# Multimodal (multilevel) Imaging in SBRT

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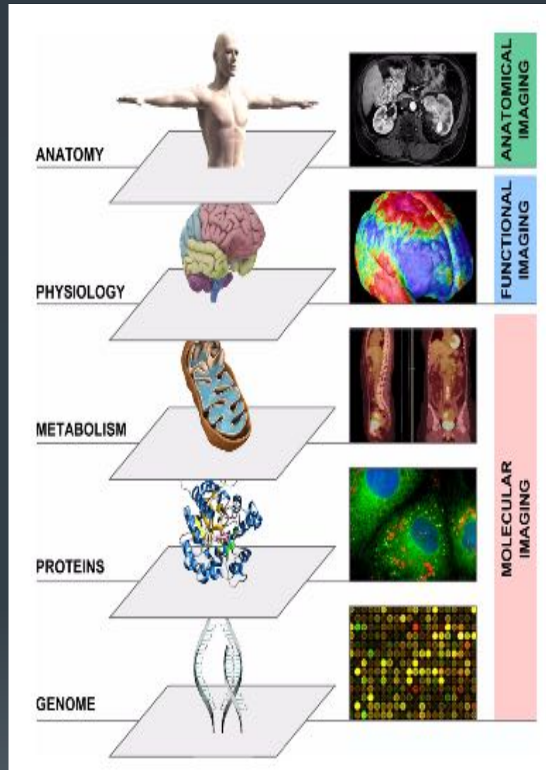


XXV CONGRESSO NAZIONALE
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PALACONGRESSI - Rimini, 7-10 novembre

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# DICHIARAZIONE

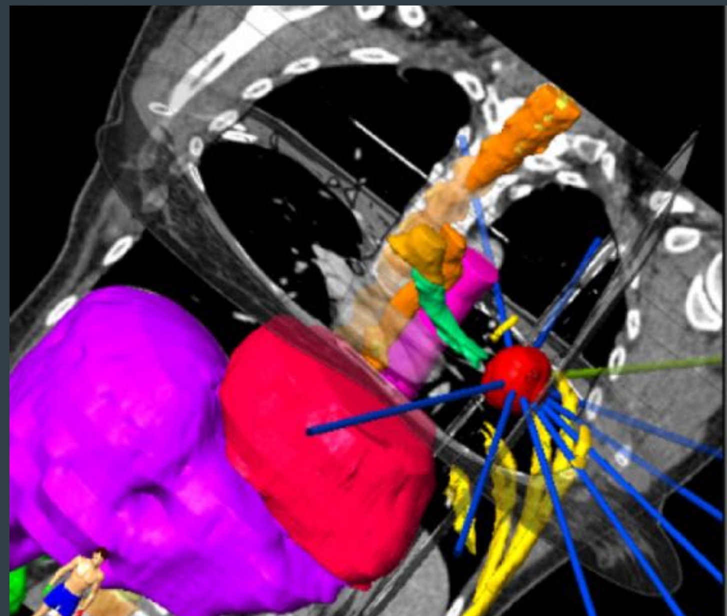
## Relatore: Mauro Iori

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(No)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(BAYER)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(ELCO, GE Healthcare, Theraclion)**
- Partecipazione ad Advisory Board **(No)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(Sordina IORT Technologies)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(No)**

# Stereotactic body radiotherapy

- SBRT refers to the precise irradiation of extracranial lesions, defined with multimodal (or multilevel) imaging, by using a small number (≤ 5) of high-dose fractions.
- Patient eligibility is limited to tumours with a maximum cross-sectional diameter of up to 5 - 7cm.
- Imaging simulation with patient in treatment position should allow non-coplanar treatments (target ± 15cm), use small slices (1-3mm) and consider any motion effect.



Rubio C, RPOR 2013

- The steep plan dose fallout outside the target volume needs a precise delineation of the target and patient anatomy, thing which involves an accurate registration and fusion of different multimodal images.
- The most appropriate imaging modalities, for a given clinical situation, are driven by the characteristic of the tissues being imaged.

# Some limitations

- If target & radiosensitive critical structures cannot be localised on a sectional imaging modality with sufficient accuracy, SBRT should not be pursued as a treatment option. (TG101, Benedict SH, MP 2010)
- In this regard, imaging limitations may arise from:
  - the poor resolution and/or accuracy of the different imaging modalities;
  - the limits of the algorithms used to integrate the multilevel information;
  - the presence of artifacts in the images (respiration, metal implants, etc.).
- Since doses in SBRT are different from conventional radiotherapy, early and late reactions can also be very different.
- Radiological evaluation (RECIST) can be difficult: misinterpretation of some lesions in case of liver tumours that become necrotic after SBRT, or lung condensation that mimic a recurrence for increases of size. Molecular Imaging can be useful to provide support, but initial inflammatory reactions caused by high doses could be responsible for false-positive results.
- The optimal supervision after SBRT is not generally known, and follow-up must be carried out by radiologists & NM physicians who are accustomed to SBRT post-therapeutic aspects.

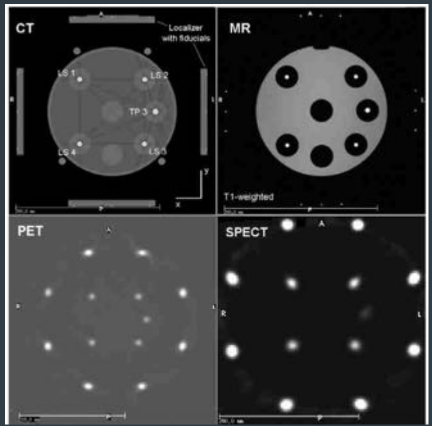
Goffrey DH, ZMP 2012

Rubio C, RPOR 2013

# Accuracy for localisation

## ❑ ACCURACY OF SRS - LOCALISATION

C.P. Karger, PMB 2003




| Deviation (mean ± standard deviation) | |
|---|---|
| Modality | $\Delta r^a$ (mm) |
| **CT** | |
| Points ($n = 5$) | 0.4 ± 0.2 |
| Tubes ($n = 72$) | 0.3 ± 0.2 |
| Maximum | |
| **MRI** | |
| Siemens Magnetom Vision plus | |
| T1-weighted | |
| Points ($n = 5$) | 1.0 ± 0.4 |
| Tubes ($n = 64$) | 0.7 ± 0.3 |
| Maximum | |
| T2-weighted | |
| Points ($n = 5$) | 0.7 ± 0.2 |
| Tubes ($n = 64$) | 0.6 ± 0.3 |
| Maximum | |
| Siemens Magnetom Symphony | |
| T1-weighted | |
| Points ($n = 5$) | 1.4 ± 0.3 |
| Tubes ($n = 68$) | 0.8 ± 0.3 |
| Maximum | |
| T2-weighted | |
| Points ($n = 5$) | 1.4 ± 0.5 |
| Tubes ($n = 68$) | 0.6 ± 0.3 |
| Maximum | |
| **PET** | |
| Siemens/CTI ECAT EXACT HR+ | |
| Points ($n = 5$) | 1.1 ± 0.5 |
| Tubes ($n = 84$) | 0.5 ± 0.2 |
| Maximum | |
| Siemens/CTI ECAT EXACT 47 | |
| Points ($n = 5$) | 2.4 ± 0.3 |
| Tubes ($n = 52$) | 0.6 ± 0.3 |
| Maximum | |
| **SPECT** | |
| Siemens MULTISPECT 3 | |
| Points ($n = 5$) | 1.6 ± 0.5 |
| Tubes ($n = 76$) | 1.2 ± 0.6 |
| Maximum | |
| Siemens MULTISPECT 2 | |
| Points ($n = 5$) | 2.0 ± 0.6 |
| Tubes ($n = 44$) | 1.8 ± 0.7 |
| Maximum | |

Accuracy of localisation for each modality has been tested to check if images reflect the real geometry of the patient.

Results are < of physical resolution for CT, SPECT, PET, while are ≅ for MRI.

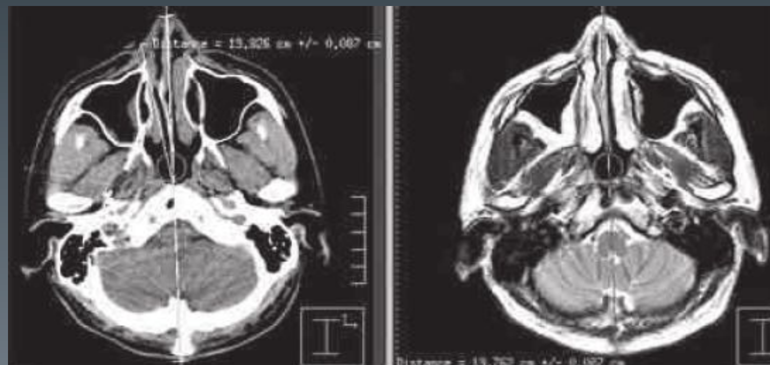
Localisation accuracy is system dependent and needs to be quantified.

## ❑ RIGID REGISTRATION

Accuracy and efficiency of 3 algorithms (mark-and-link, interactive, mutual information) were tested using CT and MRI data of 12 nasopharyngeal carcinoma.

However, no statistical difference was found between the mean registration errors: 0.68mm (LR, left-right), 1.04mm (AP, anterior-posterior), 0.58mm (SI, superior-inferior).

The time for the 3 algorithms was different: 6.25min, 5.25min, 5.15min, respectively.



Wang XS, JACMP 2009

# Registration algorithms

## ❑ Deformable Registration Algorithms

Accuracy & reproducibility of 37 different (DIR) algorithms were assessed on: i) lung 4D-CT, ii) liver 4D-CT, iii) liver MRI-CT, iv) prostate MRI.

The ranges of average absolute errors were:

i) 0.6–1.2 mm [LR], 0.5–1.8 mm [AP], 0.7–2.0 mm [SI];

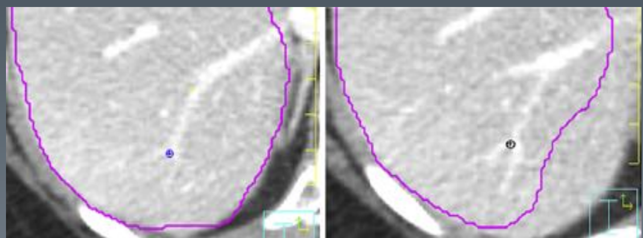
ii) 0.8–1.5 mm (LR), 1.0–5.2 mm (AP), and 1.0–5.9 mm (SI);

iii) 1.1–2.6 mm (LR), 2.0–5.0 mm (AP), and 2.2–2.6 mm (SI);

iv) 0.5–6.2 mm (LR), 3.1–3.7 mm (AP), and 0.4–2.0 mm (SI)

Large discrepancies are reported, but the majority of DIR algorithms reached the success to perform at an accuracy equivalent to the voxel size.

Brock KK, IJROBP 2010

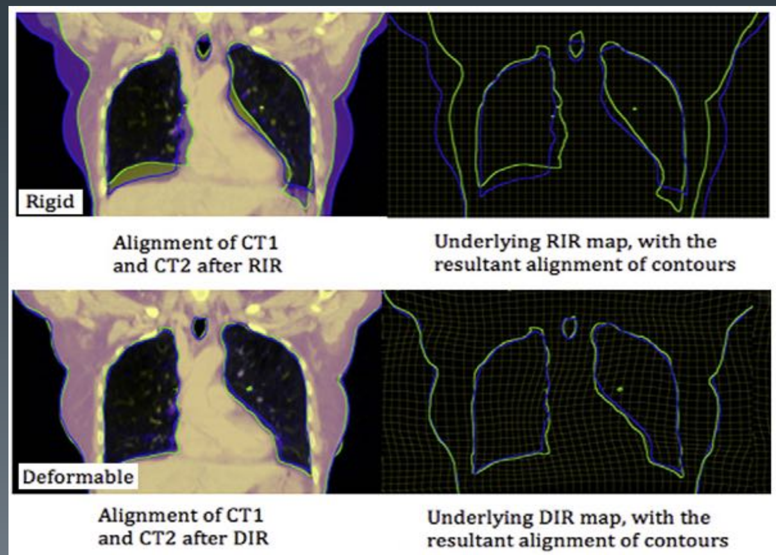


## ❑ Rigid vs. Deformable Registration

Mean spatial difference in dose registration between Rigid (RIR) and Deformable (DIR) image registration was 7mm (2-32mm, 10 patients).

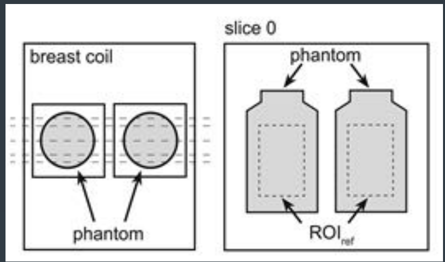
Overall, DIR improves the accuracy with which initial treatments are accounted for compared to RIR by 3mm.

Using DIR will improve the quality of correlative toxicity data, and may reduce toxicity for selected patients undergoing re-irradiation.




Senthi S, RO 2013

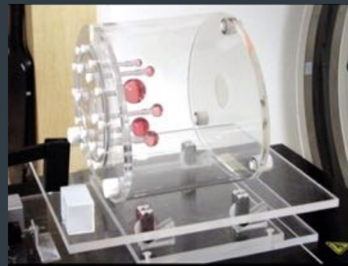
# Scanner-related factors affect quantitative imaging

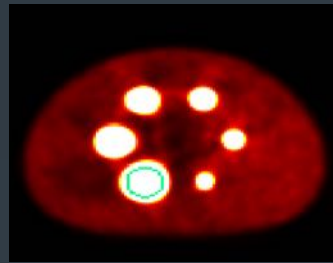



**Doped phantom**

Phantom on three MR (1,5T, DW-MRI) acquired with breast multi-channel coil.

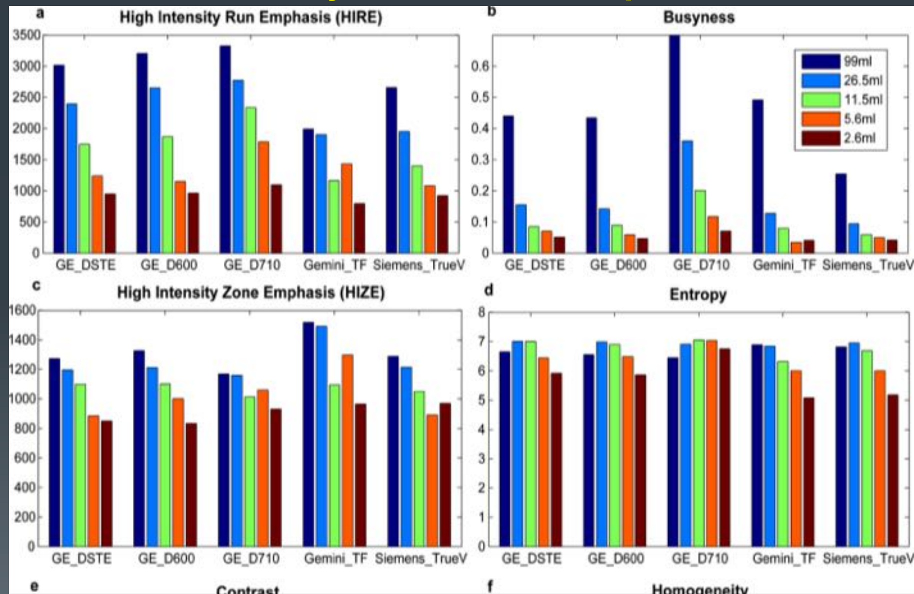
**NEMA IEC phantom (FDG-PET)**



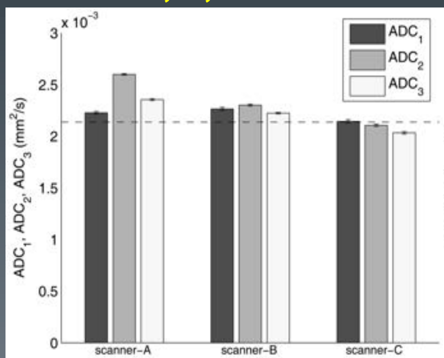


- ❑ Apparent Diffusion Coefficient and Mean Diffusivity values were not appreciably different from each other but vary substantially across MR scanners.
- ❑ MR scanner system-related factors can substantially affect quantitative diffusion-MRI of the breast. QA programs for assessing and monitoring the performance of MRI systems for diffusion-MRI is recommended, especially in multi-center trial.

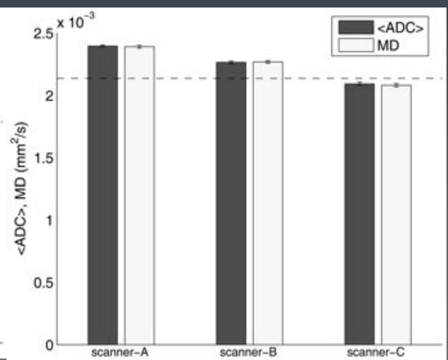
**Features variability with different sphere volume**




**ADC in X, Y, Z directions**




**ADC & MD mean values**




Giannelli M, PO 2014

- ❑ Radiomics parameters help to stratify patient in order to better personalise a therapy but depends by imaging systems and algorithms.

Feliciani G, submiitted.2015

# Motion artifacs & Sensitivity-specificity

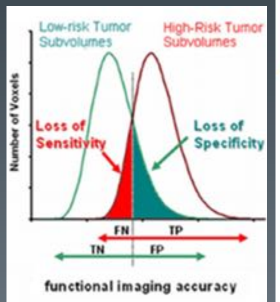
- ❑ Since targets and critical structures, located in the thorax and abdomen, move during the respiratory cycle, special imaging techniques are required to quantify these movements.
- ❑ Importance of couching patients with audio (frequency stability) & visual feedback (amplitude).

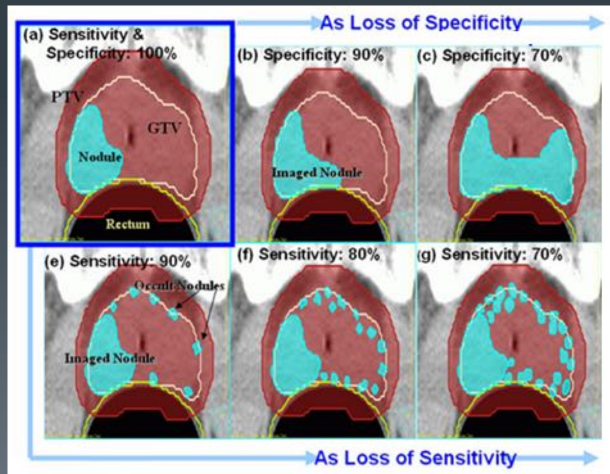
| Type | Advantages | Disadvantage |
|---|---|---|
| CT slow | ability to capture tu motion | • motion artifacts· blurring of images<br>• loss of resolution<br>• errors in delineation |
| CT at extreme phases of respiratory cycle | • theoretically – captures the entire range of motion<br>• lower workload | • unreliable for small tumors with wide range of motion |
| **4DCT – gold standard** [especially for small moving lesion] | • captures respiratory motion over few respiratory cycles<br>• inform about shape and mobility synchronously acquired | • does not take into account the daily variation breathing pattern<br>• requires regular breathing /ability to be coached |
| Breath-hold | • smallest GTV<br>• lung protection (DIBH) | • patient compliance |

Moorrees J, APESM 2012

- ❑ It is important to know the sensitivity & specificity of imaging modalities used for localisation & delineation of tumour and how their addition can affects planning.
- ❑ These inaccuracies are part of the safety margin together with setup uncertainties, machine tolerances and intra-treatment variation (margins of 2-5mm surrounding enhancing tumour for primary disease).

**Targets for high (TP) & low risk (TN)**



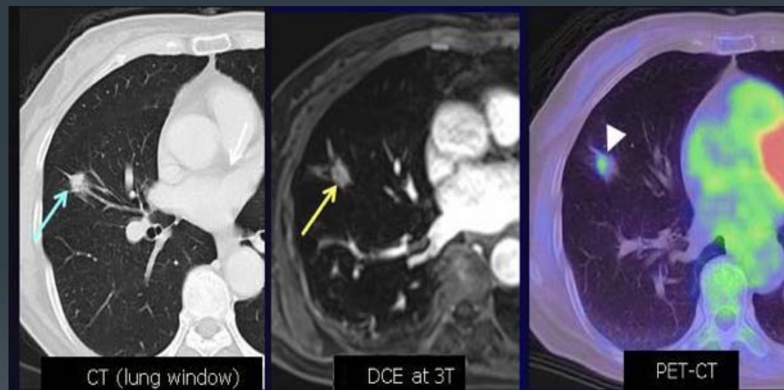

Kim Y, PM 2009

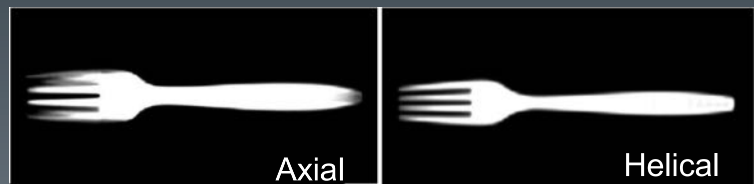
# Computed Tomography

- ❑ CT imaging is the primary imaging modality for SBRT.
- ❑ CT has a high spatial resolution and good reproducibility, does not suffer from geometric distortion, provides intrinsic information on the electronic density of various tissues and forms the basis for many treatment planning calculations.
- ❑ CT allows clear definition of tumours that border air-filled cavities, fat tissue, or bone, However, CT lack contrast resolution for differentiation between normal soft tissue structures and tumour extent
- ❑ CT is helpful in identifying pulmonary nodules (>2mm), parenchymal diseases, and chest wall involvement for superior sulcus tumours and lung disease. Suspicious and typification for ≥ 8mm.
- ❑ Large bore CT in axial & spiral modes has to be verified.

Jaffray DA, SRO 2014

**Lung tumours**



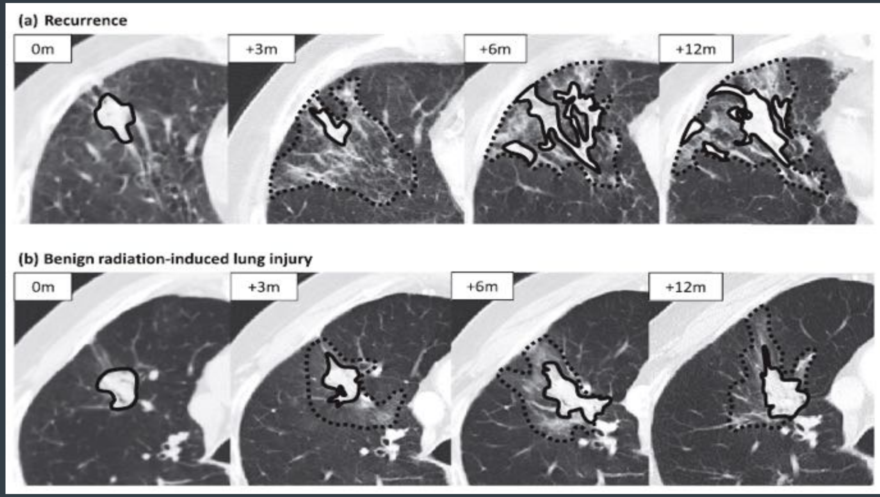

4D-CT large bore: check of longitudinal resolution with a plastic fork placed 20 cm from CT isocenter.

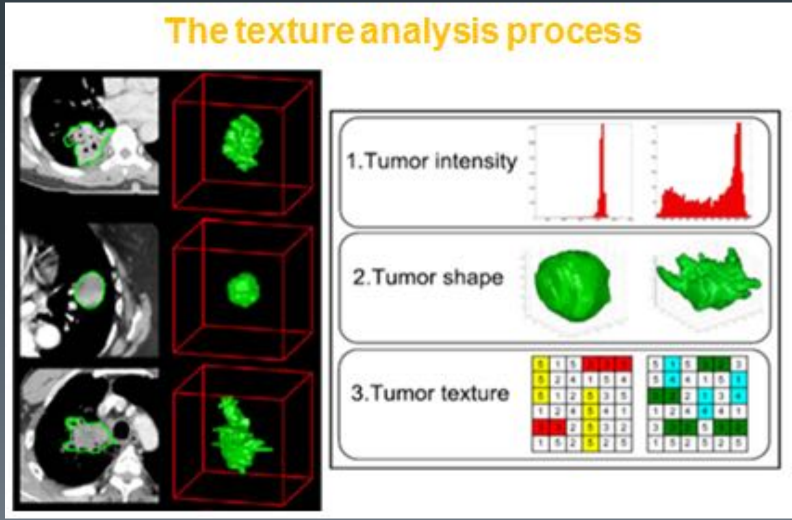
Klahr P, MP 2014

# CT and Texture metrics

- CT density changes due to radiation induced lung injury are common after SABR and can be difficult to differentiate from tumour recurrence. This may also lead to the definition of risk groups for radiation-induce lung damage.
- Texture measures of the GGO (ground-glass opacity) appearance post-SABR demonstrated the ability to predict recurrence in individual patients within 5 months of SABR treatment, compared to 12 months with RECIST criteria on consolidative regions.

Consolidative and ground-glass opacity findings throughout follow-up: solid lines (consolidative regions), dashed lines (ground-glass opacity regions).

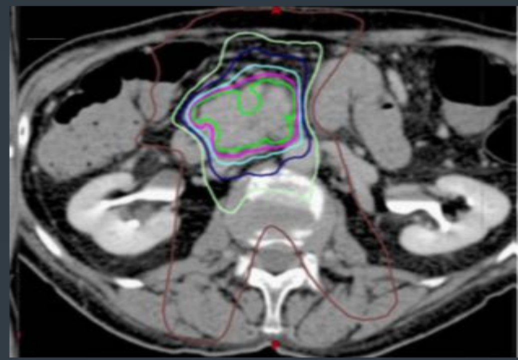


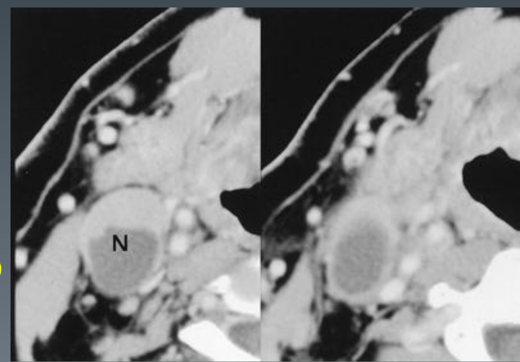

Sarah AM, MP 2014

# Dynamic Contrast-Enhanced CT

- A bolus is used to characterise the vascular properties within the body. Parameters like blood flow (BF), blood volume (BV), capillary permeability and leakage can be measured.
- DCE-CT extracted data correlates with prognosis and histological subtype of NSCLC.
- It aids in target definition (tumour micro-vascularity) but suffers for inter/intra-observer differences in manual contouring for the large inter/intra-patient data variability.
- Quantitative perfusion metrics can be extracted and investigated to predict also radiation-induced normal tissue damage.


Pancreatic tumour


Liver tumour

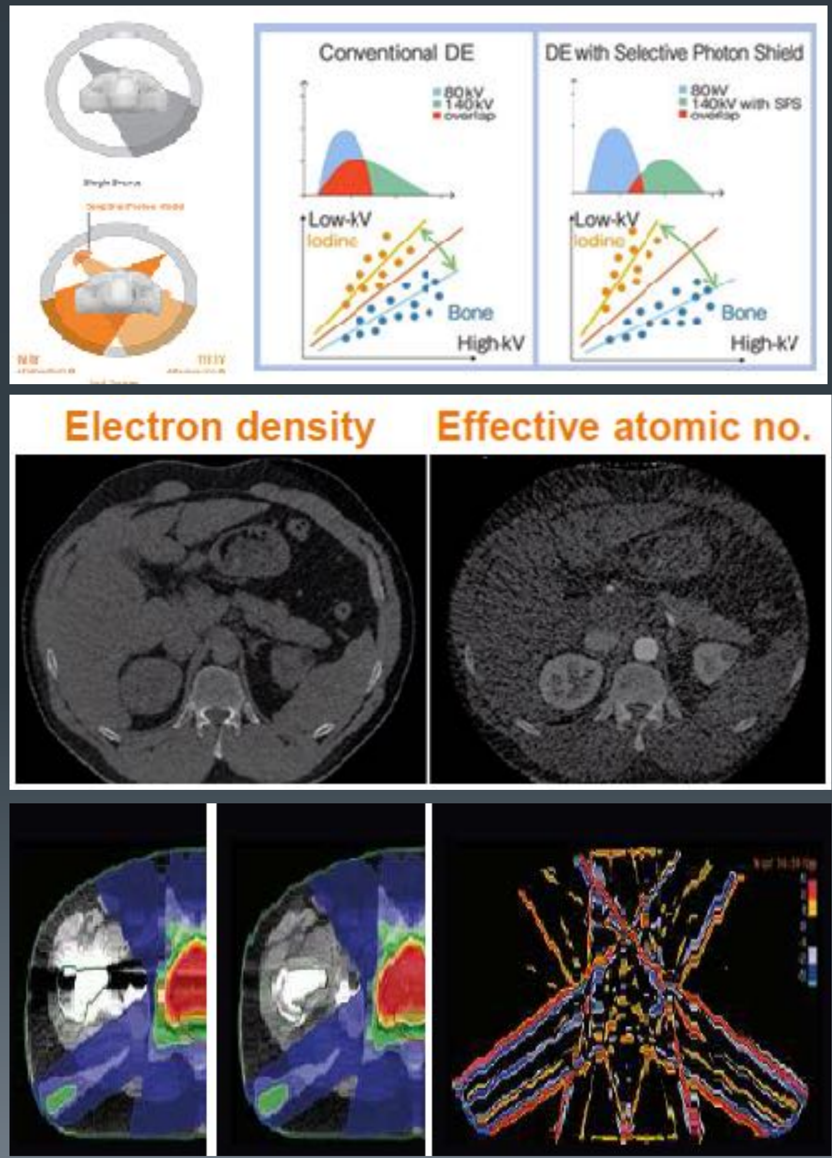


Tongue carcinoma

Cao Y, SRO 2011

# Dual-Energy CT: plan advantage

- DECT can acquire two datasets (80/140KV) and the resulting scans can be used for tissue characterisation (morphologic - functional data).
- Using a material decomposition analysis, raw data may be manipulated to generate virtual monochromatic (VMC) and virtual unenhanced (VUE) images, material-specific & iodine maps.
- Beam-hardening artefacts can be reduced.
- Better defining the tissue and electron density, more consistent attenuation data are reached and more accurate plan dose- distributions can be calculated.
- Single- and dual-source DECT are different for FOV & material decomposition (water, iodine vs. soft tissue, fat, iodine).

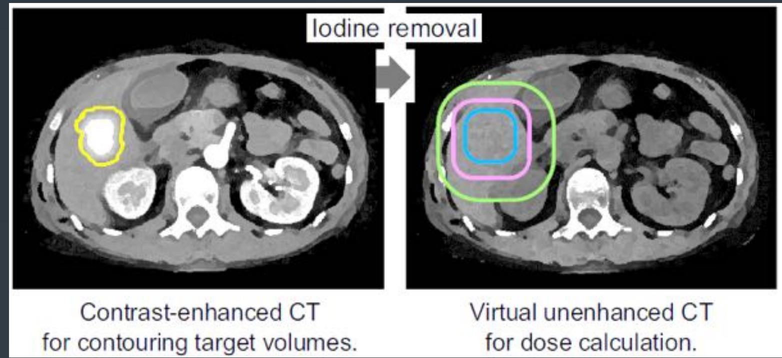



Courtesy of Siemens

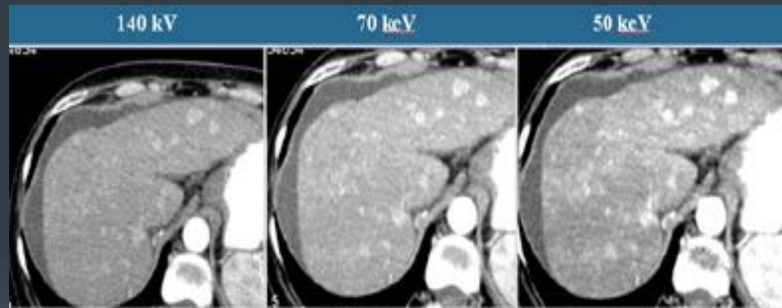
# DE-CT: imaging advantage

- Different material can be distinguished (tissue from iodine and calcium can be discriminated), different contrast agents can be used, the non-contrast-enhanced scans are no more necessary with less doses for the patient (planning and follow-up).
- Low-energy increase the images contrast and superior delineation of tumour boundaries is possible.
- Iodine mapping can help to differentiate between benign and malign nodules.
- Assuming that SBRT can alter the iodine map perfusion in the lung, it seems possible to assess the treatment effects.
- Iodine maps could be used as biomarker for tumour angiogenesis (correlation with local blood volume & vascular density in tissue).

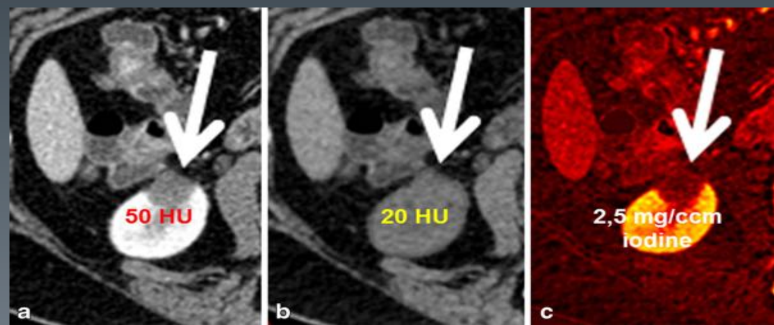
**Virtual CT - Iodine removal**




**Hepatocellular carcinoma lesions**



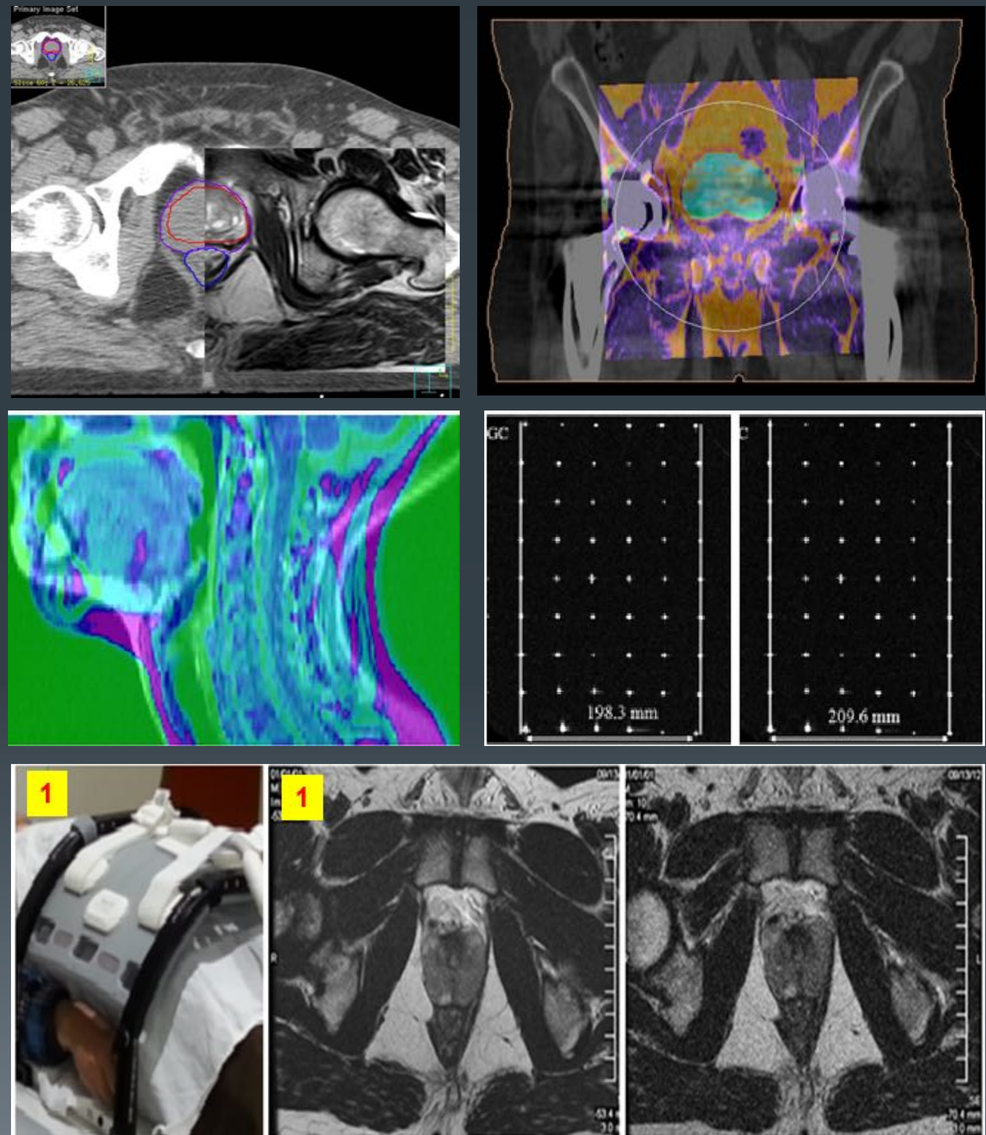

**Mixed, Virtual and Iodine uptake images**




Simons D, ER 2014

# Magnetic Resonance Imaging

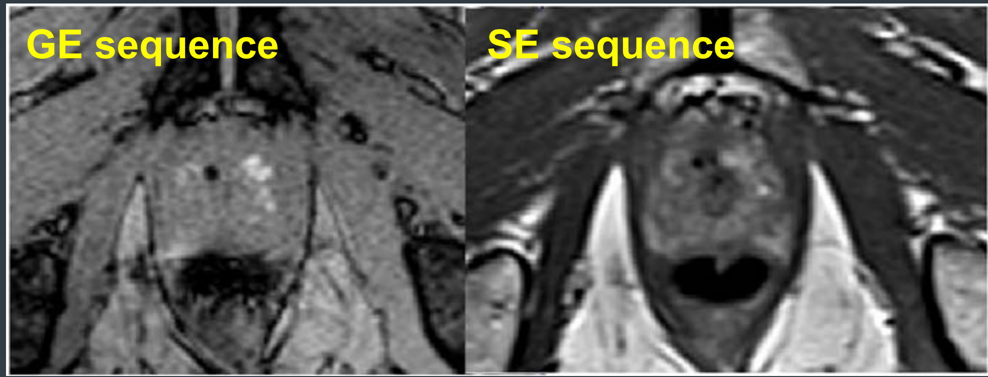
- MR imaging for target and normal tissue delineation are considered best practice in SBRT for many sites: prostate, spinal tumour, chest, solid abdominal tumour.
- MRI simulators are certainly beneficial but even existing systems with simple modifications can be profitably used.
- Aspects to be considered :
  - ✓ Higher field (3T) is beneficial for imaging, dielectric artefacts can be reduced by multiple-transmitters.
  - ✓ Geometric distortion (system and patient-related) can be minimised with appropriate sequences & tricks.
  - ✓ Image Acquisition (patient setup, RF coil, Scan protocol, FOV selection)
  - ✓ Quality Assurance (distortions, etc..)



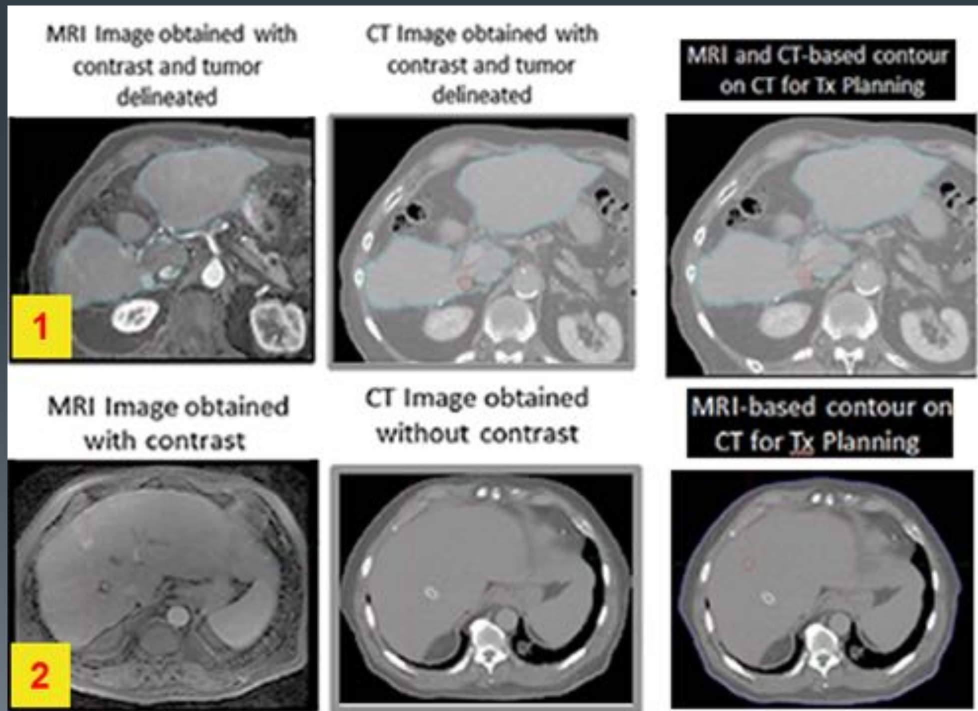

Liney GP, SRO 2014

# Scan protocols & CT/MR fusion

- MRI offers a wide variety of contrast weightings and sequences broadly classified in Spin-Echo (gold standard in terms of intensity distortion - more precise) & Gradient-Eco (faster but more liable to signal dephasing - artifacts).
- Variations in sequences (DWI acquired with GE sequences) produce variability in tumour delineation.
- Integration of MRI into CT needs different approaches, depending on the visibility (1), or not (2), of the structures to define on both dataset. In particular, to properly account for uncertainties requires: commissioned registration algorithm, clear clinical directives and plans for structure definition.



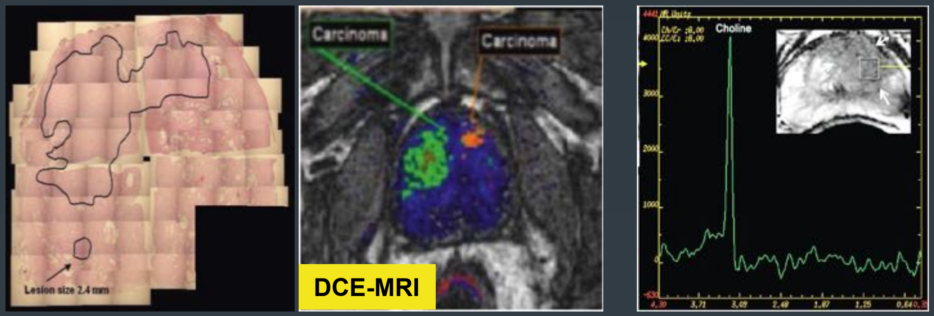

**Multimodality-based tumor definition**




Block KK, SRO 2014

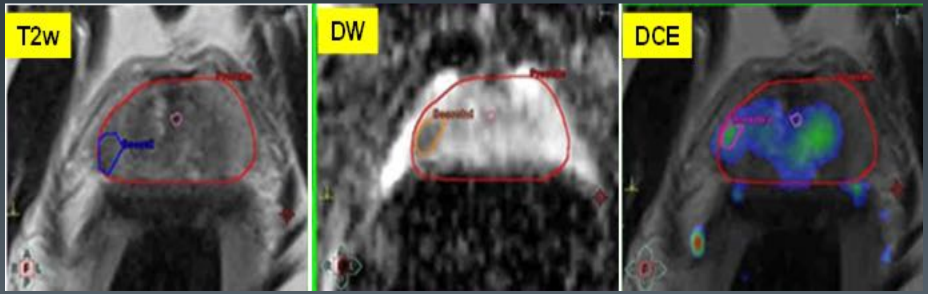
# MRI & Multiparametric imaging

- Dynamic Contrast Enhanced MRI characterises vascular properties in tumor & normal tissue (monitoring of SBRT effects).
- Diffusion weighted MRI assess the diffusion capacity of tissue and lower ADC is an index of increased cellular density in tumour.
- MR spectroscopy is an in situ method of determining the relative concentration and spatial distribution of metabolites of interest.
- BOLD MRI indirectly measures the oxygenation of the blood (hypoxia).
- DCE-MRI & MRS underestimates histologic volume in prostate.
- Multiparametric MRI plus CAD for detection of prostate cancer in the peripheral zone have shown to reach better results.




DCE-MRI & DWI underestimate the GTV pathologically determined, a margin of 5mm was suggested to improve the coverage.

Cao Y, SRO 2011

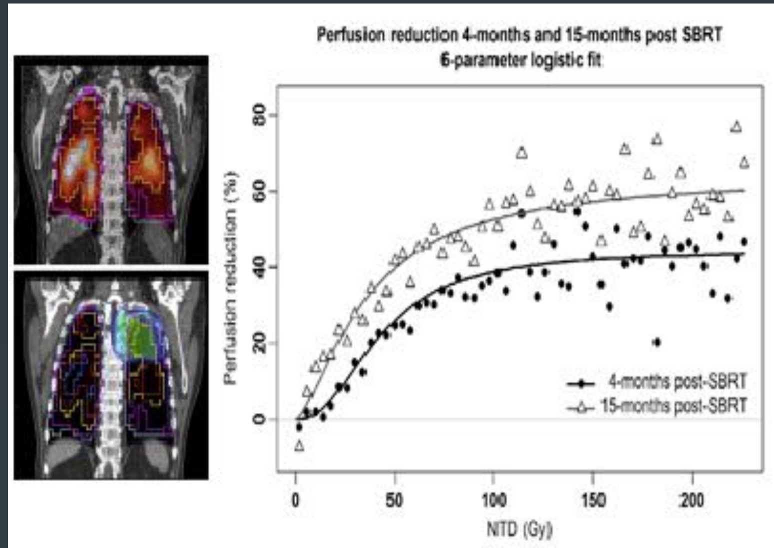



Multiparametric MRI (T2w [low intensity], DW [low ADC] and DCE [high $K_{TRANS}$]), defined $CTV_{DIL}$ combining DIL volumes.

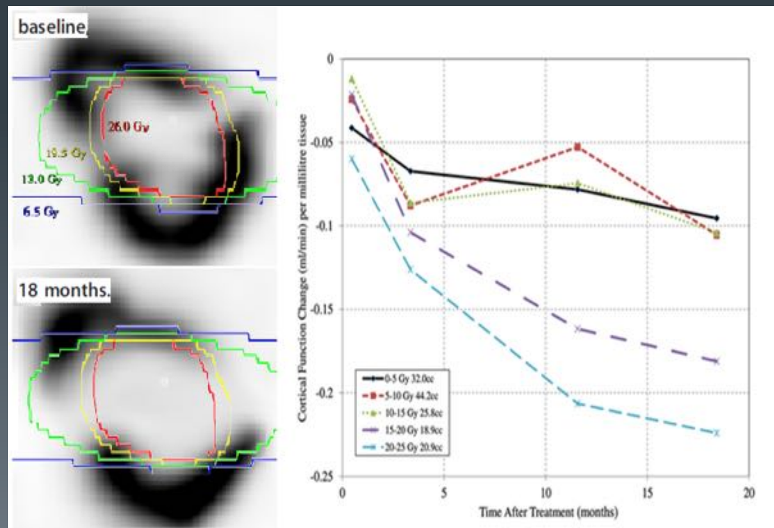
Murray LJ, IJROBP 2014

# SPECT/CT

- SPECT can probe two or more molecular pathways simultaneously by dual-isotope/dual-energy imaging, thus, different organs or functions can be monitored simultaneously (early assay of radiation response of tumour and normal tissue, pre and post treatment lung function, cardiac functionality, etc..).
- Lung toxicity is a dose limiting factor in escalating the dose to lung tumours. Perfusion alteration ($^{99m}$Tc-LyoMAA) are seen after SBRT (54Gy/3fr). Knowing the regional sensitivity and functionality may guide to generate the lowest impact treatment plan.
- The pattern of renal functional change in $^{99m}$Tc-DSMA uptake correlates with dose delivered (26Gy/1fr): function loss occurs primarily to regions (voxels) receiving a dose > 13Gy.




AEH Scheenstra, RO 2013

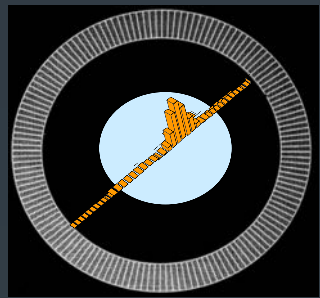



P Jackson, RO 2014

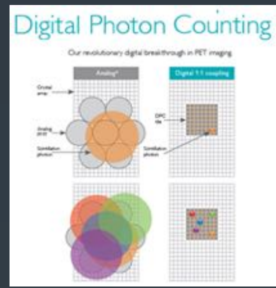
# PET/CT

- ❑ PET greatly enhance the specificity and sensitivity in diagnosis & staging compared to CT
- ❑ By exploiting increased uptake and accumulation of FDG in metabolic active cells, is used to identify smaller tumour deposit & to differentiate radiation necrosis from tumour recurrence (for lung, H&N, colon, liver, melanoma, lymphoma and ovarian cancer).
- ❑ The limitation of its spatial resolution makes PET more useful for the identification of site of active disease rather than for the precise tumour delineation.
- ❑ There was no single optimal threshold for all lesions: i.e. in lung, from 15% for large (>5cm) up to 42% for small tumours (<3cm), in H&N $GTV_{PET} < GTV_{CT}$ (75%).
- ❑ Unlike CT, PET images takes several minutes: new PET scanners are much faster and with higher sensitivity.

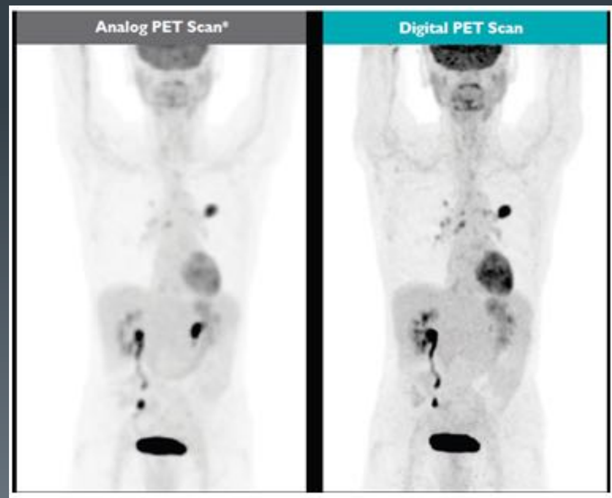
Time of Flight (timing resolution)



New digital silicon photomultiplier




**Sensitivity gain up to 2x greater**




Courtesy of Philips

# PET/CT specificity for SBRT

- **Lung tumour:**

differentiate atelectasis/fibrosis from disease and modify RT plans (smaller treatment volumes & reduced morbidity).

Pre-SBRT PET is not predictive of tumor response or clinical outcome.

Nearly all patient with local failure after SBRT have an increase in PET avidity (but hypermetabolic activity may persist for years without evidence of treatment failure).

SUV reduction is correlated with local control (but stabilization of increase after 3 months may confirm a local failure).

Appropriate window for imaging appears to be 2-3 months after SBRT (although changes may be seen as early as 4 weeks).

- **H&N cancer**

Early data suggest that PET is predictive of control after SBRT (early detection of failure may provide opportunity for intervention).

SUV reduction after 1-2 months may indicate long-term outcome.

- **Pancreatic cancer**

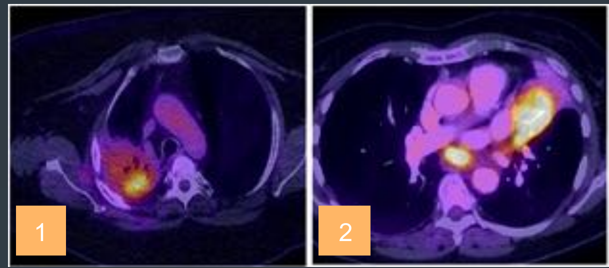
PET/CT appears to be a more effective method to evaluate tumour response than CT alone.

Trend between greater pre-SBRT SUV & reduced overall survival.

- **Liver cancer**

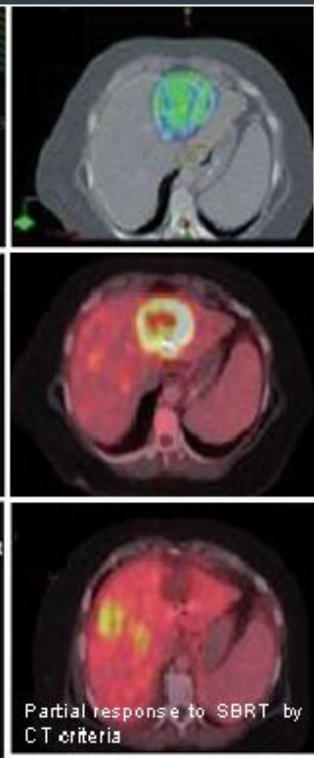
4D PET/CT imaging can help to more accurately deliver SBRT.

NSCLC with fibrosis (1 - recurrence after chemotherapy plus radiation) and atelectasis (2)




Nasopharyngeal carcinoma PET/CT


Liver metastasis 4D-PET/CT single frame

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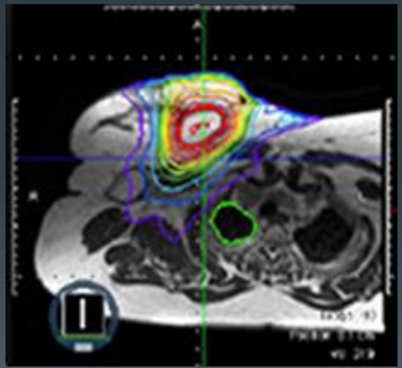
# What next ?

## MRI-guided RT system (View Ray)

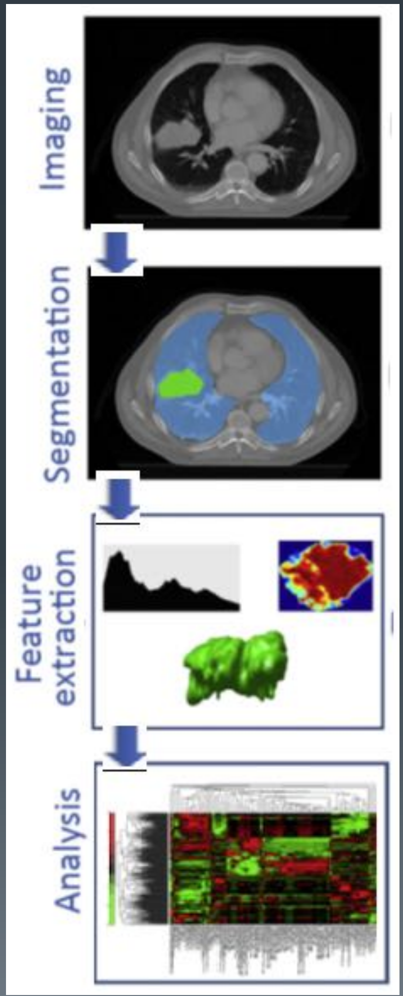


- On-line fast planar image with MR are performed to check the treatment

## Quantitative imaging (QI) & harmonisation

- The integration of accurate image signals with geometric integrity is in the design and directions of SBRT.
- QI requires new strategies based on recommendations and procedure guideline.
- International research networks are working on it (EARL, QIN, RIDER, NIST)

## PACS systems with Radiomic techniques




## Dose painting

- Individualising the treatment by using imaging information (focal hypoxia markers) to define the resistant part of the tumour.
- These areas can than be treated following the dose-painting idea & adapting the doses based either on reducing side-effects or increasing the chance of local tumour control (recurrent H&N, NSCLC)..

# Thanksgivings

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*Thank you for your attention*

*& …*

*we look forward to see you at …*