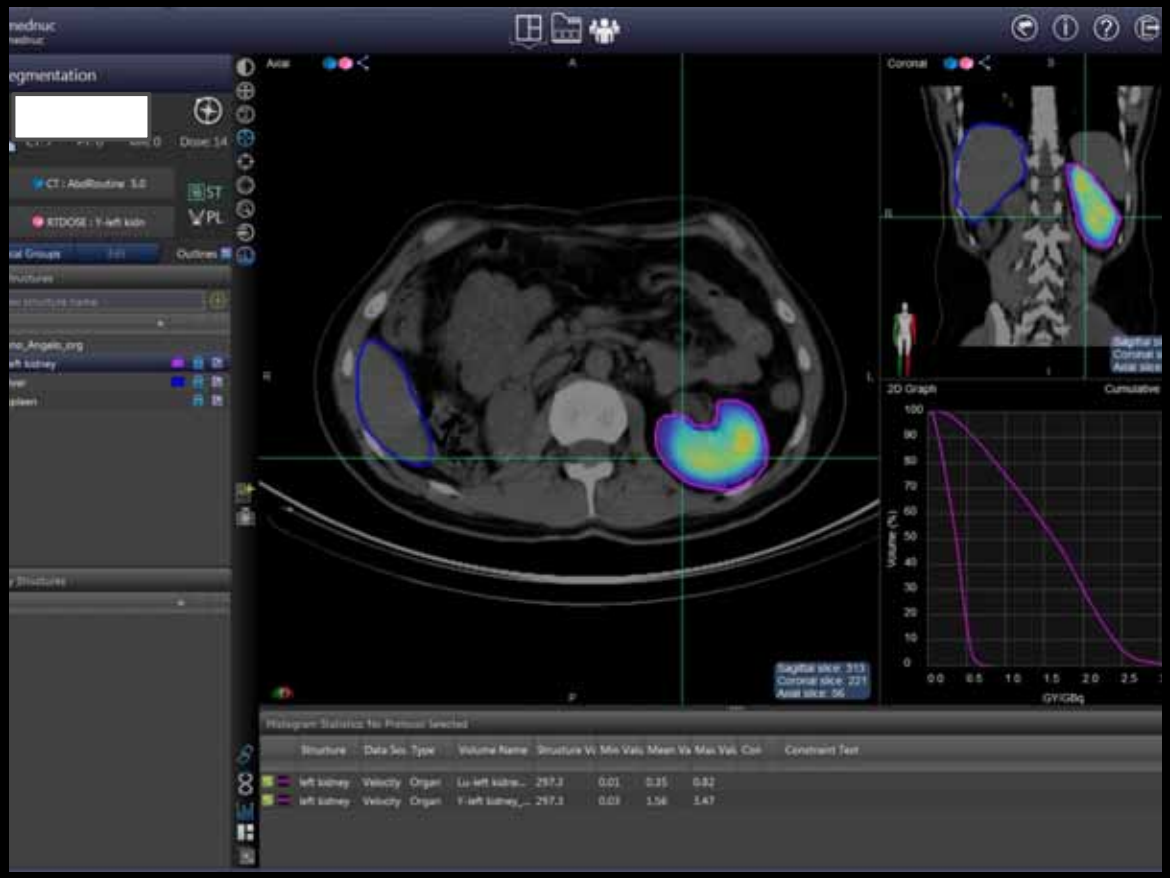
AL: 3,69 GBq ^{177}Lu-DOTATOC



Voxel-dosimetry with VoxelMed

- Cumulative DVHs for liver and 2 epatic lesions calculated for ^{90}Y and ^{177}Lu in a patient administered with 3,69GBq of ^{177}Lu-DOTATOC and scanned 4 times with a SPECT-CT scanner.
- The present DHVs are to be summed to the following adminstrations of ^{90}Y and ^{177}Lu, as planned specifically for the patient.

RA: 4,95 GBq of ^{177}Lu-DOTATOC



- Cumulative DVHs for the left kidney for ^{90}Y and ^{177}Lu in a patient administered with 4,95 GBq of ^{177}Lu-DOTATOC and scanned 4 times with a SPECT-CT scanner.
- The present DHVs are to be summed to the following adminstrations of ^{90}Y and ^{177}Lu, as planned specifically for the patient.

Combination of treatments

- ….is meant like EBRT and MRT combination

or

- ….like a combination of two kinds of MRT to better hinder the toxicities.

E.G: 177Lu-PRRT and 90Y-PRRT in a tandem

What is the best strategy?

A few works about toxicity and dose-response correlation and survival prediction

Dose Response of Pancreatic Neuroendocrine Tumors Treated with Peptide Receptor Radionuclide Therapy Using ^{177}Lu-DOTATATE

J Nucl Med 2015; 56:177–182
DOI: 10.2967/jnumed.114.148437

Ezgi Ilan[1,2], Mattias Sandström[1,2], Cecilia Wassberg[1,3], Anders Sundin[1,3], Ulrike Garske–Román[1,3], Barbro Eriksson[4], Dan Granberg[4], and Mark Lubberink[1,2]

[1]Nuclear Medicine and PET, Department of Radiology, Oncology, and Radiation Science, Uppsala University, Uppsala, Sweden; [2]Medical Physics, Uppsala University Hospital, Uppsala, Sweden; [3]Molecular Imaging, Medical Imaging Centre, Uppsala University Hospital, Uppsala, Sweden; and [4]Section of Endocrine Oncology, Department of Medical Science, Uppsala University Hospital, Uppsala, Sweden

ORIGINAL RESEARCH Open Access

Radiation exposure of the spleen during ^{177}Lu-DOTATATE treatment and its correlation with haematological toxicity and spleen volume

Svensson et al. EJNMMI Physics (2016) 3:15
DOI 10.1186/s40658-016-0153-4

Johanna Svensson[1*], Linn Hagmarker[2], Tobias Magnander[2,4], Bo Wängberg[3] and Peter Bernhardt[2,4]

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2016

Survival prediction in patients undergoing radionuclide therapy based on intratumoral somatostatin-receptor heterogeneity

Rudolf A. Werner[1,*], Constantin Lapa[1,*], Harun Ilhan[2], Takahiro Higuchi[1], Andreas K. Buck[1], Sebastian Lehner[2], Peter Bartenstein[2], Frank Bengel[3], Imke Schatka[4], Dirk O. Muegge[5], László Papp[6], Norbert Zsótér[7], Tobias Große-Ophoff[8], Markus Essler[8] and Ralph A. Bundschuh[8]

Wishes for the future:

- Harmonization, standardization of each modality of nuclear medicine, because only accurate and robust imaging data can provide reliable data analysis to build predictive and descriptive models in oncology.
- Multidisciplinary approach beyond the multiprofessional figures in medicine.