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ESTRO Course Book

ESTRO/ESMIT Course on

Molecular Imaging and Radiation Oncology

10 - 13 April, 2017
Bordeaux, France

NOTE TO THE PARTICIPANTS

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Faculty

Ursula Nestle & Wouter Vogel

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Imaging in Radiation Oncology

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Kliniken Maria Hilf, Mönchengladbach
and Universitätsklinikum Freiburg, Germany

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Medical imaging in radiation oncology

- Imaging for diagnosis and staging:
  - treatment indication
- imaging for radiotherapy planning
  - target volumes
  - normal tissues
  - movements
- Imaging during RT application
  - repositioning
  - adaptive radiotherapy
  - normal tissue reactions
- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

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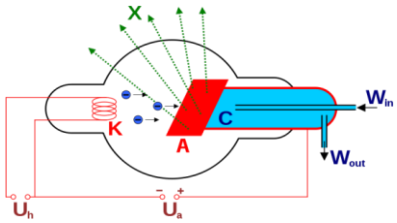
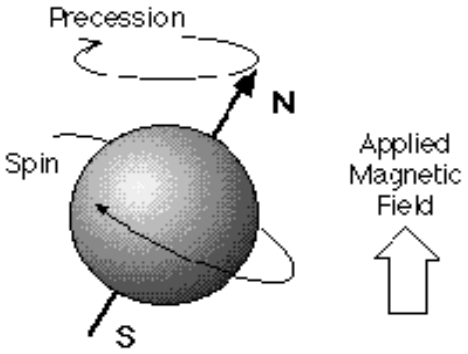
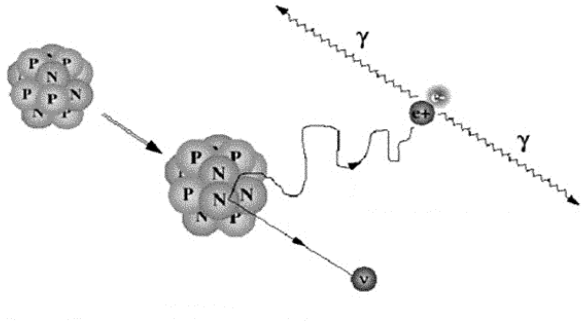
Types of medical imaging

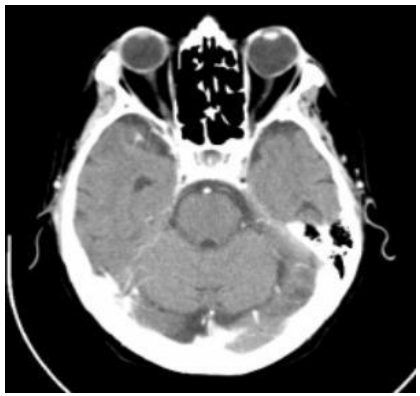
	Morphological imaging	**Functional or „molecular“ imaging**
Methods	CT, morph. MRI	PET, SPECT, MRS, DWI
imaged aspect	Morphology	Biological process
imaged detail	physical density magnetic properties	positron anihilation metabolism
example	(Pathologic) anatomy	Tumor metabolism Perfusion Organ function

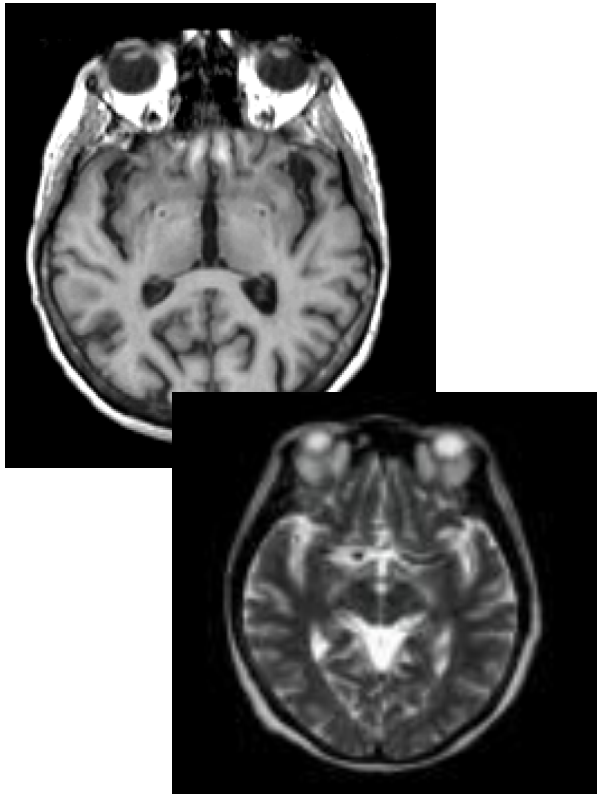
Types of medical imaging

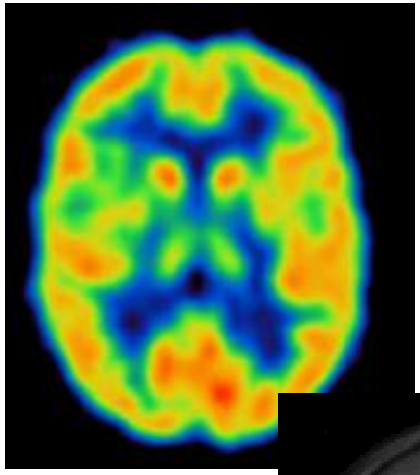


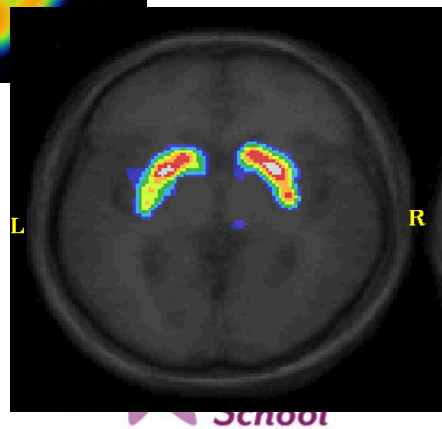






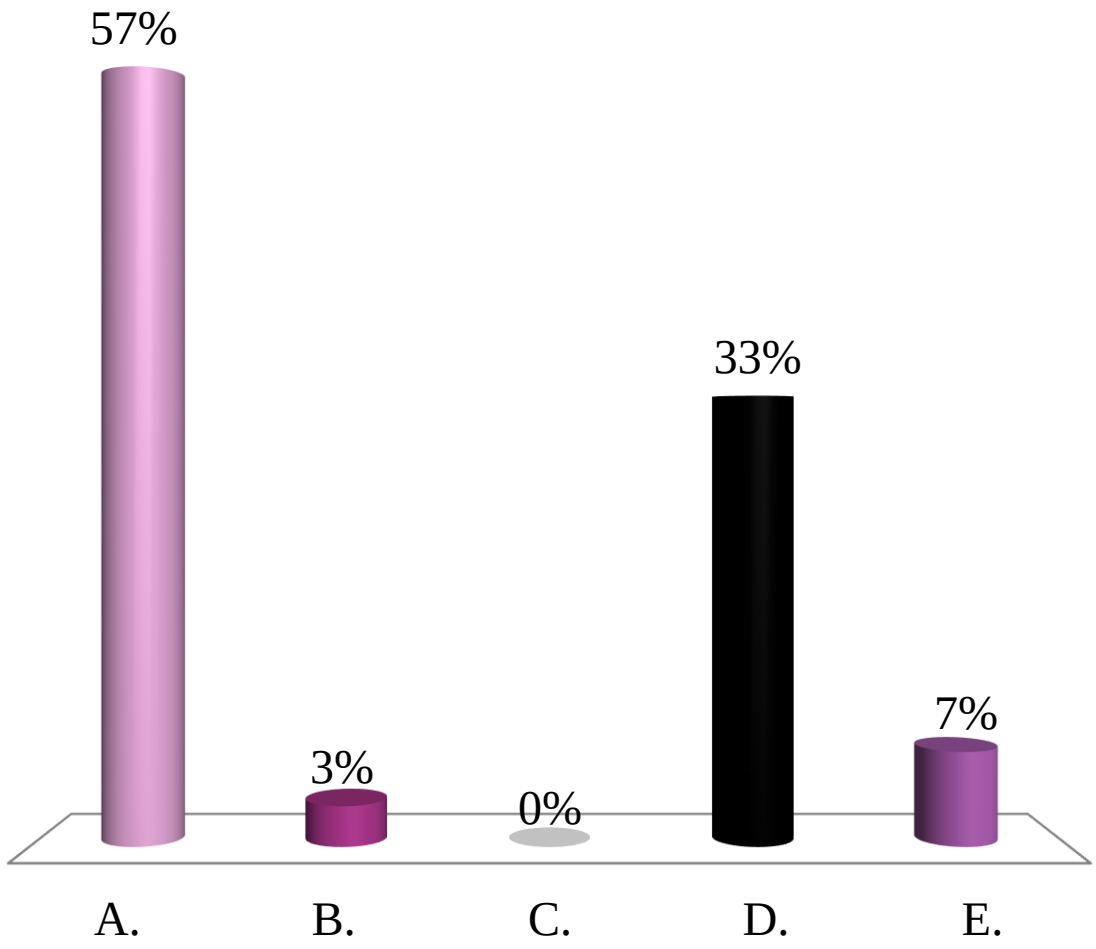






Are you involved with imaging in radiation oncology as:

A. radiation oncologist
B. physicist
C. RTT
D. nuclear medicine physician
E. radiologist



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Questions to medical images

diagnostic imaging:

What is this?

How sure can I give a diagnosis?

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Imaging literature, example PET

TABLE 2

FDG PET in Colorectal Cancer: Results of Literature Search

COLORECTAL CANCER	ARTICLE TYPE	PURPOSE	Total No. Patients	Total No. Studies	Total Lesions	Non-Ded PET	SENS PET (%)	SENS CT (%)	SPEC PET (%)	SPEC CT (%)	PPV PET (%)	PPV CT (%)	NPV PET (%)	NPV CT (%)	ACC PET (%)	ACC CT (%)	GOLD STD	MGMT(%) EFFECT
Diagnosis																		
No Articles																		
Staging																		
Arnthauer, 2000	A	management	49	49													biop/surg/follow-up	42
Oyen, 2000	A	management	48	48													histopath/follow-up	15
Seltzer, 2000[1]	A	management	53	53													follow-up	42
Meta, 2000[2]	A	management	51	51													clin follow-up	40
Baehre, 2000	A	dual head coincidence	18		24	yes	96										immunoscintigraphy	
Beets, 1994	RA	management	35	35													histol/serial radiol follow-up	40
	Summary		**254**	**236**														**36**
		by lesions			**24**		**96**											
Dx/Staging																		
Abdel-Nabi, 1998[3]	RA	dx prim	48	44			100		43		90		100		91		CT/surg/histopath	
		staging LN mets		14			29											
				33				29		85								
		staging liver mets		43			88	38	100	97	100	50	97	86	98	81		
	Summary	**by patients**	**48**	**134**			**85**	**34**	**71**	**92**	**95**	**50**	**99**	**86**	**94**	**81**		
Recurrence																		
Whiteford, 2000[4]	RA	susp met or recur colorectal adenocarc																
		overall	105	105			87	66	68	59							histopath/clin follow-up	26
		detecting mucinous cancer		16			58											
		detecting nonmucinous cancer		93			92											
		locoregional recurrence		70			90	71										
		hepatic metastasis		101			89	71										
		extrahepatic metastases		101			94	67										
Zhuang, 2000	A	hepatic	72	72			100	76									surg/clin follow-up	
Lang, 2000	A	whole body/overall	156	156			88	80									CT/MRI	24
		whole body/local recurrence					73	61										
		whole body/distant mets					93	92										
Baehre, 2000	A	dual head coincidence	18		24	yes	96										immunoscintigraphy	
Montravers, 2000[5]	A	dx/recurr	53		85	yes									71	48	post surg histol	
Schirrmeister, 2000[6]	A	recurr/mgmt	100	100			98	91	90	72							histopath/clin follow-up	61
Peterson, 2000[7]	A	resid/recurr/post local ablation to liver mets	7		9		89	44									serial CT/CEA/biopsy	
Gamez, 2000[8]	A	whole body	18	18			100										histol/clin follow-up	

Medical imaging in radiation oncology:

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  - target (GTV – CTV – PTV)
  - normal tissues
  - movements
- Imaging during RT application
  - repositioning
  - adaptive radiotherapy
  - normal tissue reactions
- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

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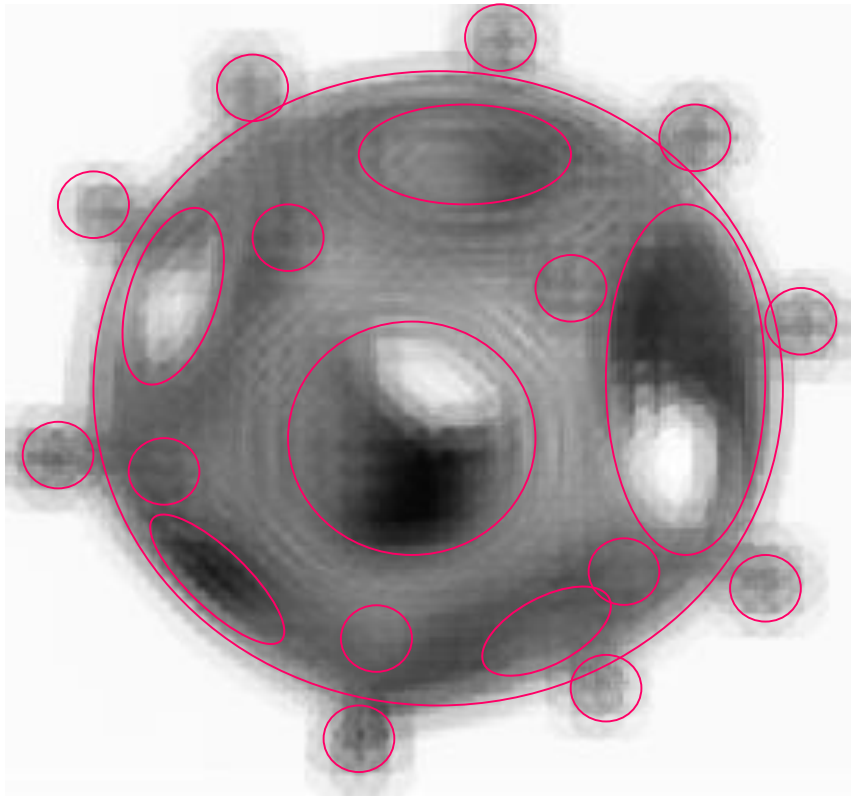
Questions to medical images



diagnostic imaging:

What is this?

treatment planning:

Where is this?
what exactly is around it?

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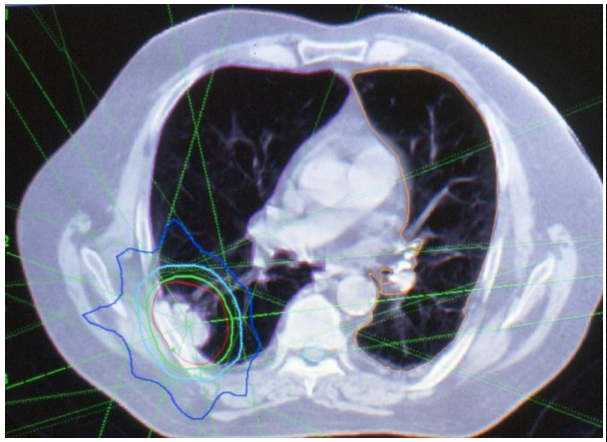
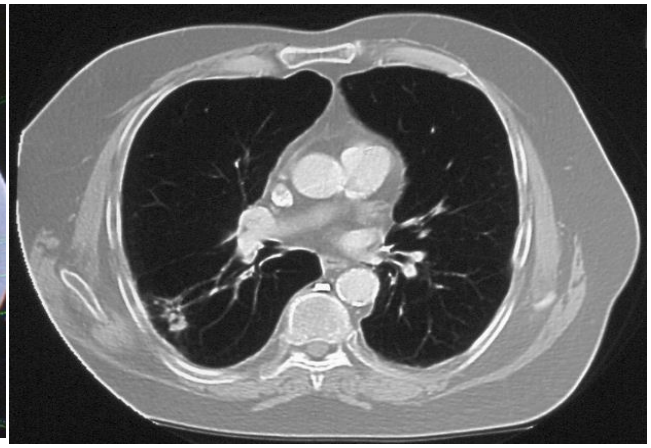
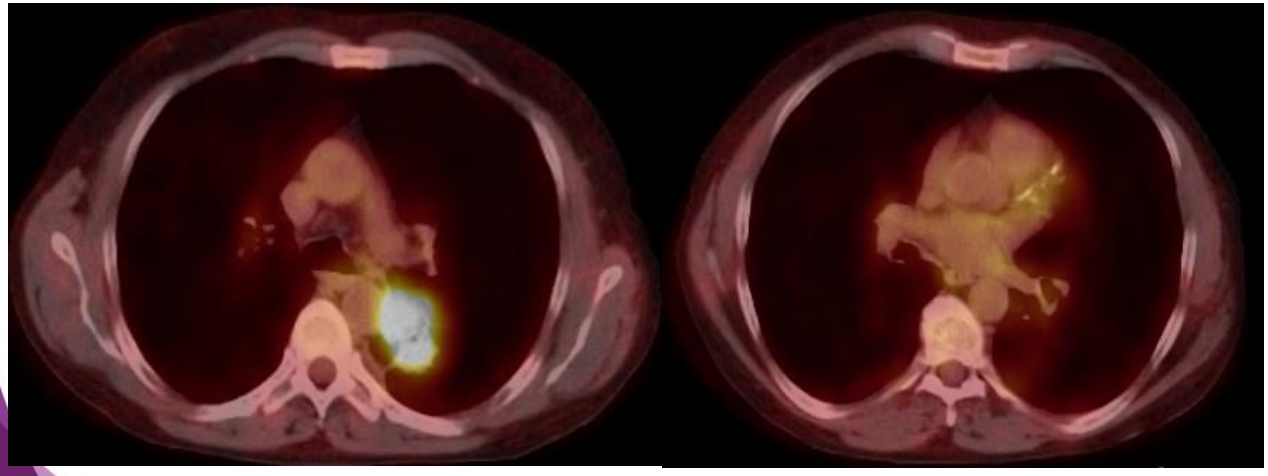
High precision radiotherapy for lung cancer



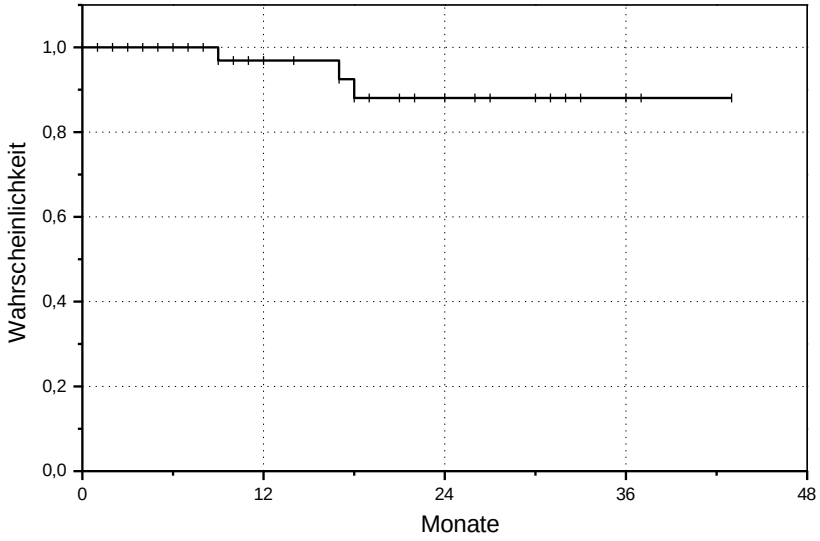


before RT treatment 1 year after RT



before RT treatment 1.5 year after RT

local tumor control



1 year	97 %
2 yrs	92 %
3 yrs	88 %

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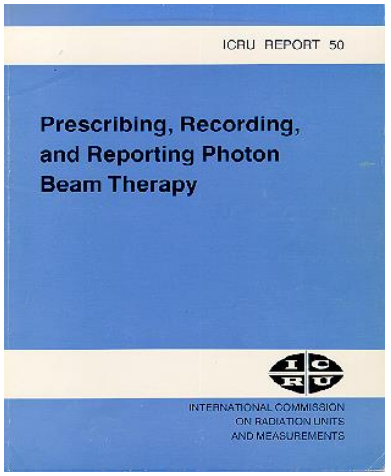
Radiation therapy treatment planning

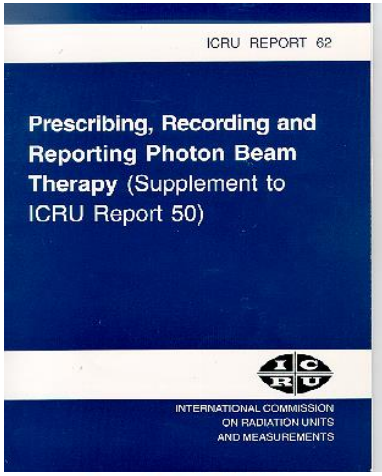
Main steps in the Radiation Treatment Planning process

1. Define treatment volumes / risk organs
2. Define optimal beam setup
3. Calculate dose distribution within the patient and treatment times per beam (Monitor Units)
4. Plan evaluation



Successful radiotherapy requires a uniform dose distribution within the target (tumor).

- ICRU 50/62 recommends target dose uniformity within +7% and -5% of the prescribed tumor dose



New

Bonus slide!

Radiation therapy treatment planning

Main steps in the Radiation Treatment Planning process

1. Define treatment volumes / risk organs
2. Define **constraints and objectives**
3. Calculate dose distribution by **IMRT optimiser**
4. Plan evaluation

Successful radiotherapy may require a **non-uniform** dose distribution within the target (tumor).

- Exploration of IMRT dose sub-distributions on the way
- Imaging main source of information for subvolumes

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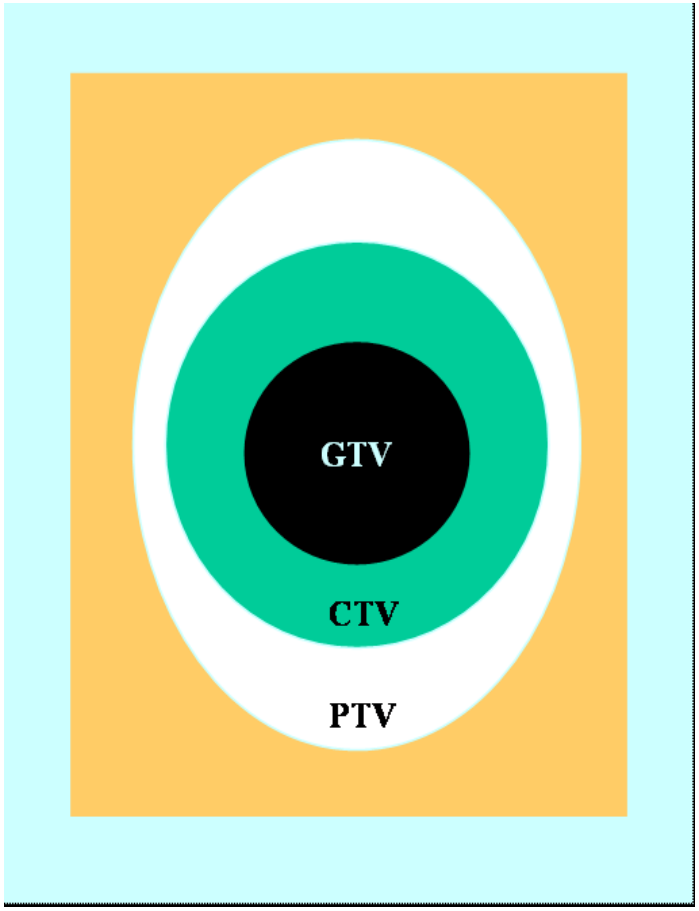
ICRU Target Volumes



- GTV
- CTV
- PTV

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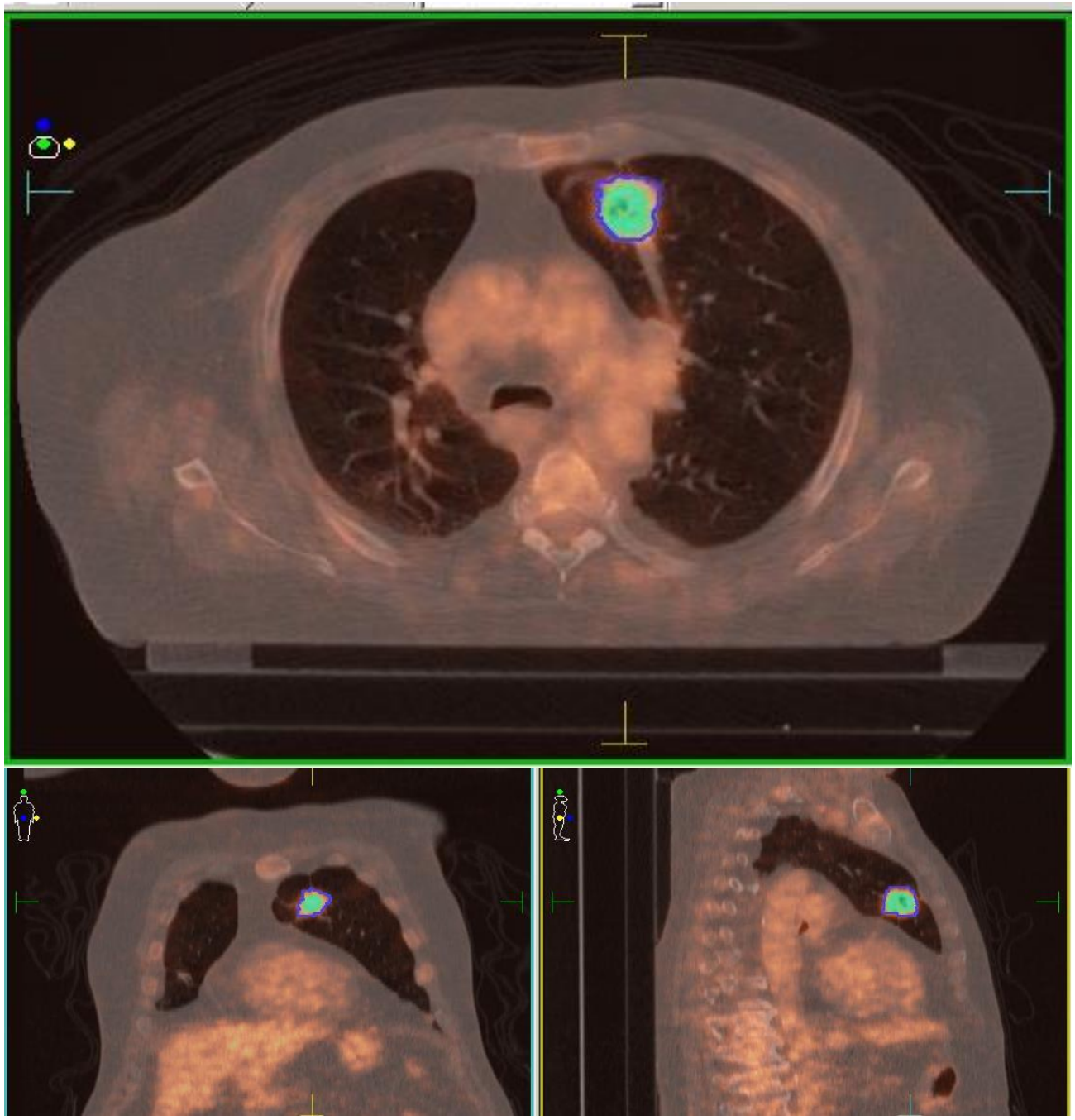
ICRU target volumes

GTV

„Gross Tumor Volume“

based on:

- Imaging
- other diagnostic information (pathology/histology)
- Clinical, endoscopic examination



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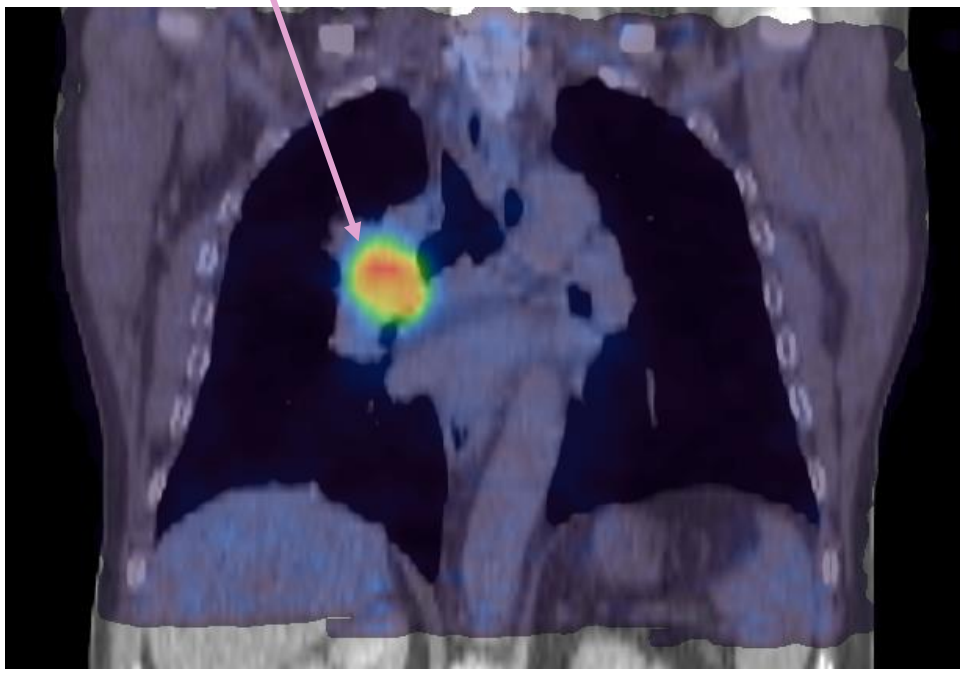
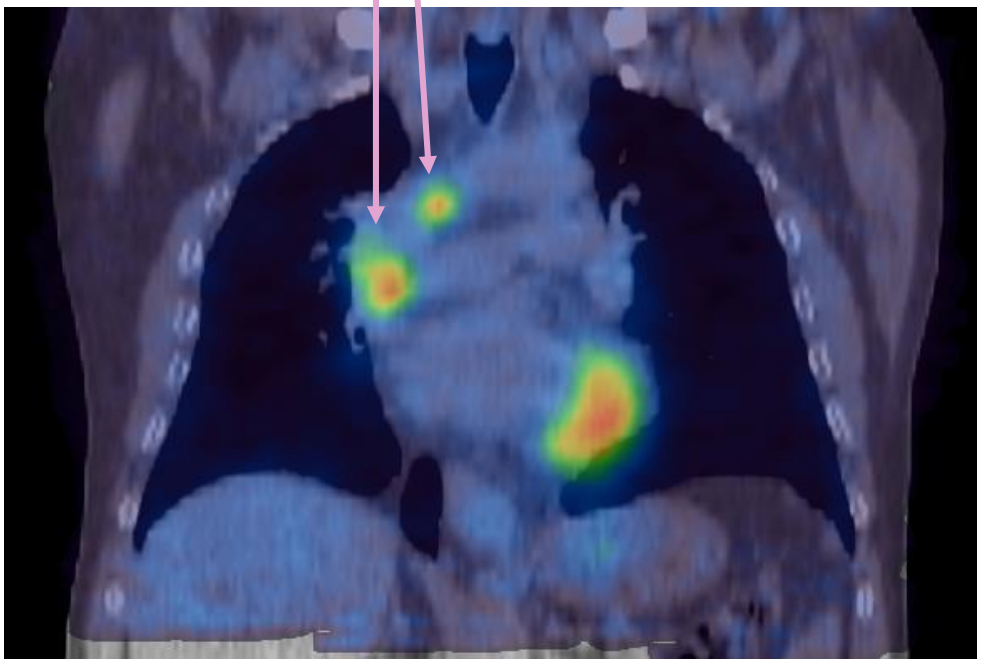
MI for GTV delineation

primary tumor

lymph nodes





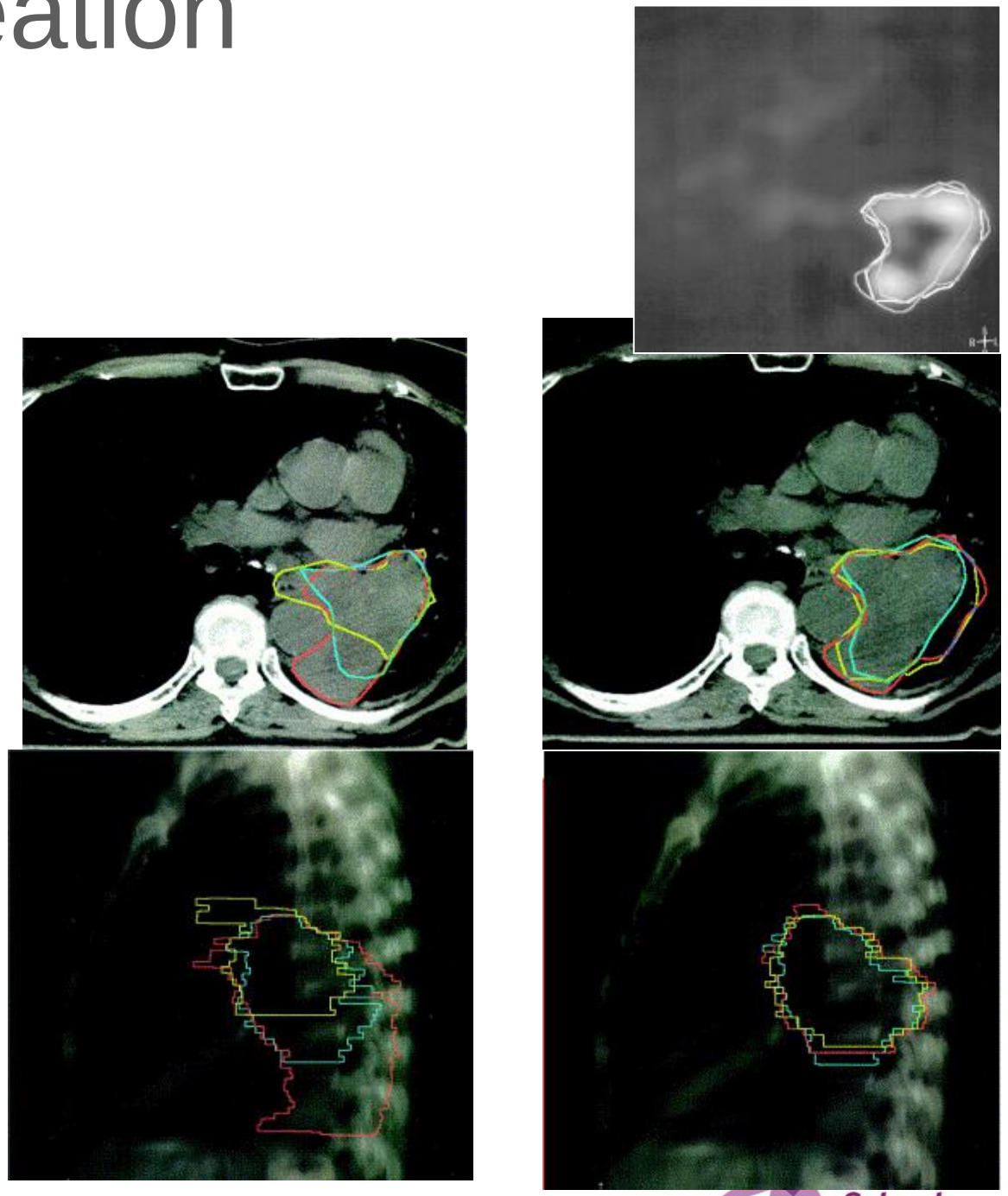
MI for GTV-delineation

GTV-Definition (3 RO)

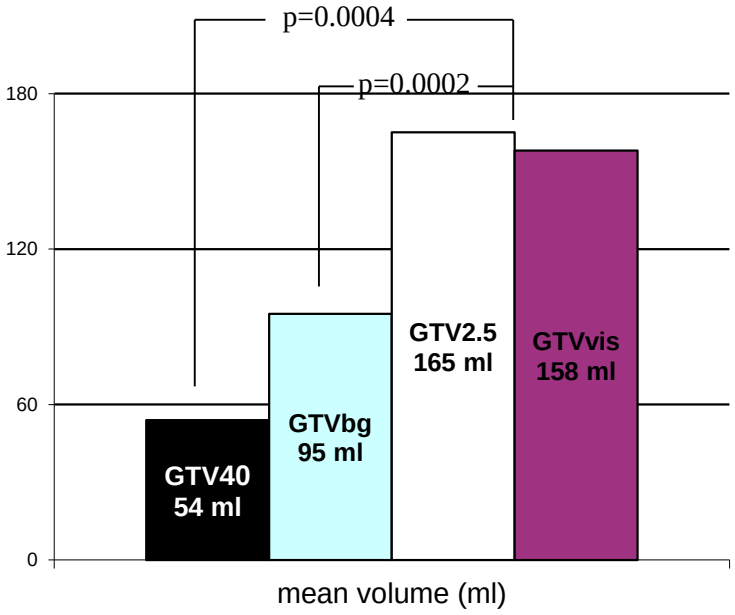
large interindividual differences in GTV-Definition

Use of FDG-PET: significant improvement

Caldwell IJROBP 2001



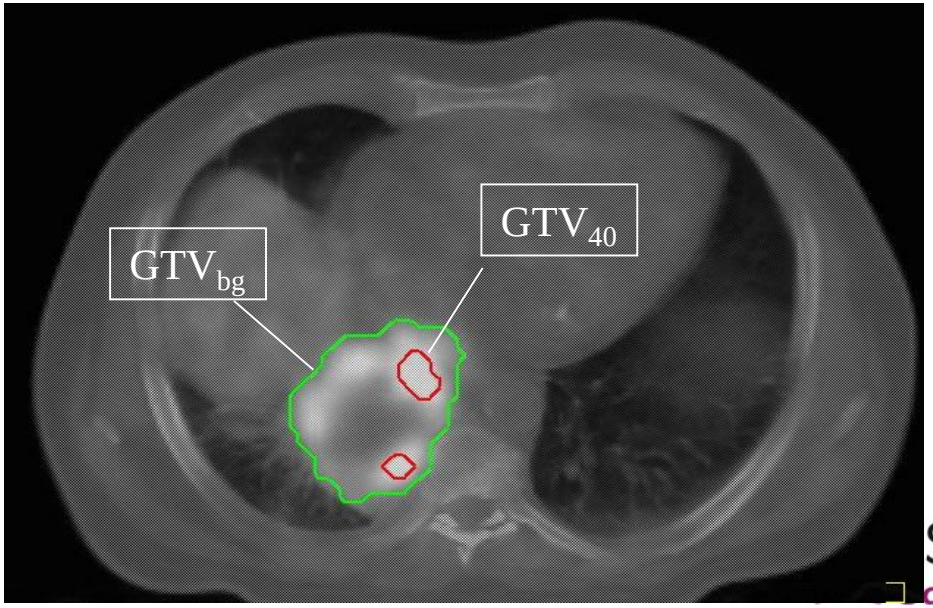
But: how?



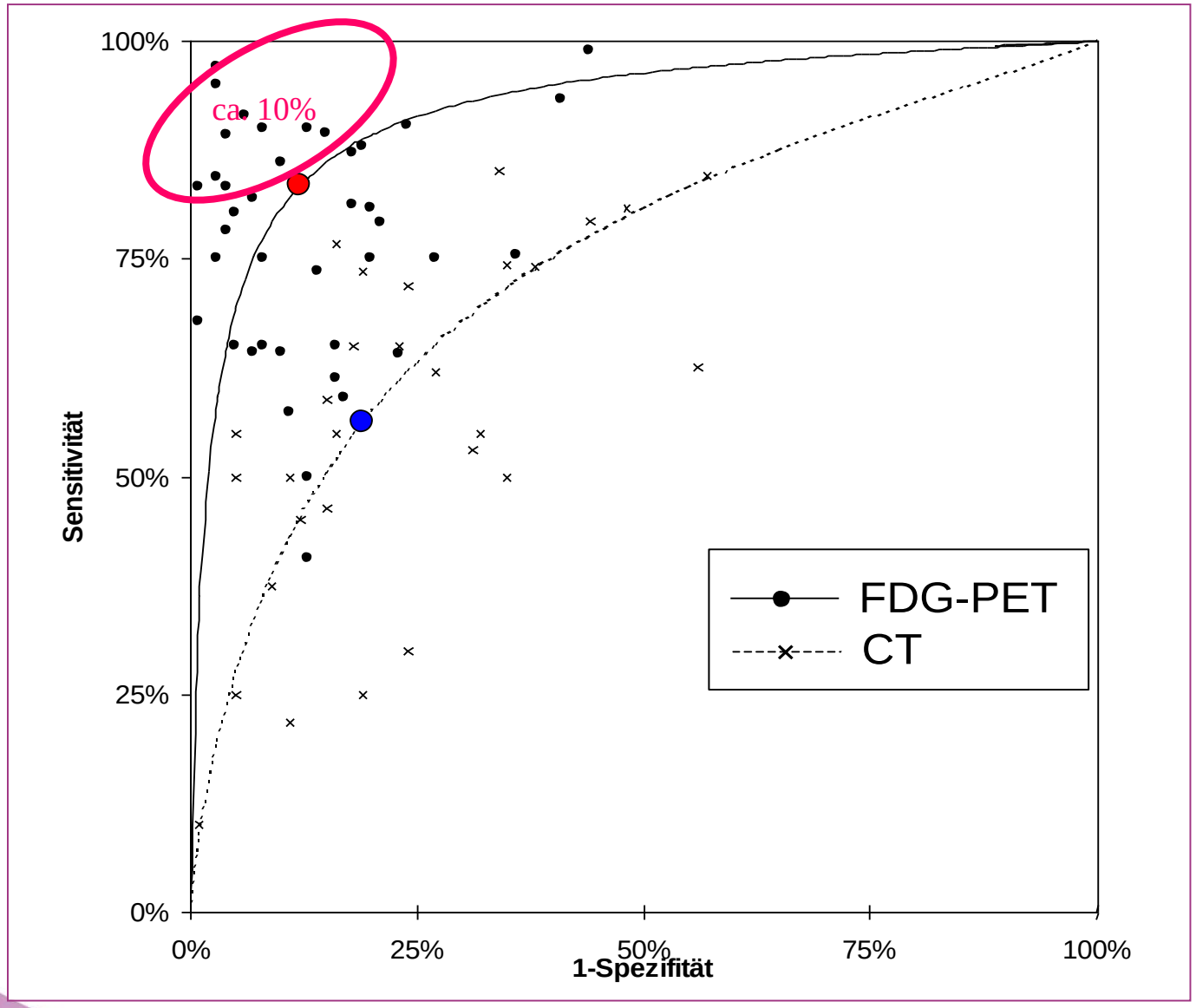
Nestle JNM 2005

25 primary NSCLC ,
4 conturing methods:
1 visual, 3 thresholding

correlation of differences with
- SUV_{max}
- size of lesion
- FDG-inhomogeneity



Thinking about CTVs …



Hellwig 2009: Metaanalysis
21 studies, 691 patients

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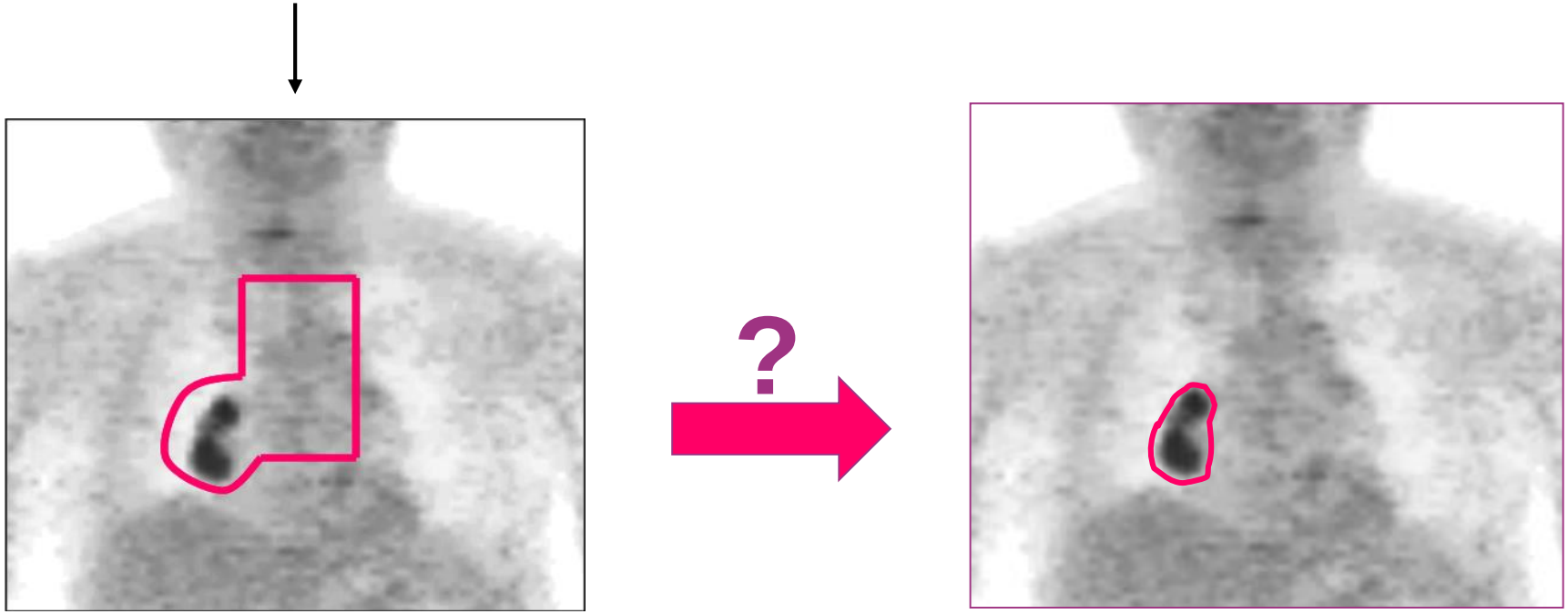
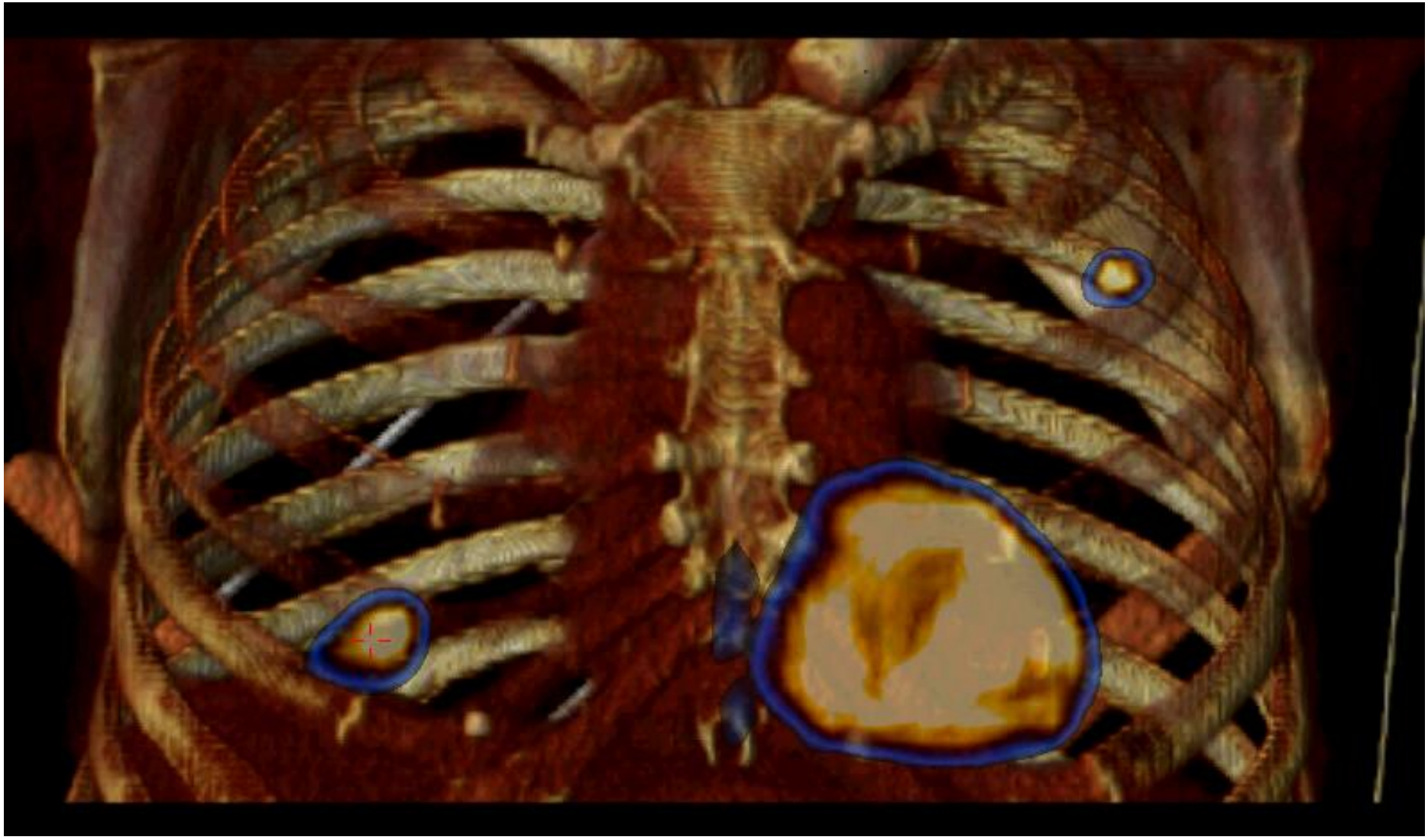
Can we change our CTV concepts with better imaging?



PTV: movements



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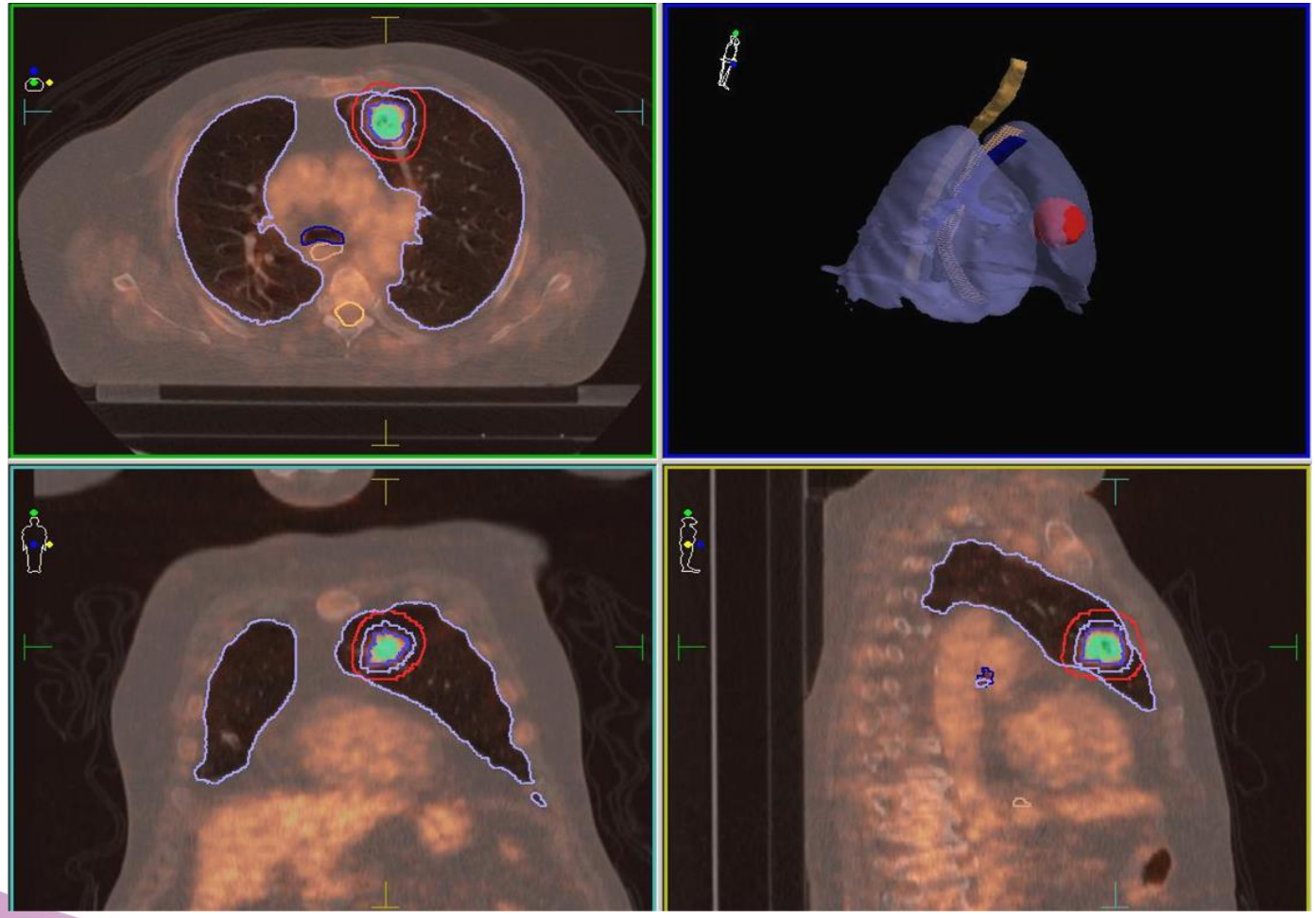
Organs at Risk (OAR)

Depending on treatment area and planned method of planning (3DCRT vs. IMRT)

- E.g.: Spinal Cord, Oesophagus, Healthy Lungs,…



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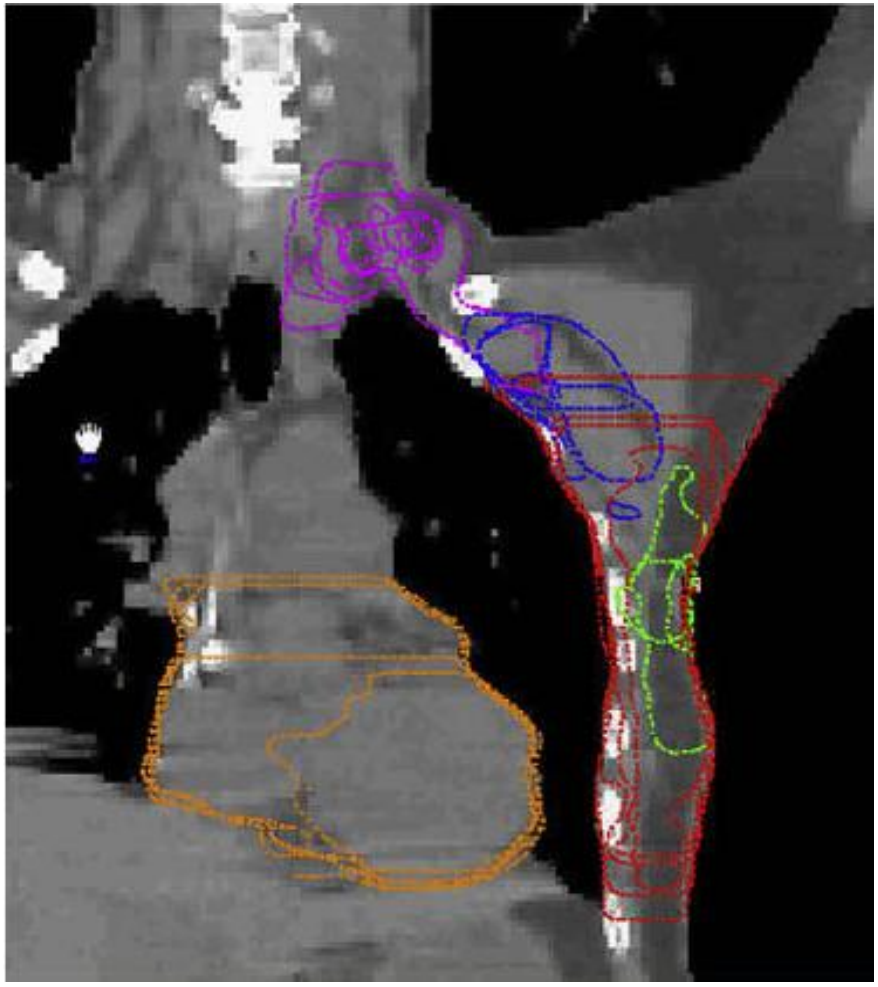
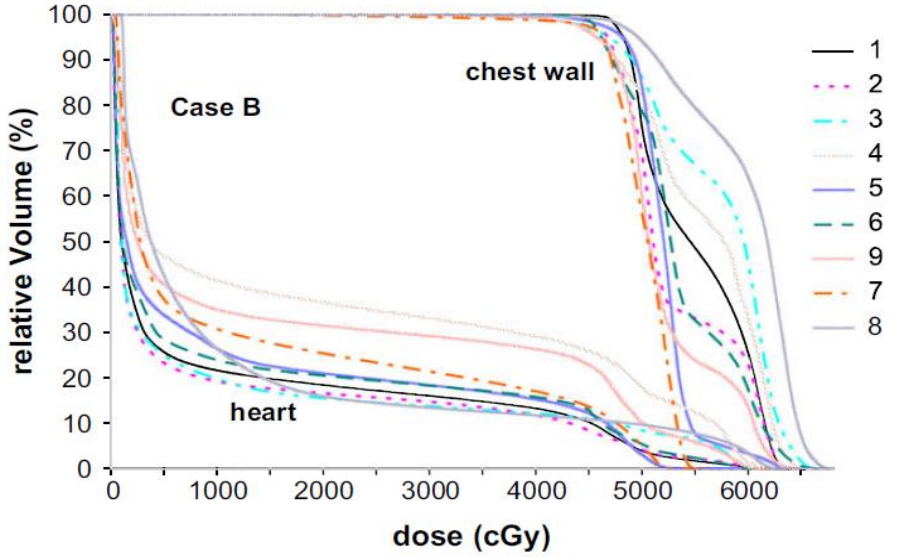
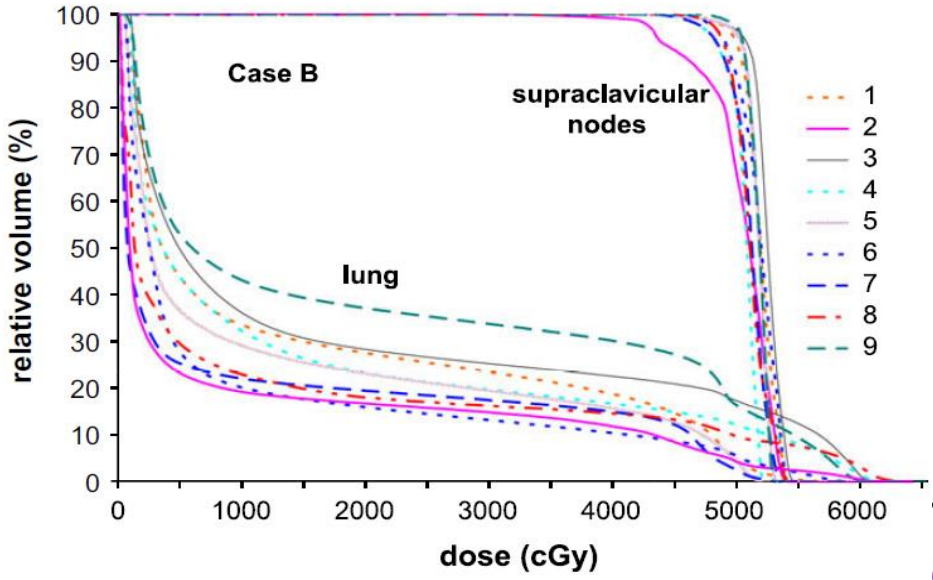
IOV in NT contouring: impact on dose calculation and plan optimisation

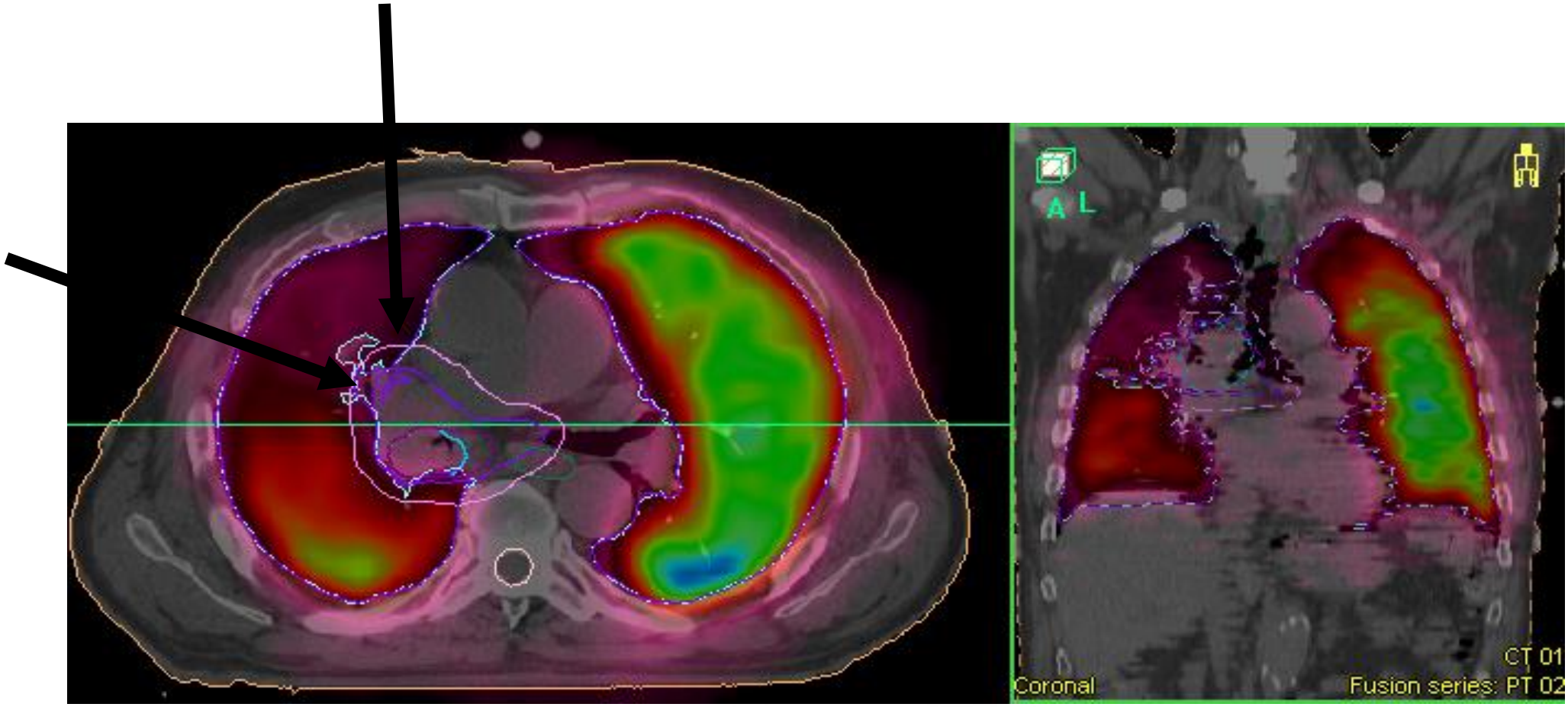






Li, IJROBP 2009; 73(3); 944-51

Perspectives of PET and SPECT in RT-TP



integration of functional normal tissue imaging

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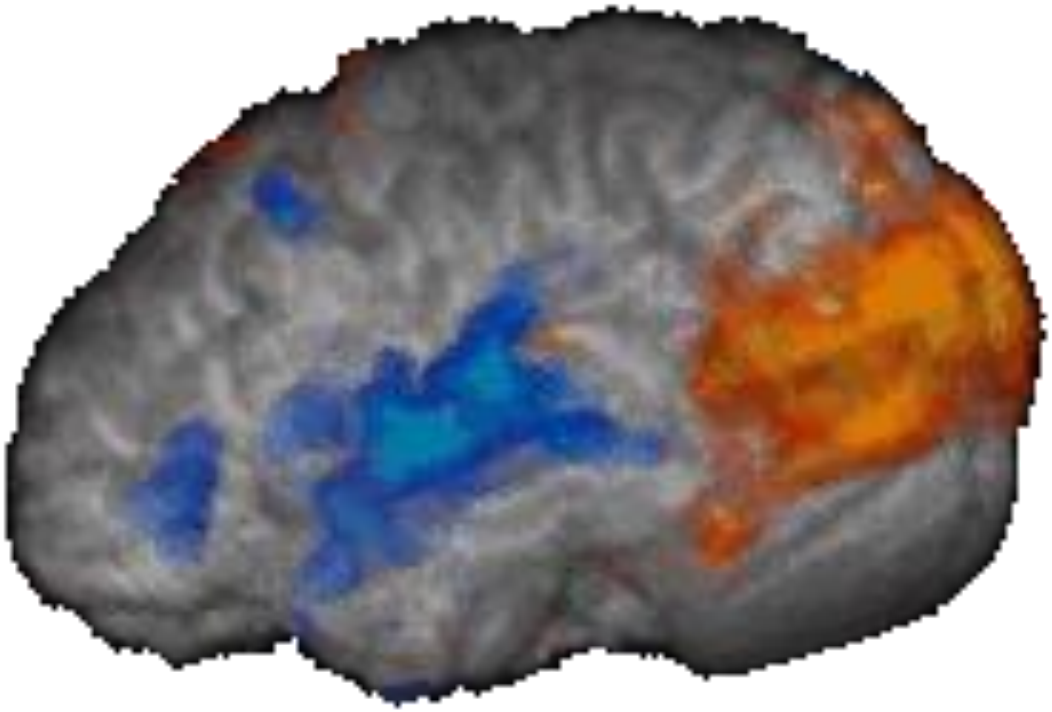
Perspectives of PET and SPECT in RT-TP

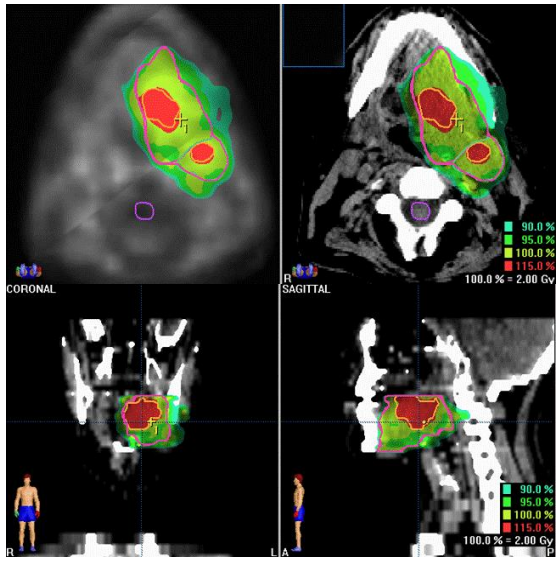


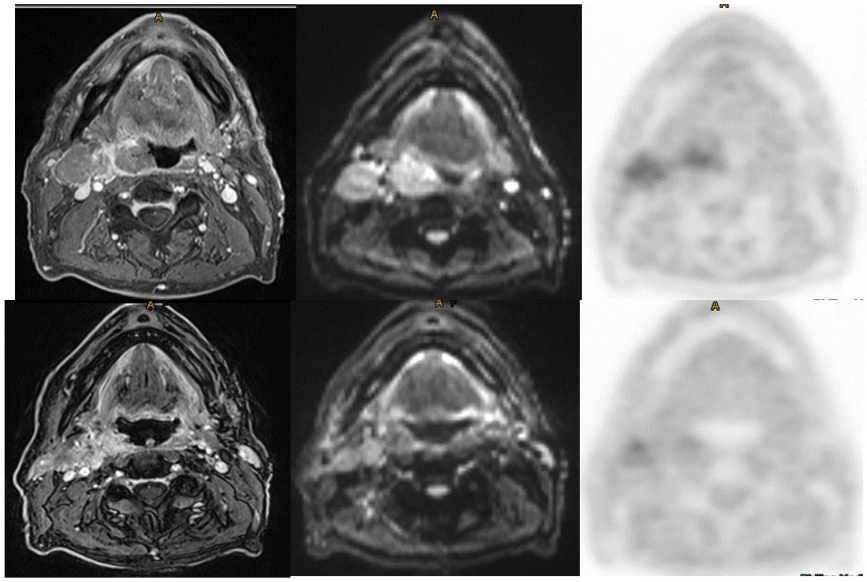
integration of functional normal tissue imaging

Perspectives by combination of imaging and IMRT/IGRT

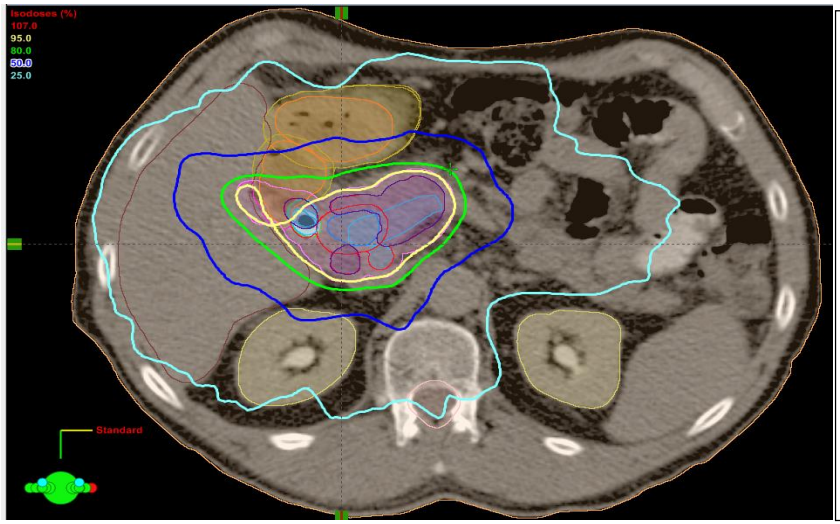
Bonus slide!

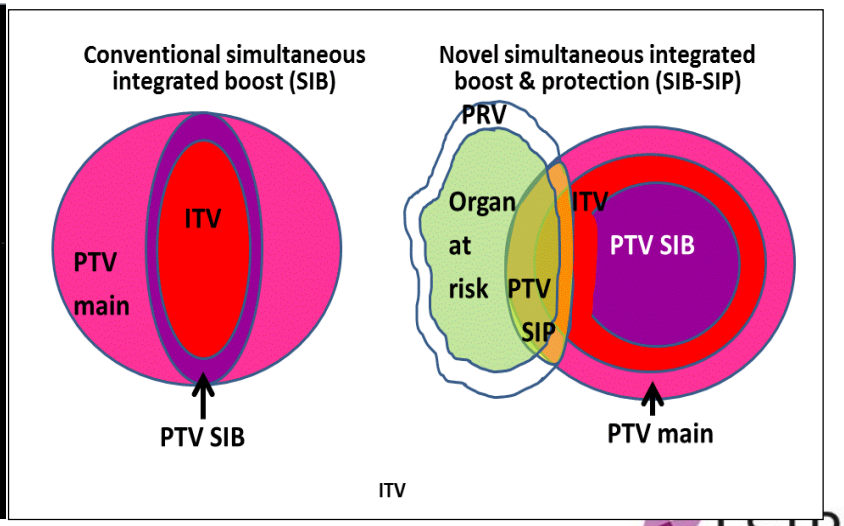
Biologically interesting Subvolumes





Normal tissue protection





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Medical imaging in radiation oncology:

- Imaging for diagnosis and staging:
  - treatment indication

- imaging for radiotherapy planning
  - target (GTV – CTV – PTV)
  - normal tissues
  - movements

- Imaging during RT application
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  - adaptive radiotherapy
  - normal tissue reactions

- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

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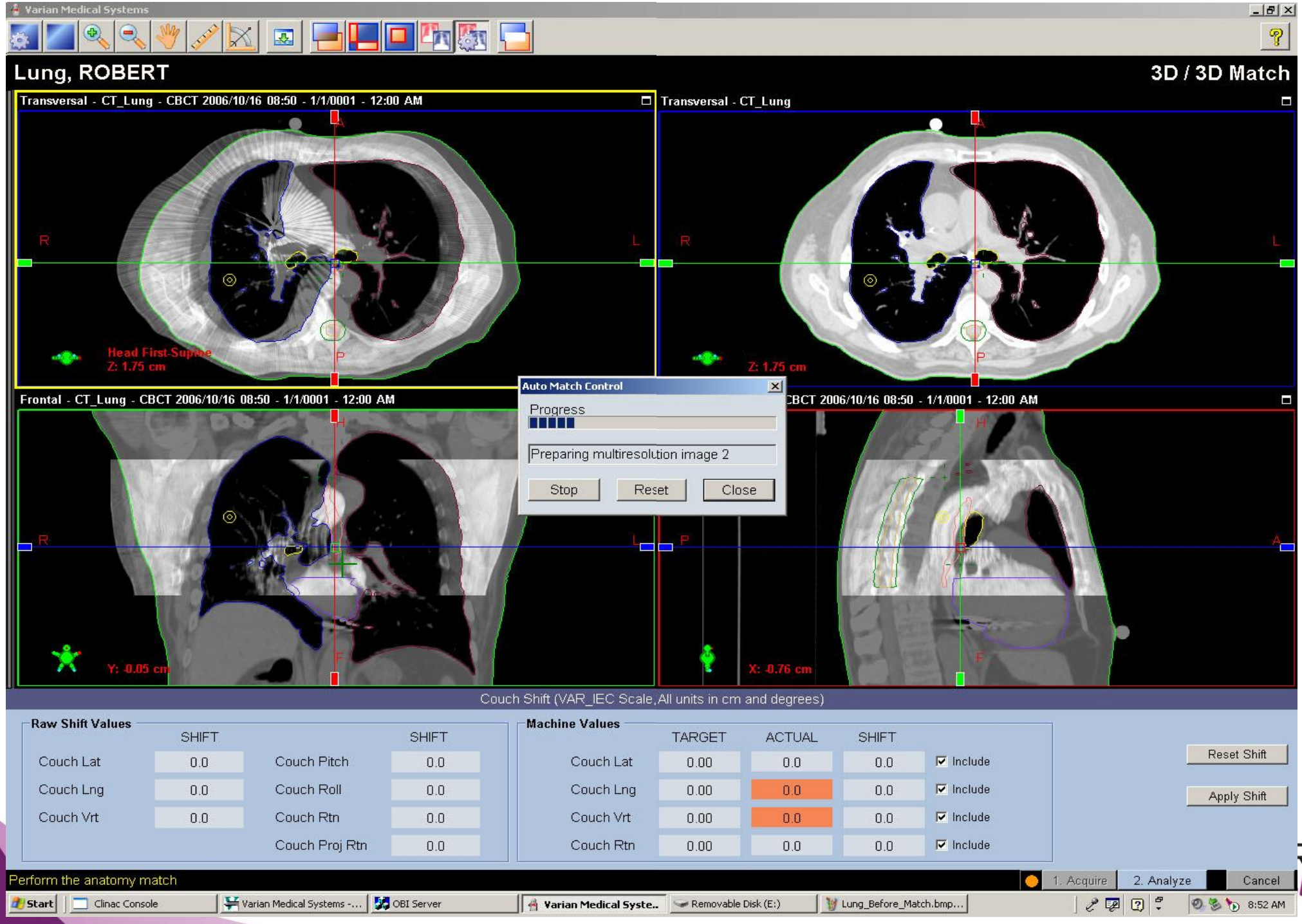
Cone-Beam CT


Varian Medical Systems
Lung, ROBERT
3D / 3D Match
Transversal - CT_Lung - CBCT 2006/10/16 08:50 - 1/1/0001 - 12:00 AM
Head First-Supine
Z: 1.75 cm
Transversal - CT_Lung
Z: 1.75 cm
Frontal - CT_Lung - CBCT 2006/10/16 08:50 - 1/1/0001 - 12:00 AM
Y: -0.05 cm
CBCT 2006/10/16 08:50 - 1/1/0001 - 12:00 AM
X: -0.76 cm
Auto Match Control
Progress
Preparing multiresolution image 2
Stop
Reset
Close
Couch Shift (VAR_IEC Scale,All units in cm and degrees)
Raw Shift Values
SHIFT
Couch Lat 0.0
Couch Lng 0.0
Couch Vrt 0.0
Couch Pitch 0.0
Couch Roll 0.0
Couch Rtn 0.0
Couch Proj Rtn 0.0
Machine Values
TARGET ACTUAL SHIFT
Couch Lat 0.00 0.0 0.0 Include
Couch Lng 0.00 0.0 0.0 Include
Couch Vrt 0.00 0.0 0.0 Include
Couch Rtn 0.00 0.0 0.0 Include
Reset Shift
Apply Shift
Perform the anatomy match
1. Acquire
2. Analyze
Cancel
Start
Clinac Console
Varian Medical Systems -...
OBI Server
Varian Medical Syste..
Removable Disk (E:)
Lung_Before_Match.bmp...
8:52 AM

Imaging for adaptive radiotherapy

Imaging of tumor during treatment

- size
- biology

imaging of normal tissues

- filling (bladder/bowel)
- changing anatomy (h&n; lung)

perspectives …

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Questions to molecuar imaging during radiotherapy

clinical situation	question to imaging	consequence
neoadjuvant R(C)T		
during	response prediction	early resection? change of CHT?
end	response y/n?	resection y/n further RT
radical R(C)T		
during	response prediction topography of response prediction of NT-reactions	modify RT/CHT? modify dose distribution? modify dose to NT?
end	residual disease	additional dose? „adjuvant“ CHT?
follow up after RT	recurrence vs. side effects	treatment y/n

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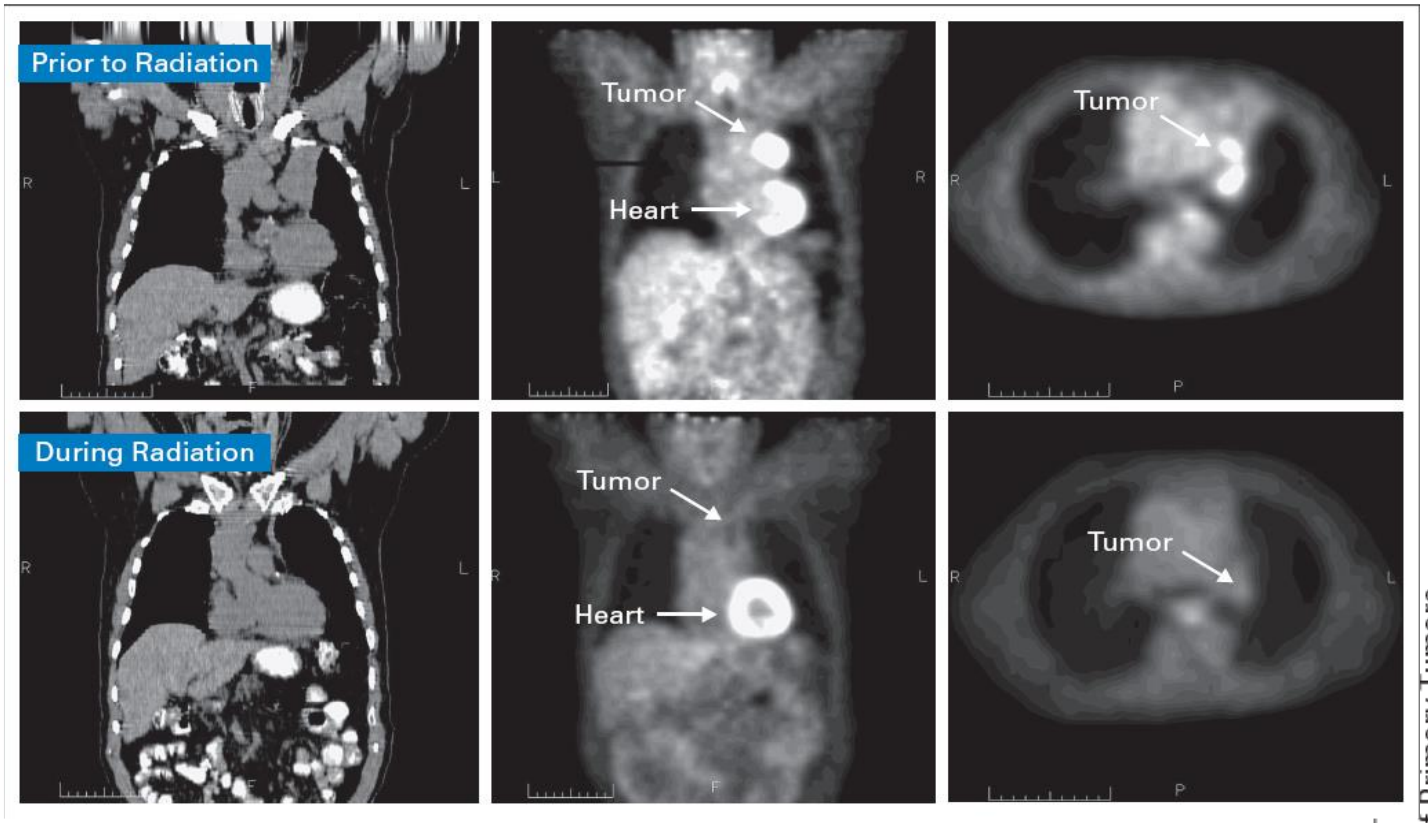
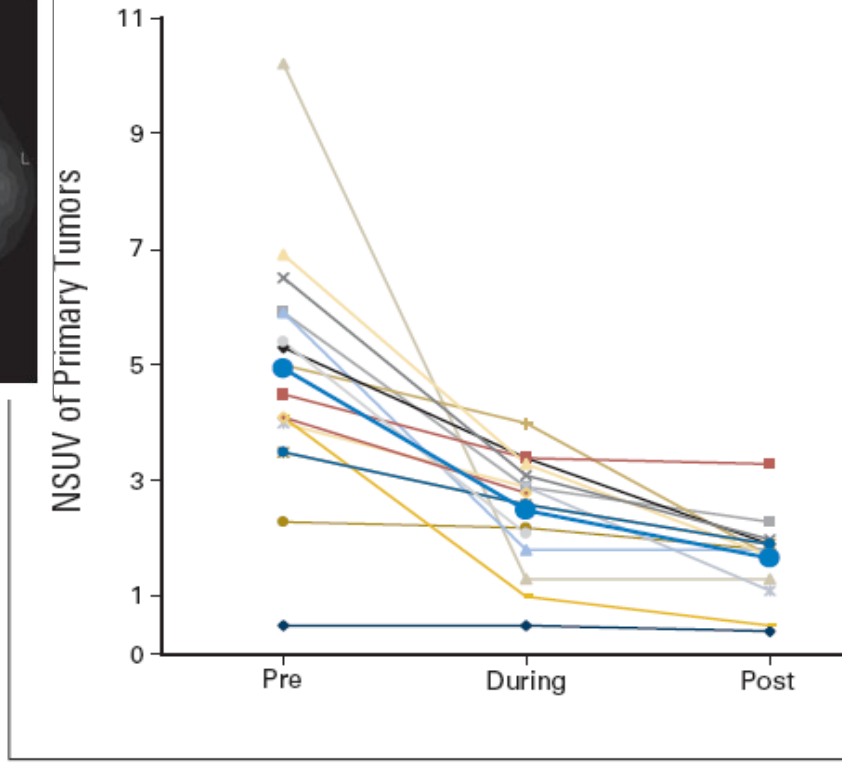
Response prediction during RT?

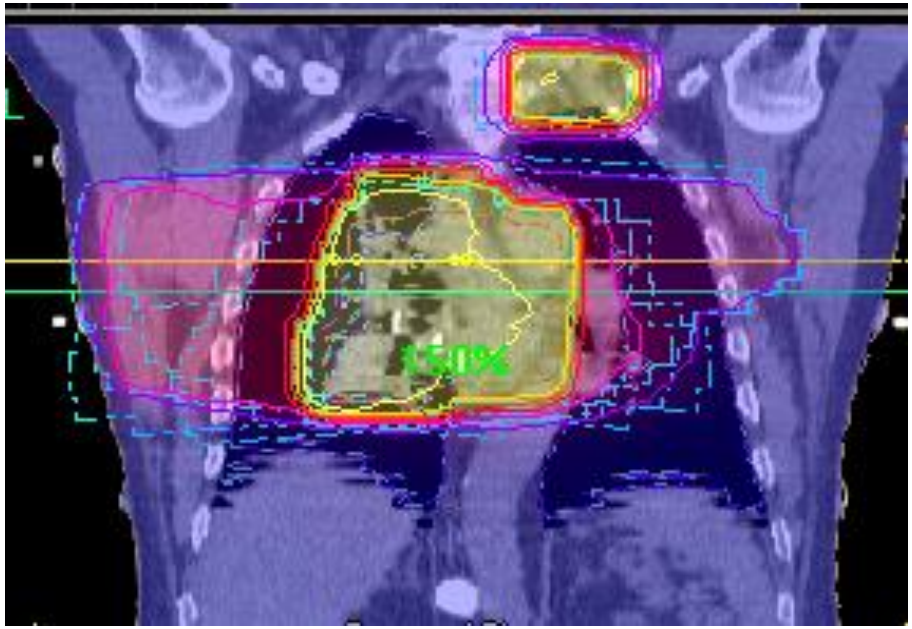


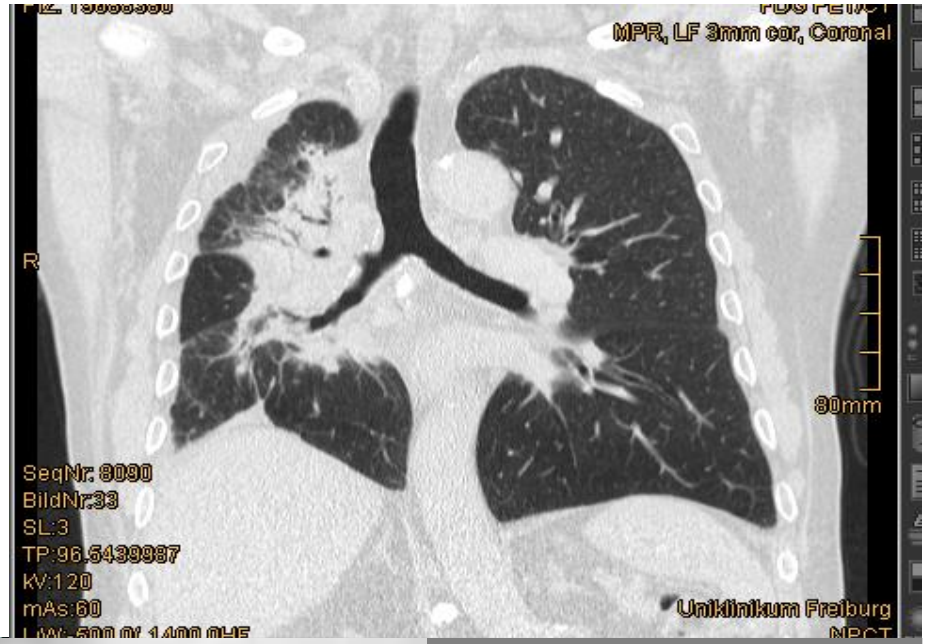


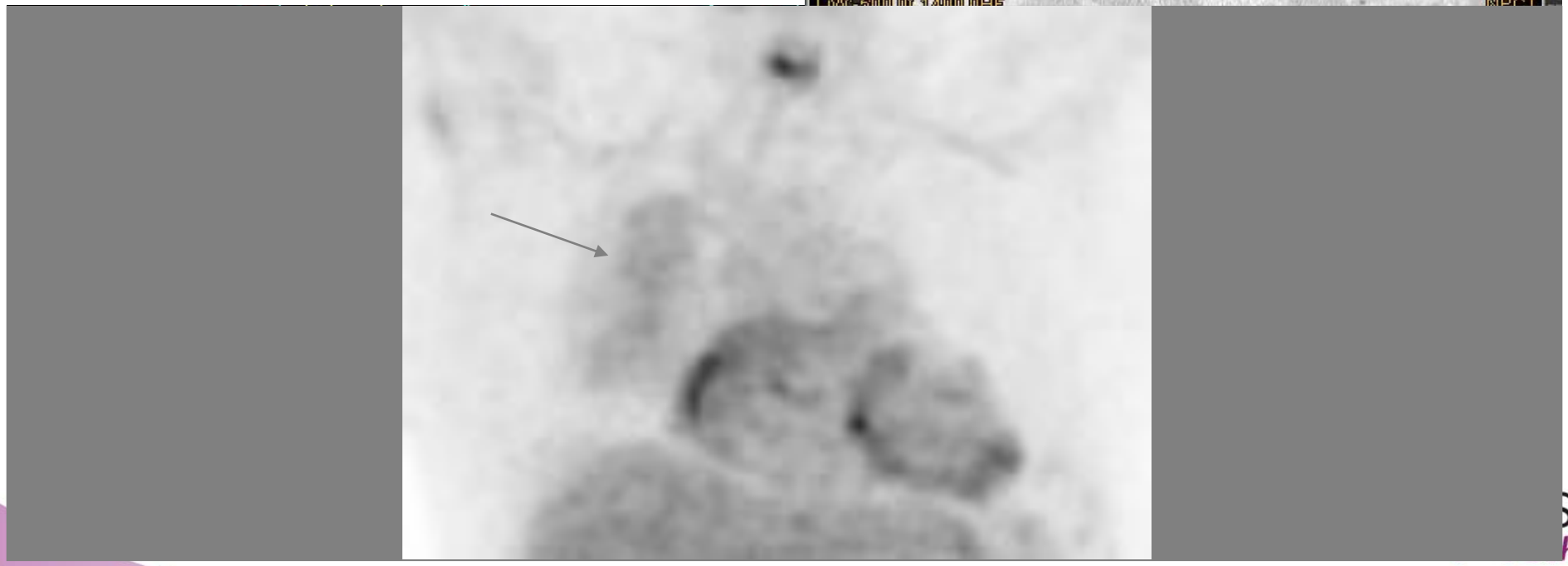
significant correlation
PET-response during vs. after RT

Kong, JCO 2007

RT-Dose compromized by normal tissue tolerance

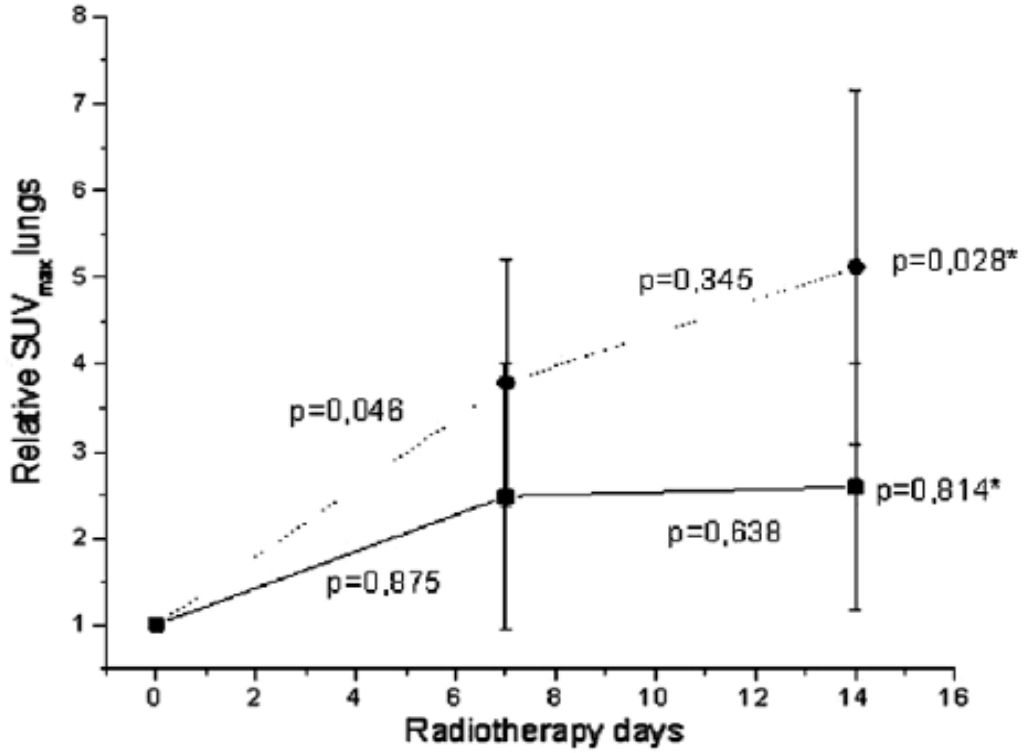


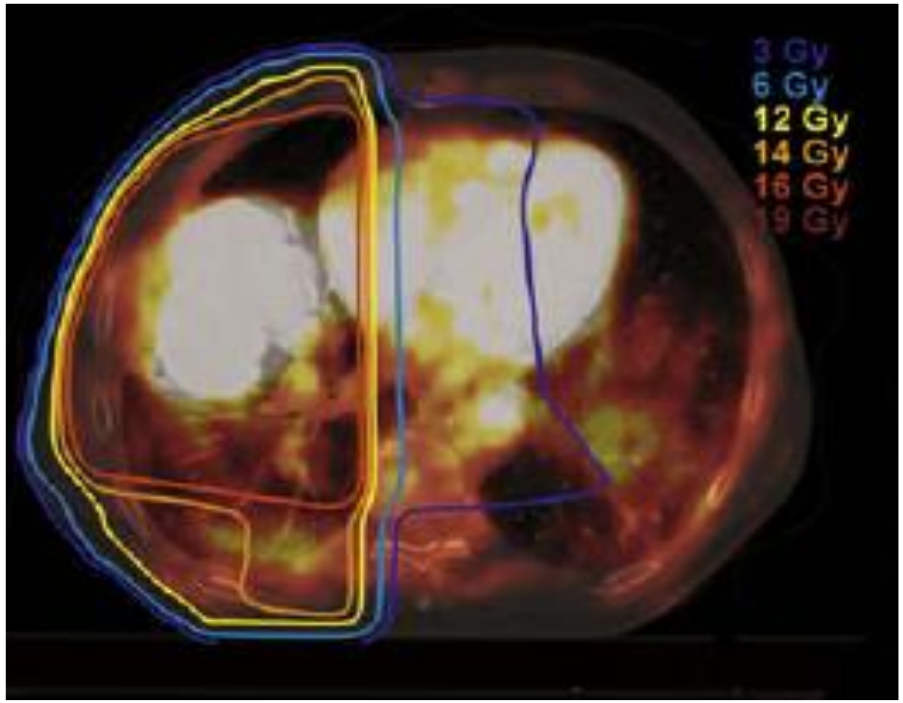




Prediction of NT-reactions?

Time	SUV_{max} of the lungs				
	No RILT	*p*-Value no RILT	RILT	*p*-Value RILT	*p*-Value no RILT vs. RILT
Day 0	3.40 ± 1.04	Day 0 vs. 7 = 0.39	2.09 ± 0.87	Day 0 vs. 7 = 0.17	Day 0 = 0.345
Day 7	2.69 ± 0.39	Day 7 vs. 14 = 0.75	3.74 ± 0.99	Day 7 vs. 14 = 0.25	Day 7 = 0.053
Day 14	2.88 ± 0.74	Day 0 vs. 14 = 0.48	**5.20 ± 1.41**	**Day 0 vs. 14 = 0.03**	**Day 14 = 0.032**





day 8 of RT

De Ruysscher 2009

Medical imaging in radiation oncology:

- Imaging for diagnosis and staging:
  - treatment indication

- imaging for radiotherapy planning
  - target (GTV – CTV – PTV)
  - normal tissues
  - movements

- Imaging during RT application
  - repositioning
  - adaptive radiotherapy
  - normal tissue reactions

- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

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EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247

ELSEVIER

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

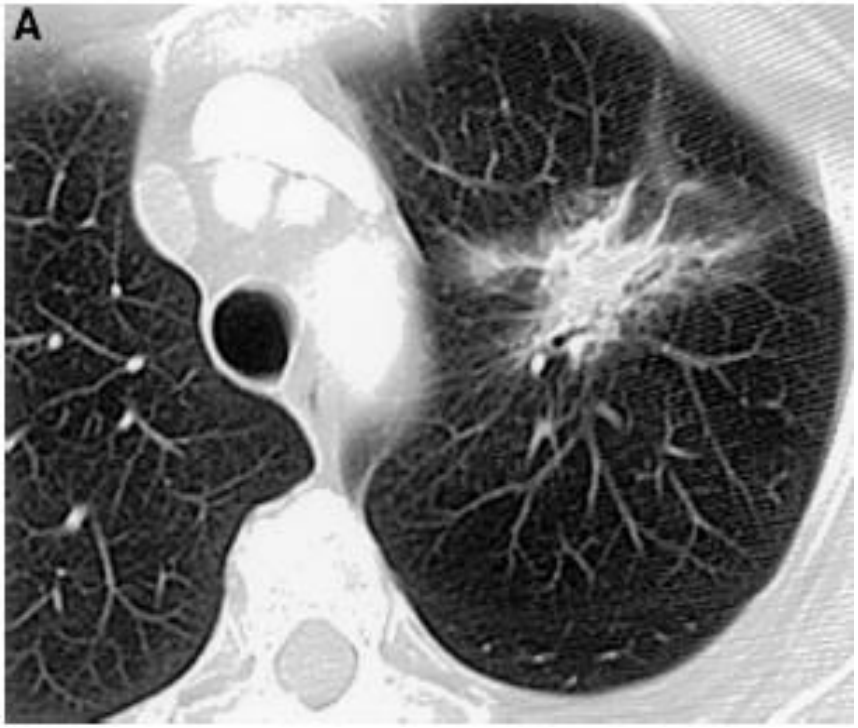
New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer[a,*], *P. Therasse*[b], *J. Bogaerts*[c], *L.H. Schwartz*[d], *D. Sargent*[e], *R. Ford*[f], *J. Dancey*[g], *S. Arbuck*[h], *S. Gwyther*[i], *M. Mooney*[g], *L. Rubinstein*[g], *L. Shankar*[g], *L. D*
R. Kaplan[j], *D. Lacombe*[c], *J. Verweij*[k]

[a]*National Cancer Institute of Canada – Clinical Trials Group, 10 Stuart Street, Queen's University, Kingston, ON, Canada*
[b]*GlaxoSmithKline Biologicals, Rixensart, Belgium*
[c]*European Organisation for Research and Treatment of Cancer, Data Centre, Brussels, Belgium*
[d]*Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[e]*Mayo Clinic, Rochester, MN, USA*
[f]*RadPharm, Princeton, NJ, USA*
[g]*Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA*
[h]*Schering-Plough, Kenilworth, NJ, USA*
[i]*East Surrey Hospital, Redhill, Surrey, UK*
[j]*National Cancer Research Network, Leeds, UK*
[k]*Erasmus University Medical Center, Rotterdam, The Netherlands*

Morphological assessment of response

How large is this tumor?



40 tumors, 5 radiologists
Interobserver variability: 140%
Intraobserver variability: 37%

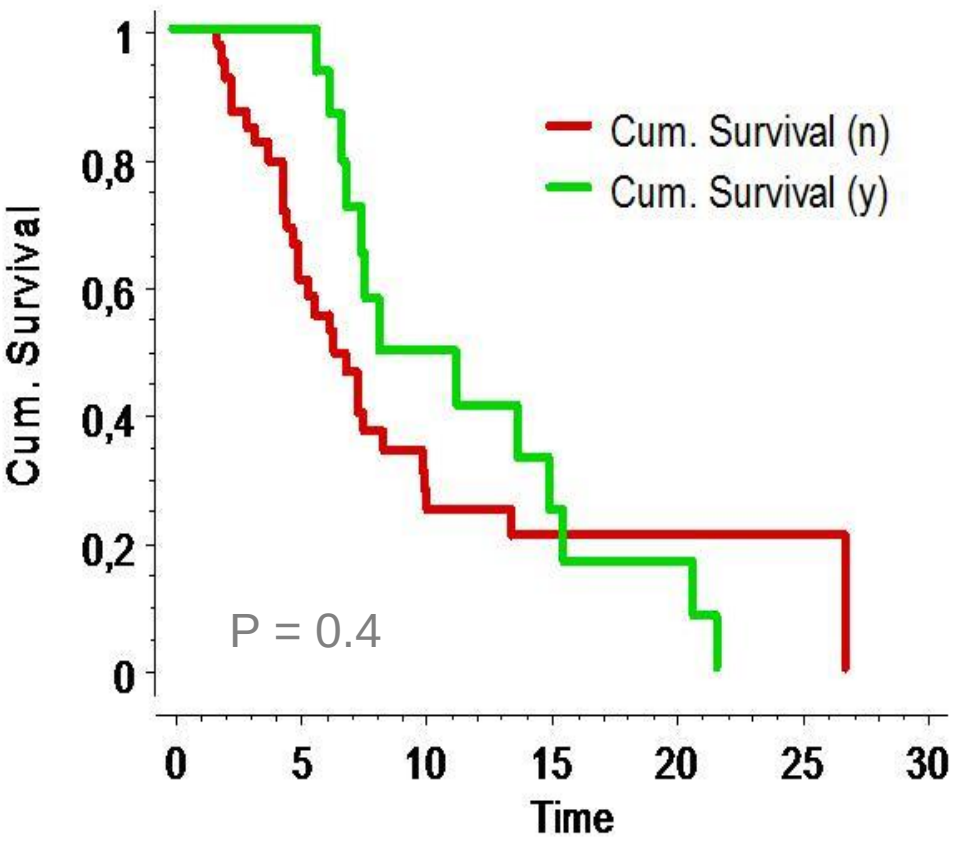
Assessment of PD in CT

Unidimensional	
Minimum RD, %	0.00
Maximum RD, %	50.00
Median RD, %	5.20
No. of misclassifications	7
% of tumors	17.50
Bidimensional	
Minimum RD, %	0.00
Maximum RD, %	183.33
Median RD, %	8.74
No. of misclassifications	9
% of tumors	22.50

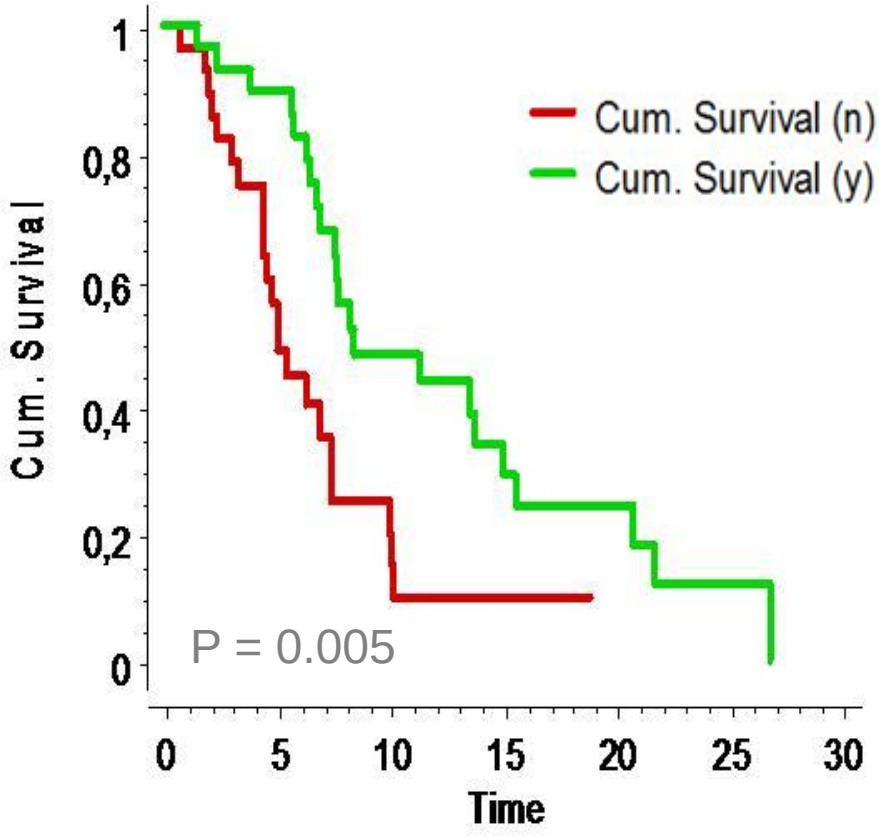
Erasmus, JCO 2003

“Functional” response assessment

CT response after 2 cycles

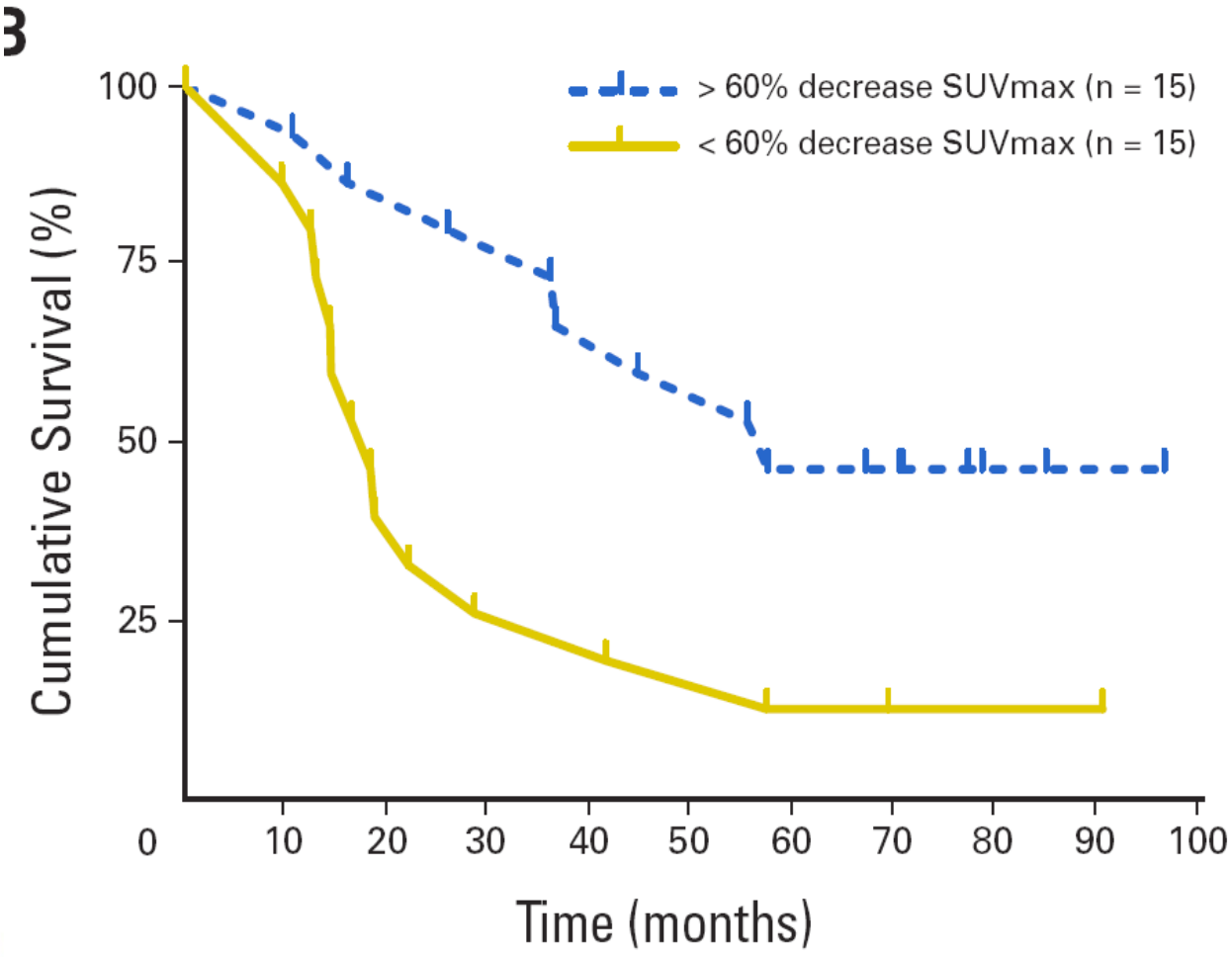


PET response after 1 cycle



Data from Weber, JCO 2003

Tumor response in FDG-PET after neoadjuvant chemotherapy vs. histopathologic response and survival

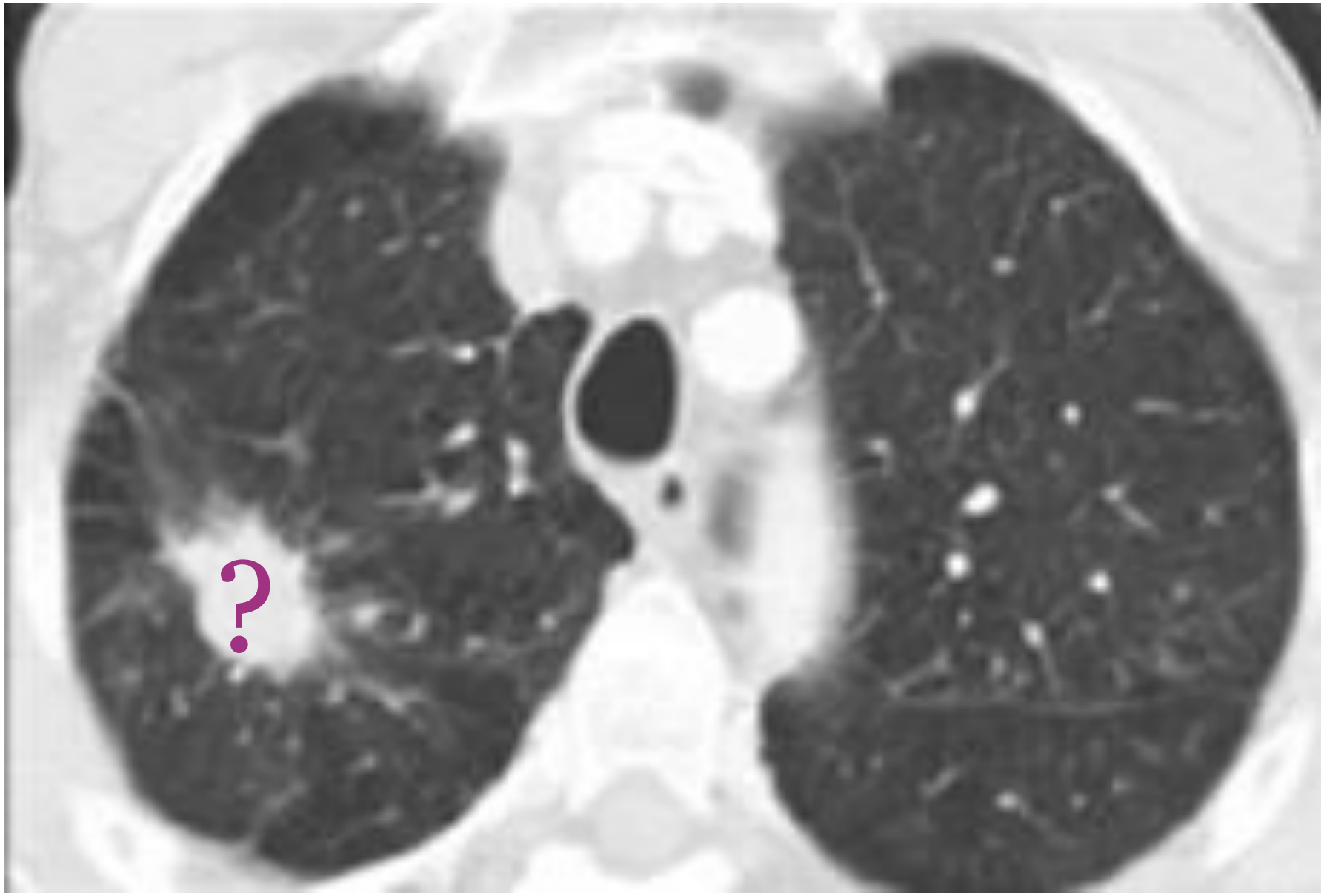


NSCLC:
FDG-PET before and after induction chemotherapy followed by resection

→ Change of CHT?

Dooms, JCO 2008

what is this?

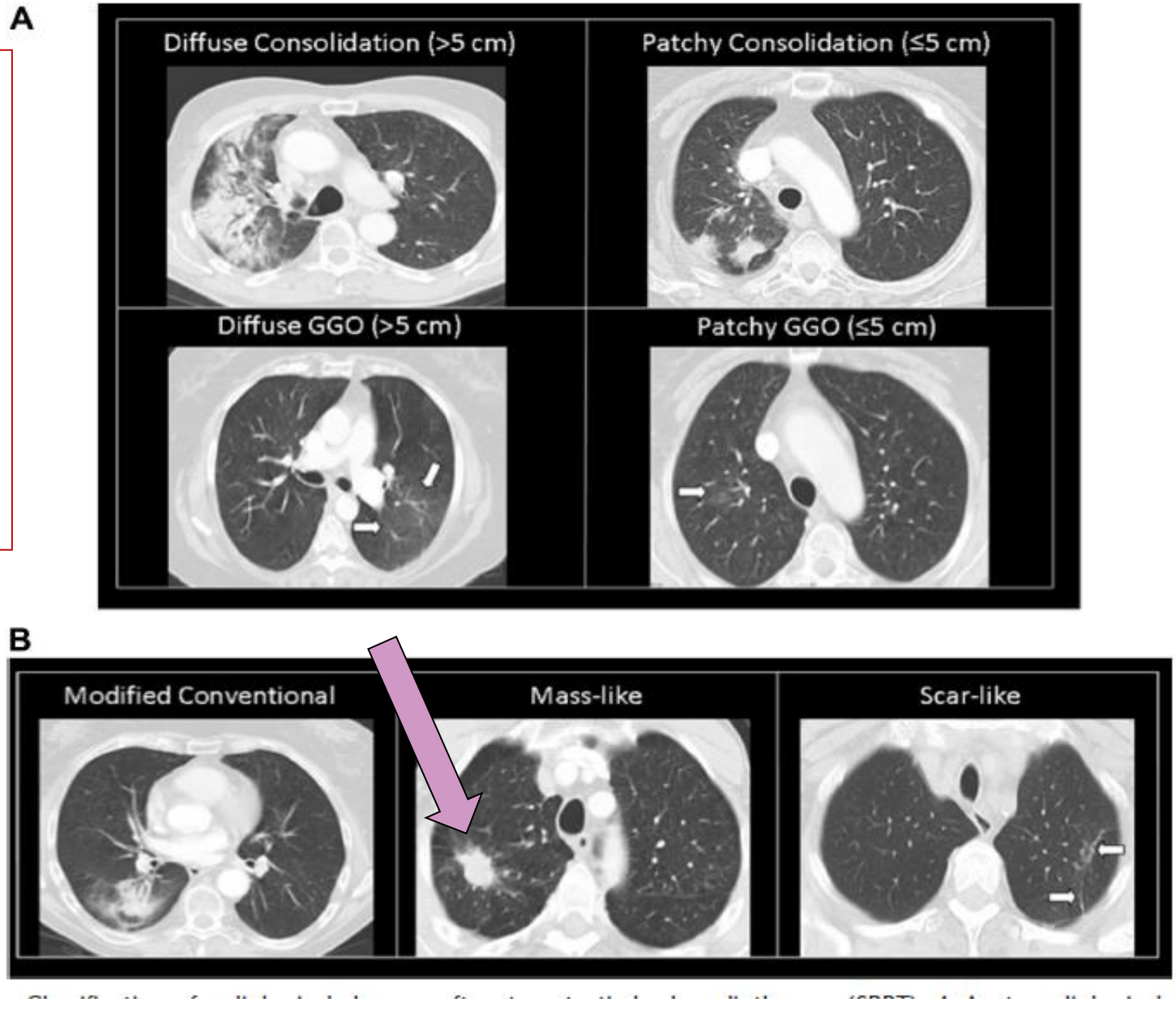


Lung reactions after SBRT

Imaging post SBRT:

mass like fibrosis
or recurrence?

diagnostic
learning curve



Dahele JTO 2011

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  - normal tissues
  - movements
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  - repositioning
  - adaptive radiotherapy
  - normal tissue reactions
- imaging during follow up
  - response
  - recurrence
  - normal tissue injury

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Questions?

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WWW.ESTRO.ORG/SCHOOL

PET basics: physics

Wouter Vogel

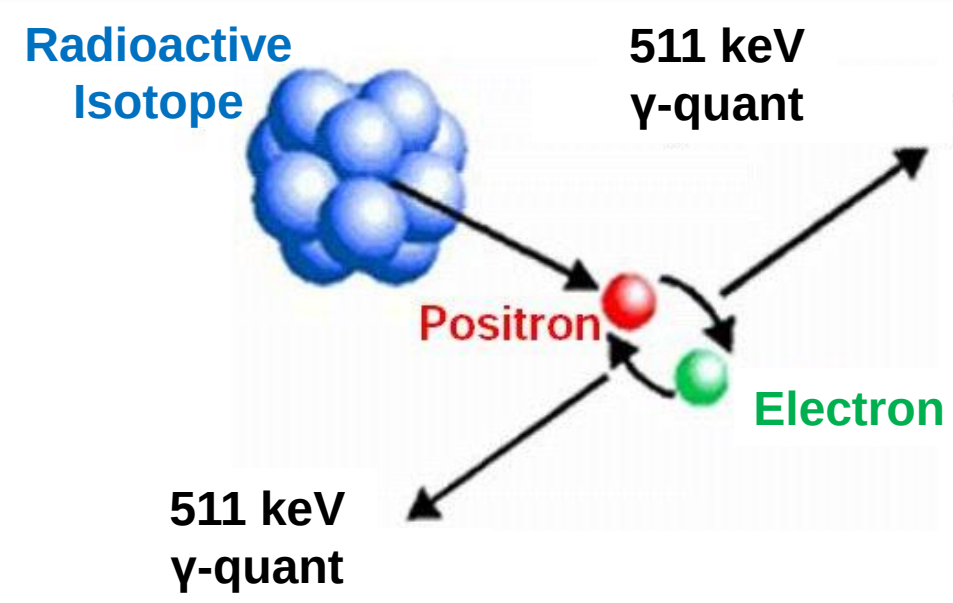
Overview

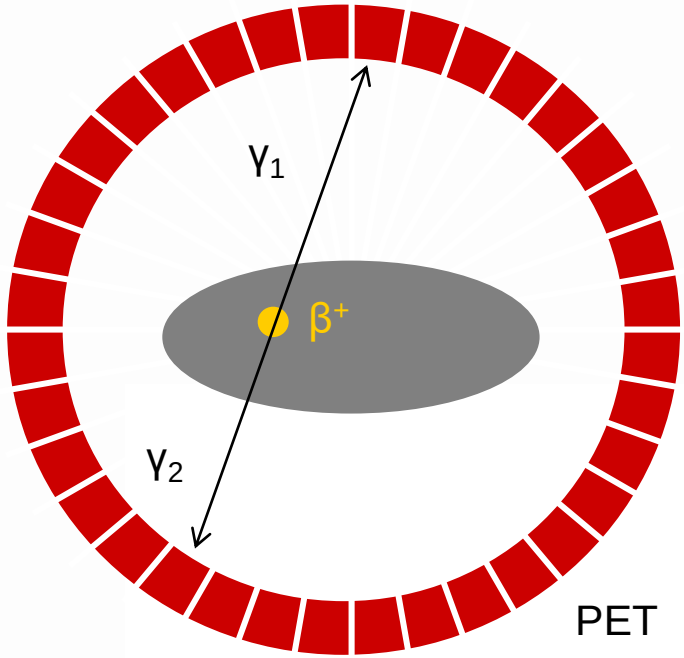
- Positron emission
- Detection of 511 keV
- Coincidence detection, trues, randoms, scatter
- Image reconstruction

- Standardisation of quantitative FDG-PET for multi-center trials
- Factors affecting SUV and image quality
- Standardisation protocol

Basic principle of PET

- Positron emitters (β+) used as biomarkers
- Positron-electron annihilation
  ⇒ Two γ-quanta with 511 keV each are emitted under approx. 180°
- Coincidence detection in a detector ring





Radionuclides for diagnostic applications

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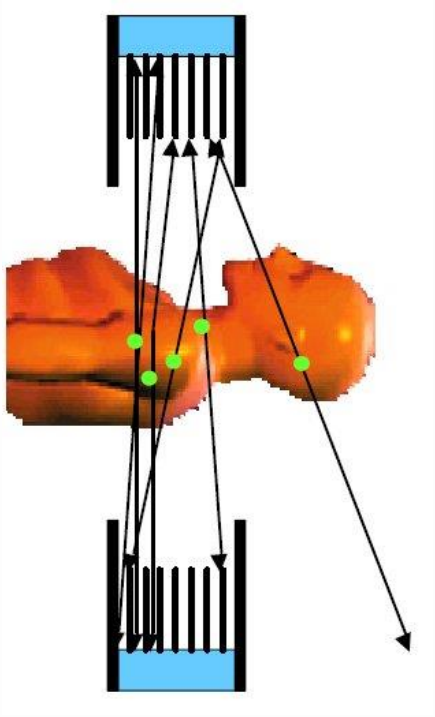
Nuclide	γ-Energy [keV]	Half life	Radioactive decay (max. β+-Energy)	Production
^{11}C	511	20,3 min	β+ (0,97 MeV)	cyclotron
^{13}N	511	9,93 min	β+ (1,2 MeV)	cyclotron
^{15}O	511	124 s	β+ (1,74 MeV)	cyclotron
^{18}F	511	109 min	β+ (0,64 MeV) EC	cyclotron
^{81m}Kr	190	13 s	IT	
^{99m}Tc	140	6,03 h	IT	
^{123}I	159	13 h	EC	cyclotron
^{133}Xe	81 31(Cs-Kα)	5,3 d	β-	nuclear reactor

Max. β+-energy determines mean free path length of β+ !

2D-/3D-PET

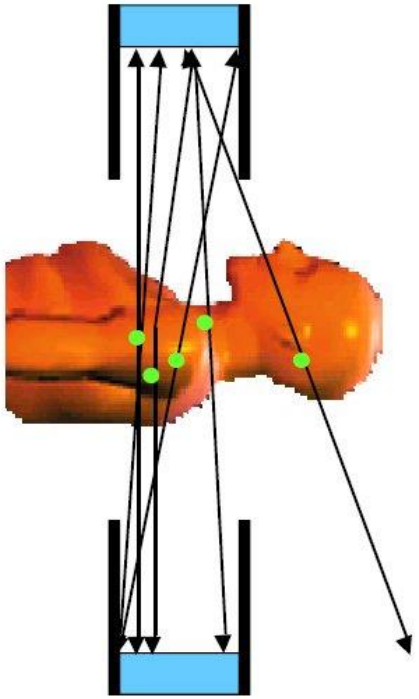
2D-PET

- Geometric collimation with septa
- Data sampling only with θ=0°
- Lower overall sensitivity
- Lower fraction of scattered photons



3D-PET

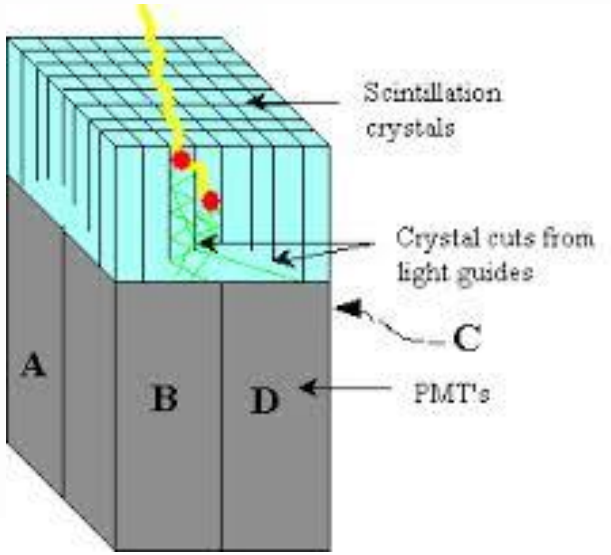
- Projections at polar angles θ>0° measured
- Increased sensitivity
- Higher scatter fraction
- Special reconstruction algorithms are necessary



Detection of 511 keV photons

Scintillation detectors

- Inorganic crystal that emits visible light photons after interaction of photons with detector.
- Number of scintillation photons is proportional to the energy deposited in the crystal.
  - NaI(Tl): sodium iodide doped with thallium
  - BGO: bismuth germanate (Bi4Ge3O12)
  - LSO: lutetium oxyorthosilicate doped with cerium(Lu2SiO5:Ce)

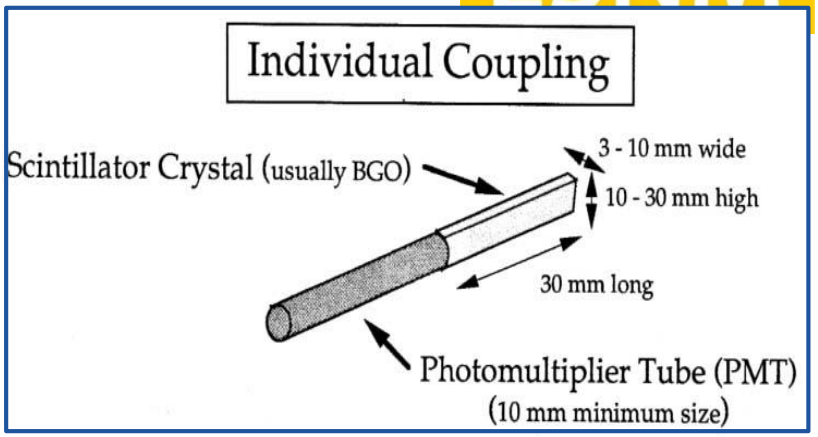


Photomultiplyer tubes (PMTs)

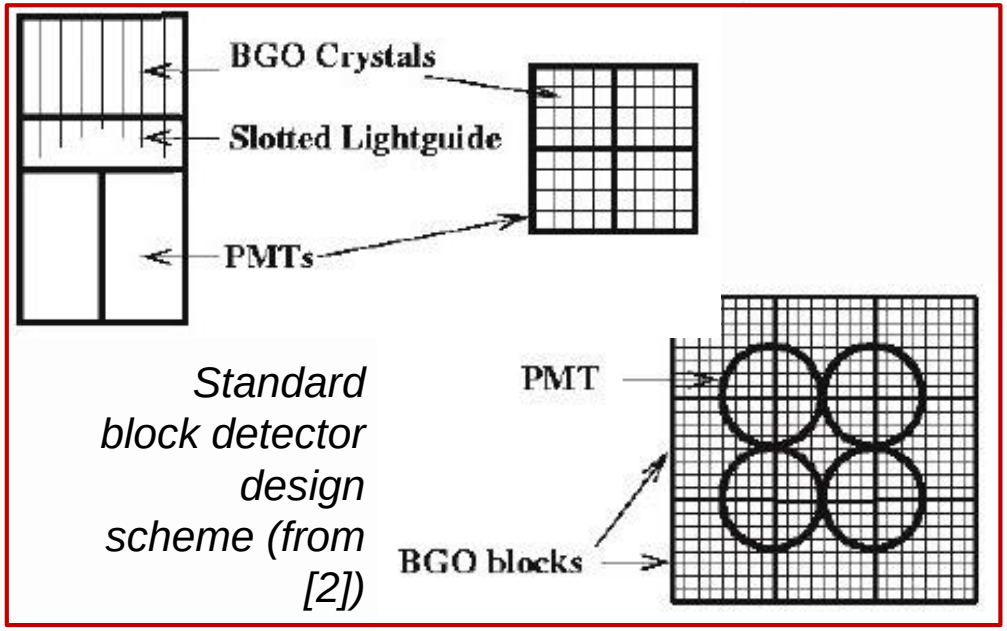
- Incoming photons from scintillation blocks are converted into electrical signal

Detector Designs used in PET

- One-to-one coupling:
  - Single crystals glued to individual photo-detector
  - Spatial resolution limited by discrete crystal size



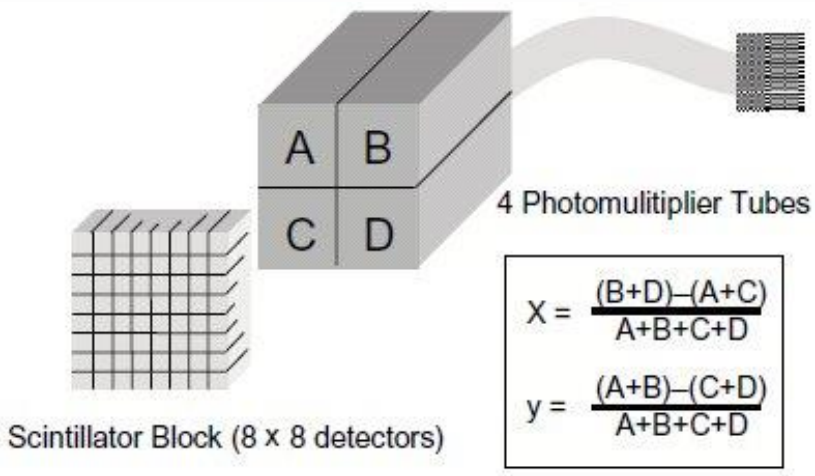
- Block detector design:
  - Rectangular scintillator
  - block sectioned by
  - partial saw cuts of
  - different depth into
  - discrete elements
  - Usually 4 attached PMTs
  - Anger positioning



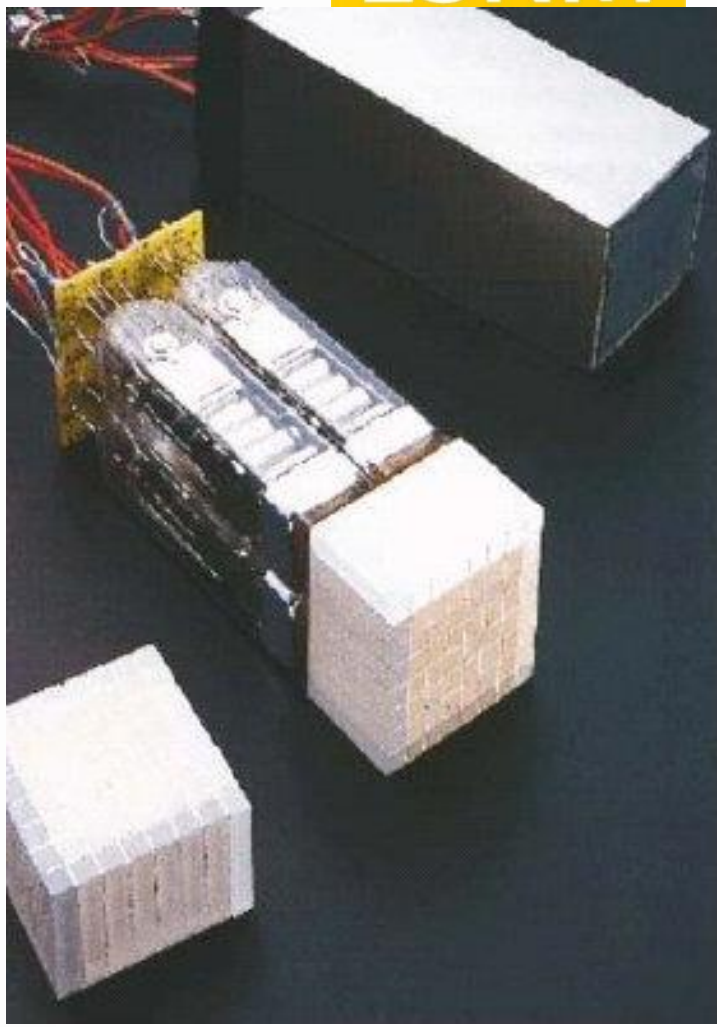
Standard block detector design scheme (from [2])

Detector Designs used in PET

- Anger detector:
  - Large scintillator crystal glued to array of PMTs
  - Weighted centroid positioning algorithm used to estimate interaction position within the detector



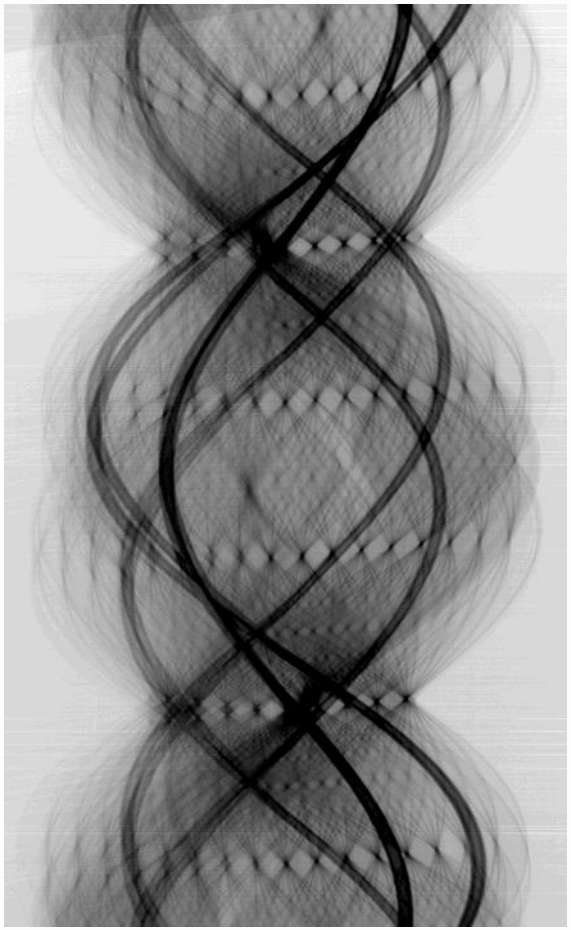
Block detector system + Anger logic [3]



Block detector Siemens-CTI ECAT 951, 8x8 block BGO with 4 PMTs (from [2])

Raw data stored in sinograms

Sinograms:
Measurement of the activity distribution of a radioactive tracer.



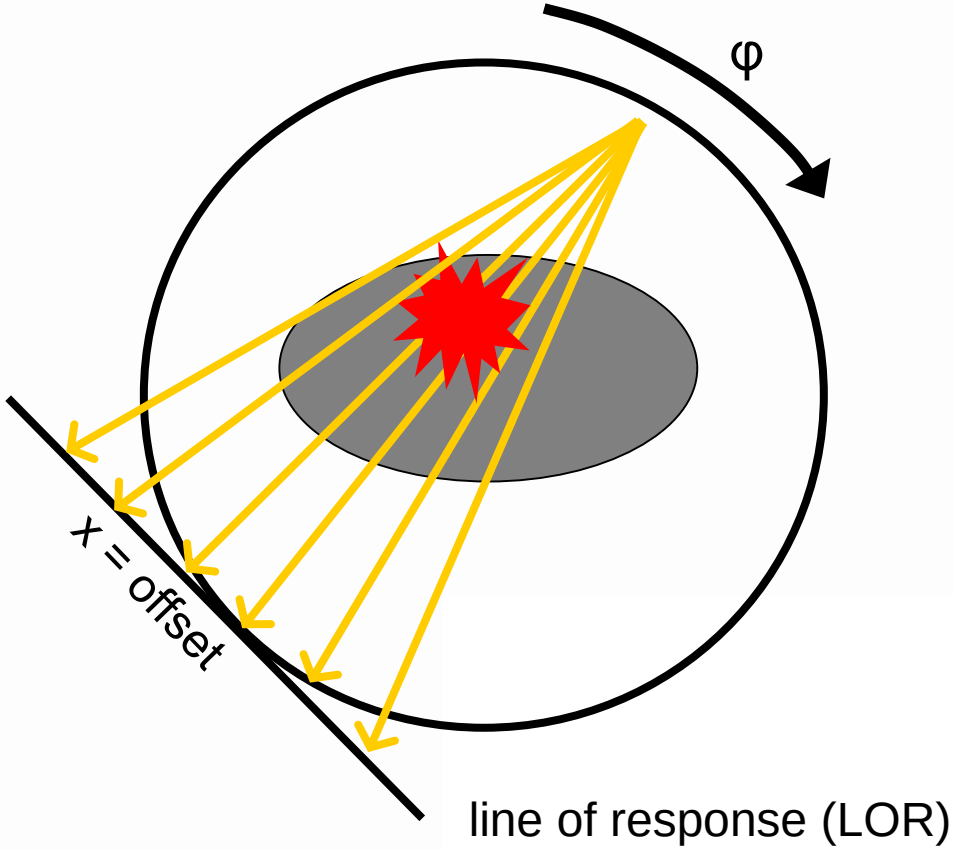
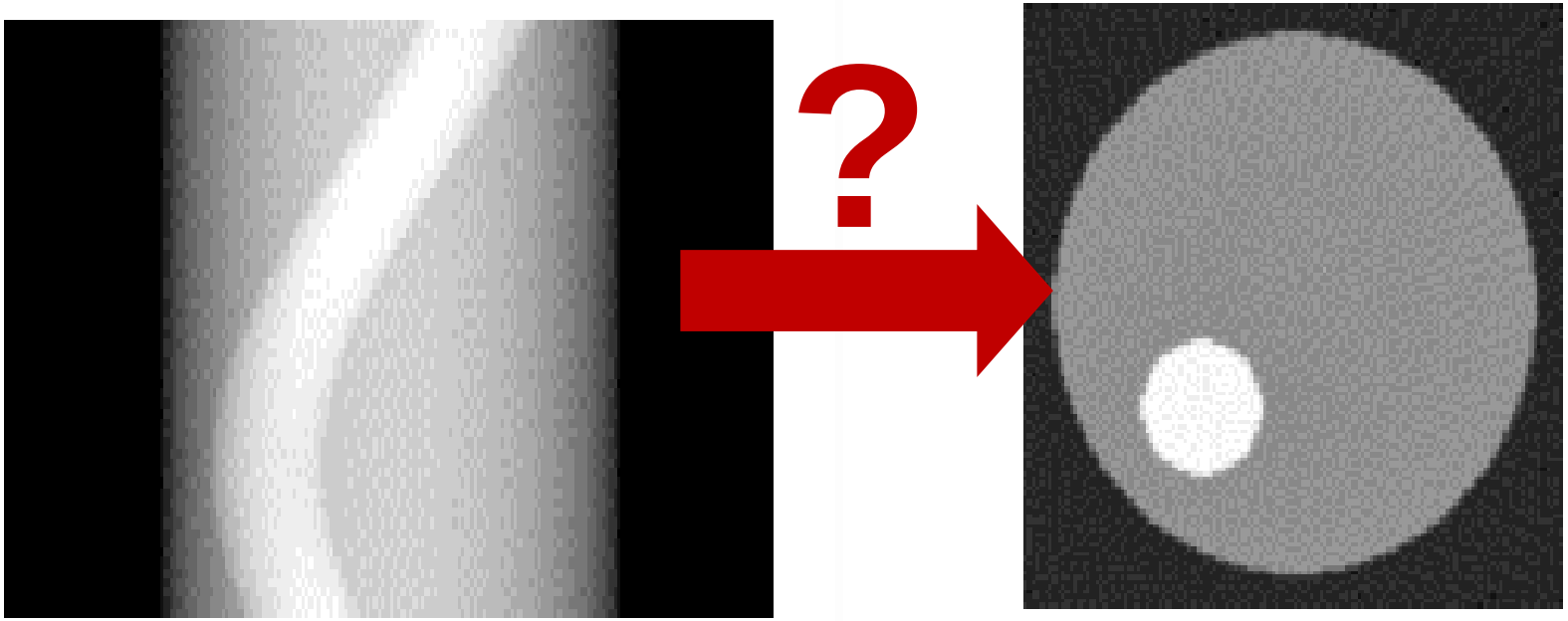


Image Reconstruction

sinogram ***Reconstructed image***



1. Filtered Backprojection
2. Iterative Reconstruction Methods

Timing Resolution and Coincidence Detection

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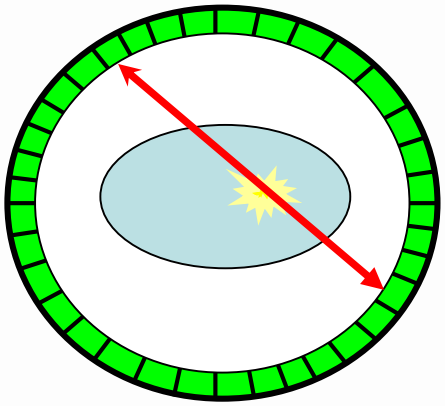
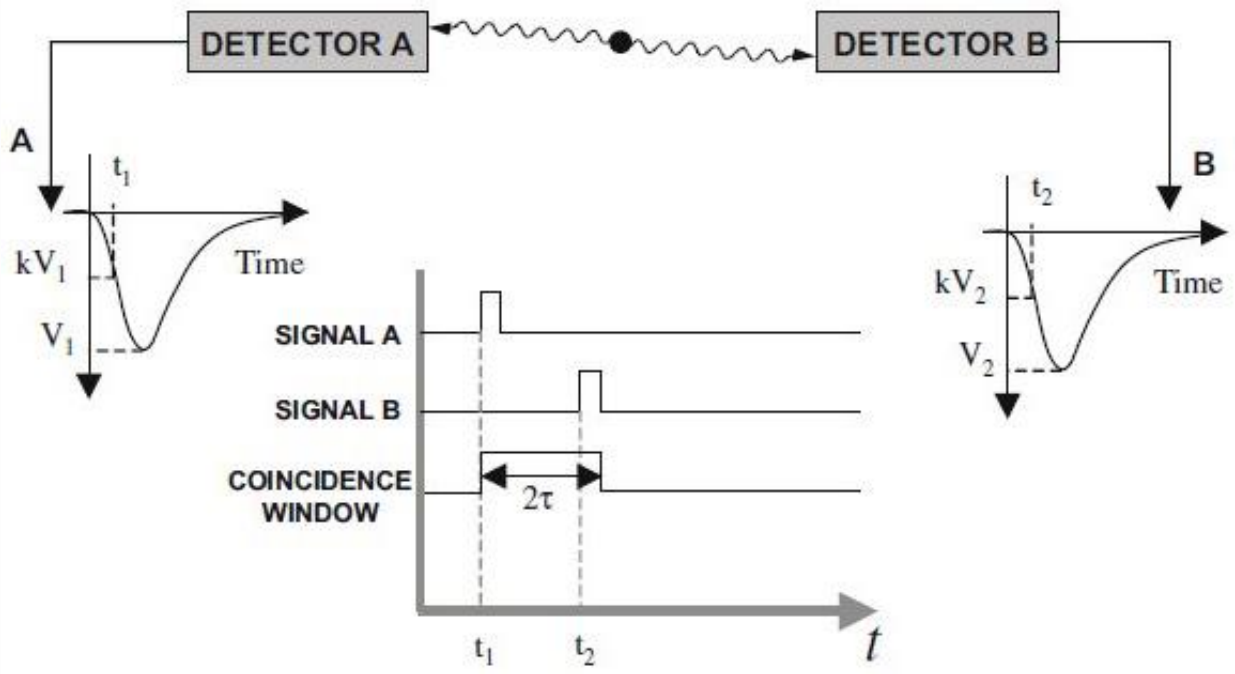


Coincidence time window: 2τ

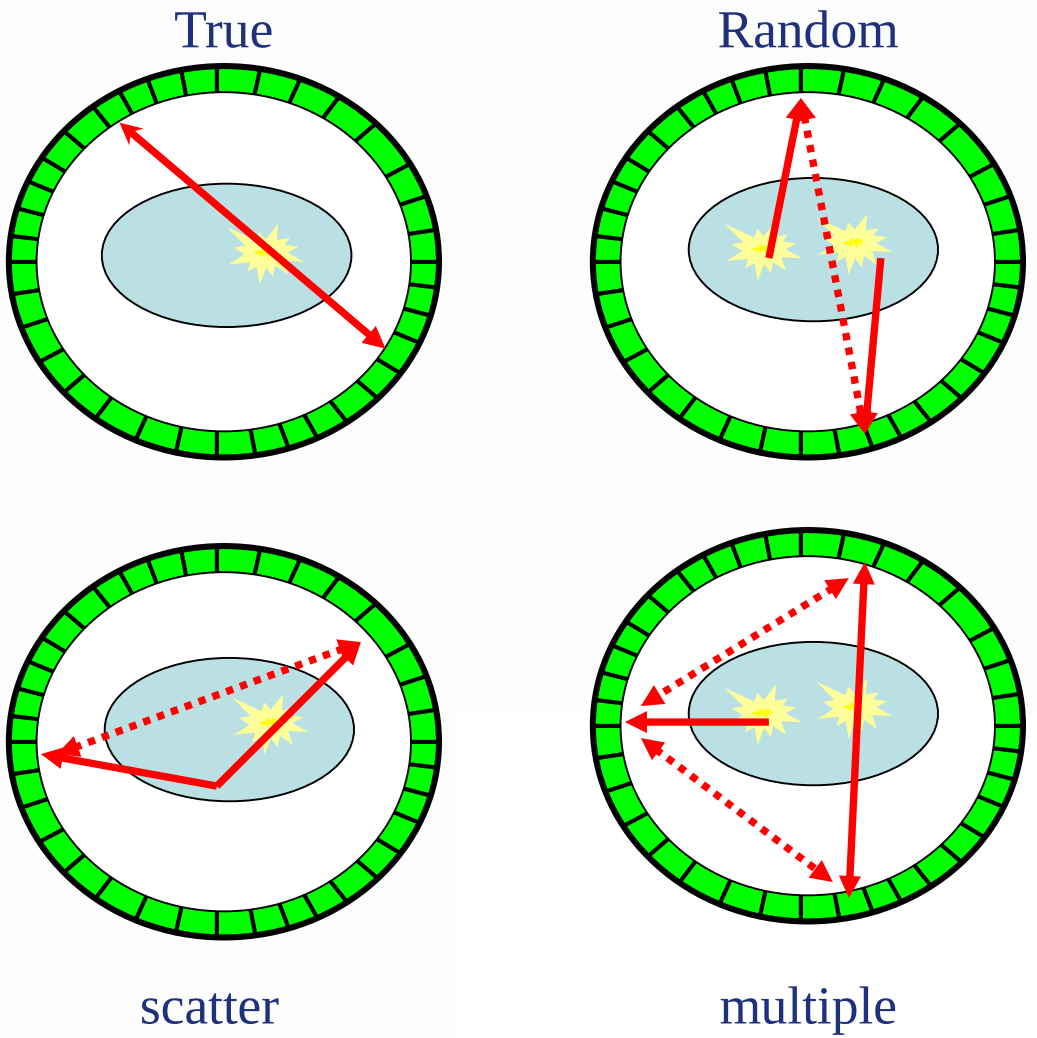


Time-of-Flight PET uses the time difference to improve estimate of origin of photons

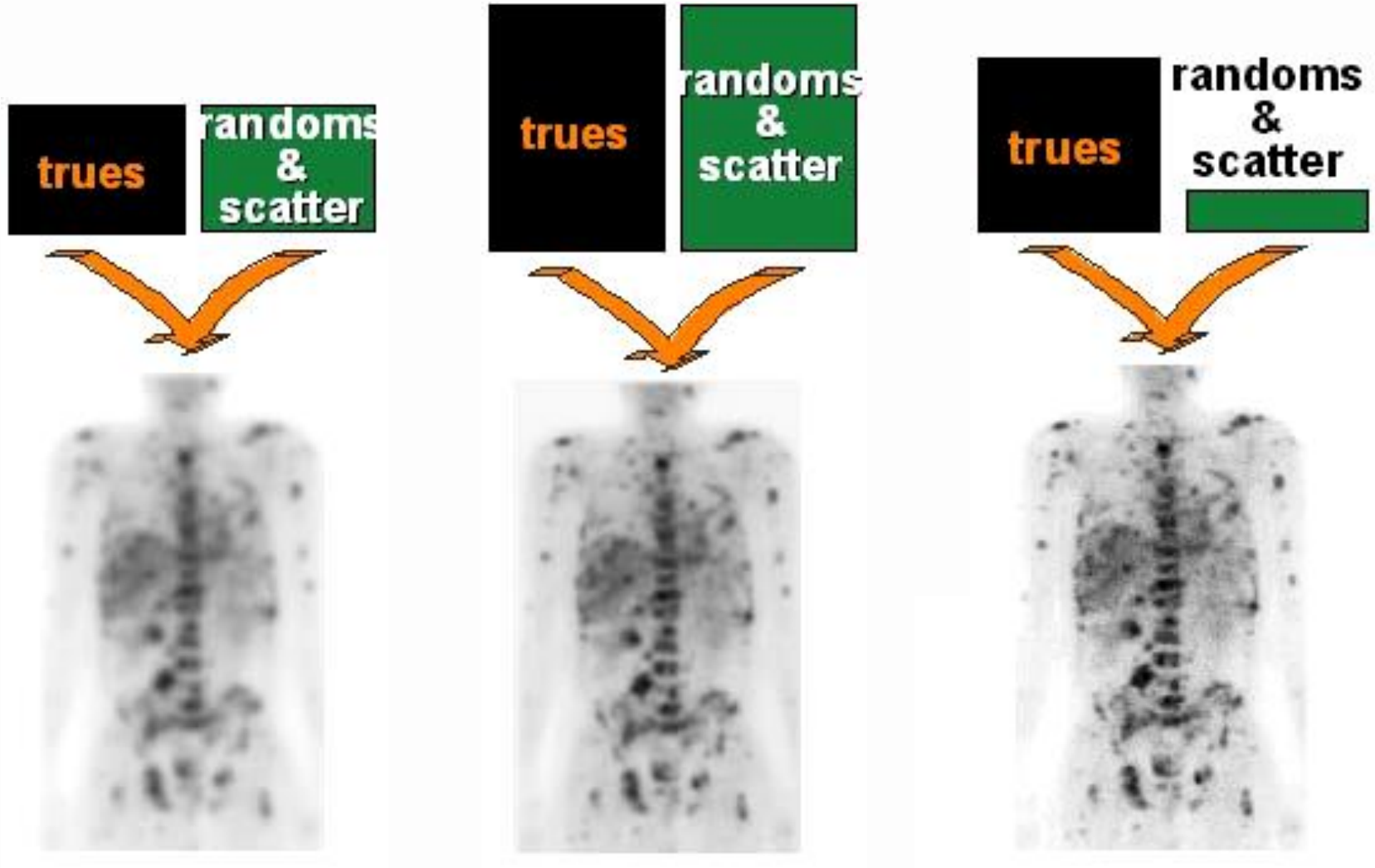
Not all coincidences are correct

Detection event is valid (= prompt event) if

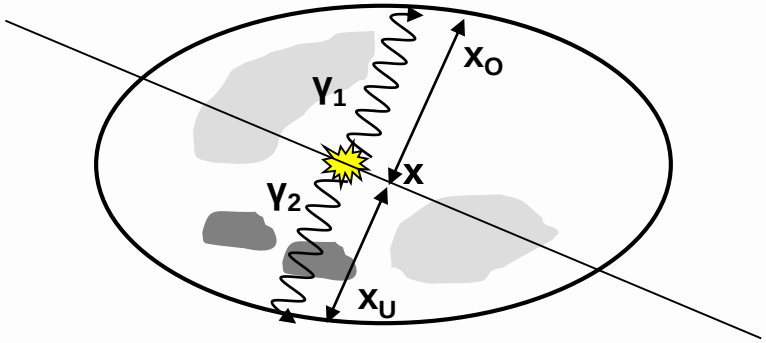
- Two photons are detected in coincidence window
- LOR is within valid acceptance angle
- Energy of both photons within selected energy window



Improved image quality due to random and scatter correction



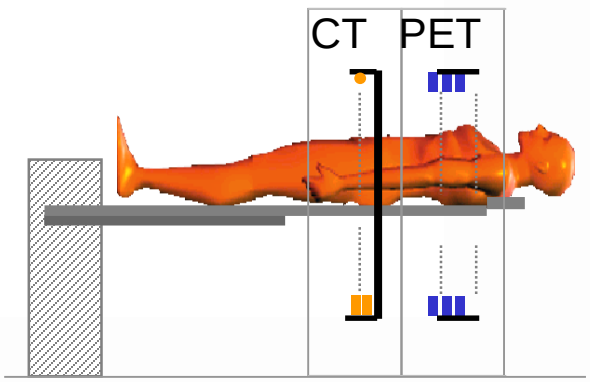
Attenuation correction



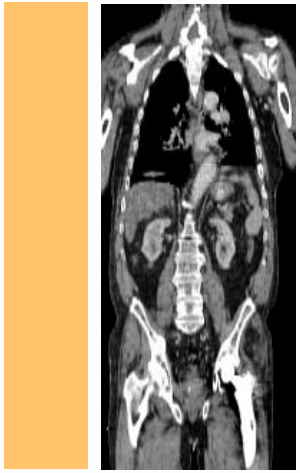
Accurate attenuation correction is possible if the line integral $\int_{x_u}^{x_o} \mu(x)dx$ can be obtained from a transmission measurement.

CT is used for attenuation correction!

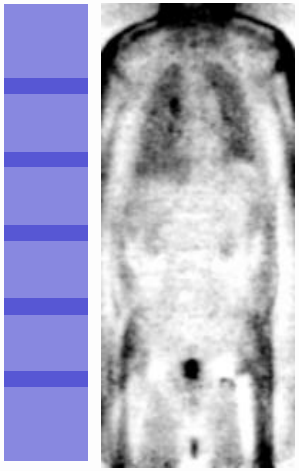
CT-based attenuation correction



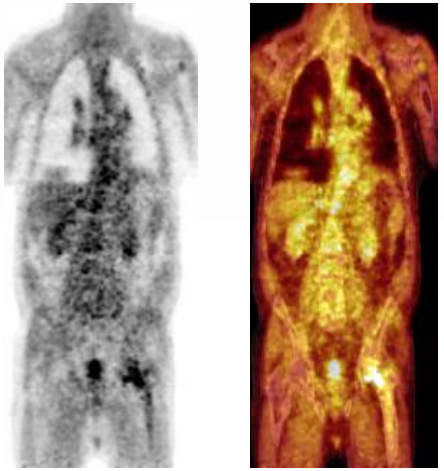
Topogram



CT



Emission



Attn-corr Emission

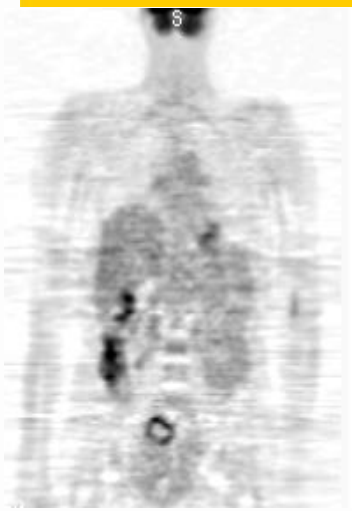
Image reconstruction

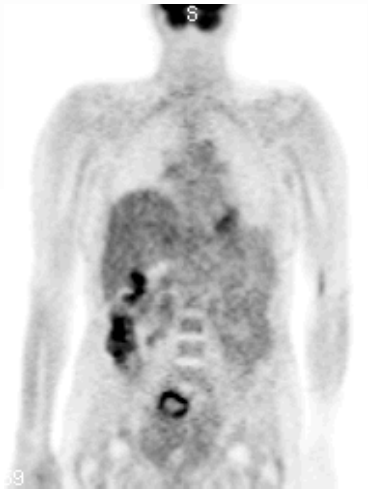
Analytical reconstruction

- Filtered back projection (FBP)
- Linear and thus quantitatively robust, but suffers from streak artefacts, noisy

Iterative reconstruction

- Ordered subset expectation maximisation(OSEM)
- Row-action maximum-likelyhood algorithm (RAMLA)
- Performance of iterative reconstruction is affected by number of iterations, subsets etc – convergence problems





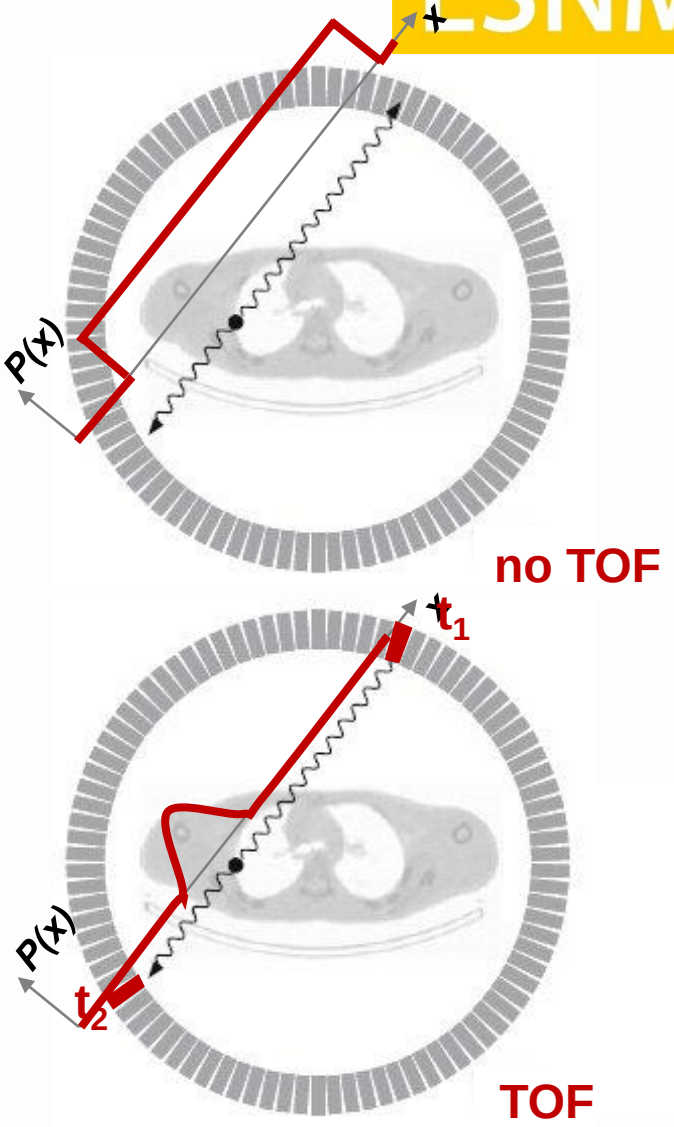
Time-of-Flight (TOF) PET

- Difference in flight time of photons is registered

$$\Delta t = \frac{2\Delta x}{c}$$

- Probability of event occurrence is limited to a certain area along the LOR

- Better SNR
  - Especially in the abdomen / heavy patients

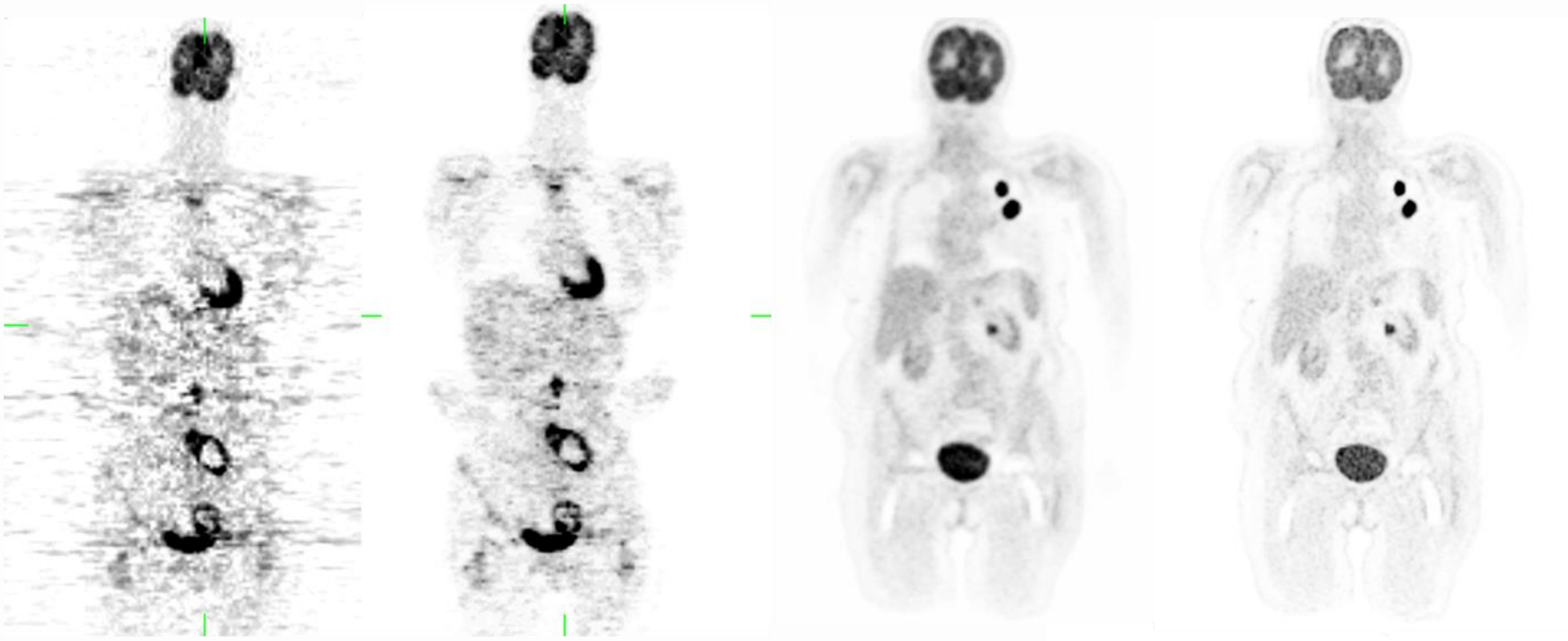


Improvement of PET/CT Image Quality

[18F]-FDG PET study performed on a PET-only BGO system:

[18F]-FDG PET study performed on a state-of-the art PET/CT system:

(A) (B) (C) (D)



FBP Reconstruction

Iterative Reconstruction

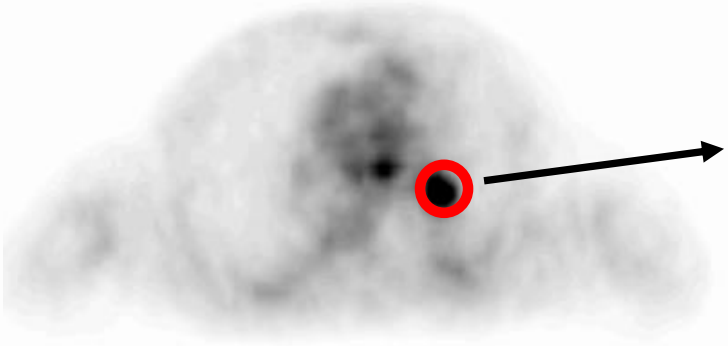
Iterative Reconstruction

TOF+PSF Iterative Reconstruction

Courtesy R. Boellaard, Amsterdam

Standardized uptake value (SUV)

SUV is a measure of mean uptake of activity into a tumour, normalised to administered activity and e.g. body weight or LBM or BSA

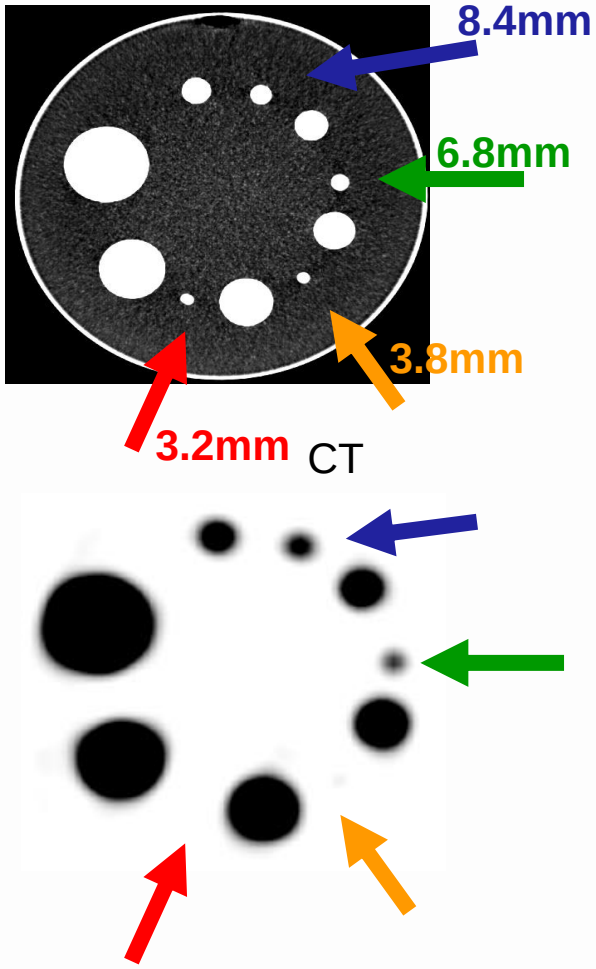


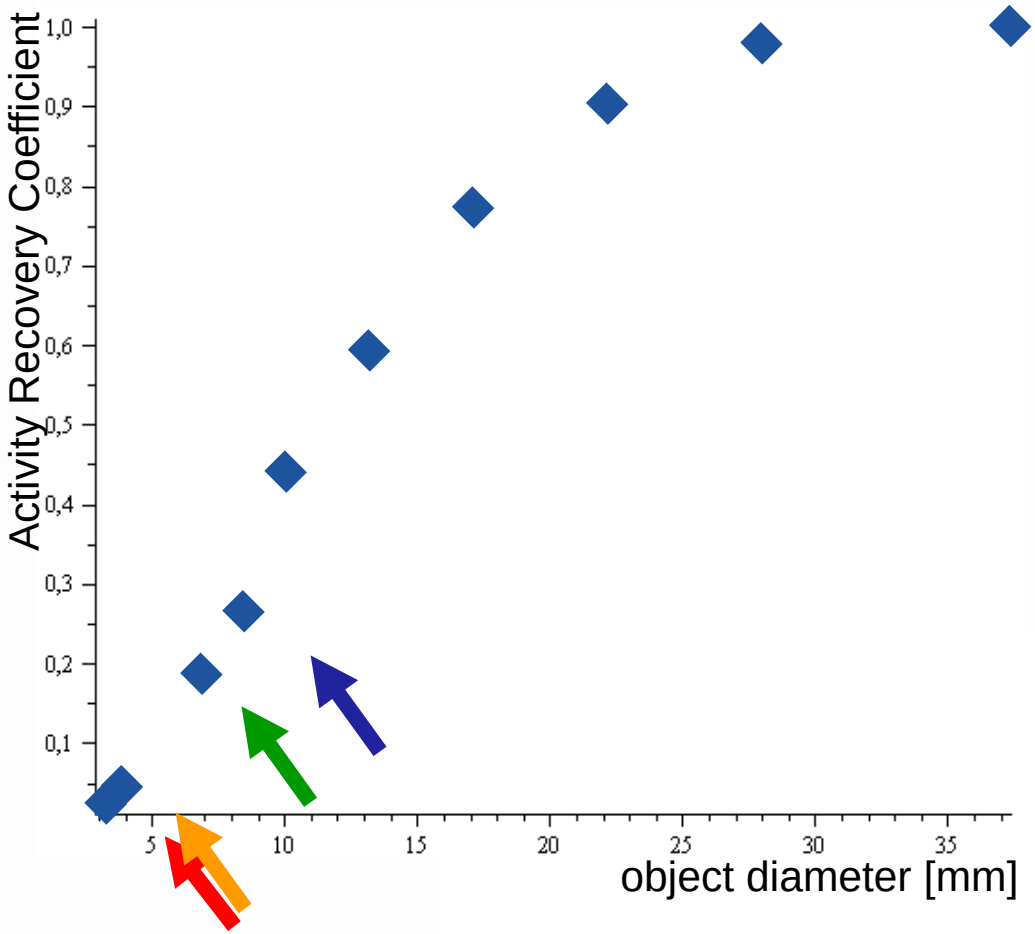
Region of Interest analysis: mean uptake (Bq/cc)

$$SUV_{TBW} = \frac{c_t\,[kBq/ml]}{Dose[MBq]/weight[kg]}$$

Activity Recovery, Partial Volume Effect

^{68}Ga Phantom measurements:





Factors affecting SUV

Biological factors

- blood glucose level
- patient motion
- patient comfort
- Inflammation

Technical factors

- scan acquisition parameters
- image reconstruction settings
- region of interest strategies
- SUV calculation/normalization
- use of blood glucose level correction
- use of contrast agents

Errors

- cross-calibration PET versus dose calibrator
- rest/remaining activities in syringe
- incorrect synchronization of clocks
- use of injection time rather than dose calibration time
- paravenous injection

SUV requirements

- Accurate measurement of net injected dose
  (remaining activities, clocks, calibration vs injection time)
- Accurate measurement of weight, length of patient & (plasma glucose level) before scanning
- Accurate calibration of PET scanner
- Accurate corrections of PET data
- Standard patient preparation procedures
- Standard image acquisition procedures
- Standard reconstruction and filtering methods
- Standard data analysis methods (ROIs)

Protocol for standardization of FDG-PET provides recommendations for:

- Minimizing physiological or biological effects by strict patient preparation
- Procedures to ensure accurate FDG dose and administration
- Matching of PET study statistics by prescribing FDG dosage as function of patient weight, type of scanner, acquisition mode and scan duration
- Matching of image resolution by specifying image reconstruction settings and providing activity concentration recovery coefficients specifications
- Standardization of data analysis by prescribing obligatory and preferred region of interest strategies and SUV measures and corrections
- Multi-center QC procedures for PET and PET/CT scanners
- During start up phase: central data analysis using standard data analysis and QC software tools (freely available for participating centers)

Eur J Nucl Med Mol Imaging. 2015; 42: 328–354.
Published online 2014 Dec 2. doi: 10.1007/s00259-014-2961-x
PMCID: PMC4315529

FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0

Ronald Boellaard, Roberto Delgado-Bolton, Wim J. G. Oyen, Francesco Giammarile, Klaus Tatsch, Wolfgang Eschner, Fred J. Verzijlbergen, Sally F. Barrington, Lucy C. Pike, Wolfgang A. Weber, Sigrid Stroobants, Dominique Delbeke, Kevin J. Donohoe, Scott Holbrook, Michael M. Graham, Giorgio Testanera, Otto S. Hoekstra, Josee Zijlstra, Eric Visser, Corneline J. Hoekstra, Jan Pruim, Antoon Willemsen, Bertjan Arends, Jörg Kotzerke, Andreas Bockisch, Thomas Beyer, Arturo Chiti, and Bernd J. Krause

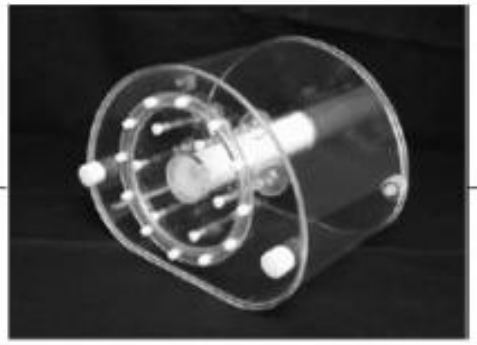
EARL accreditation

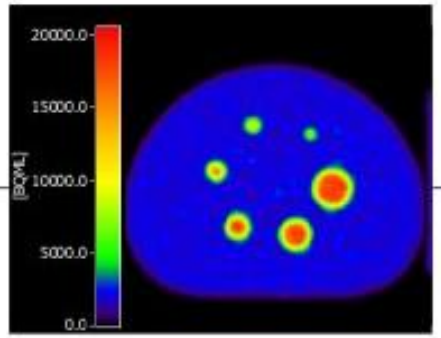
- to provide a minimum standard of PET/CT scanner performance in order to harmonise the acquisition and interpretation of PET scans
- ensure similar performance of PET/CT systems within a multicentre setting
- characterisation of imaging site by continuing quality control, making it highly eligible as a participant in multicentre studies
- high quality of routine patient examinations

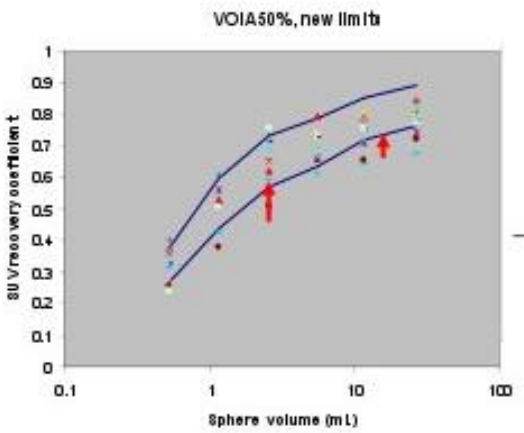
EARL: Multicenter QC and calibration

- Calibration
  - Minimum allowable deviation: +/- 10%

- SUV recovery
  - For SUV_{max}
  - For SUV_{mean}







http://www.earl.eanm.org

Acknowledgments

Daniela Thorwarth

Uulke van de Heide

PET tracers and biology

Wouter Vogel
NKI-AVL, Amsterdam

May 2016, Lisbon
Course on Molecular Imaging and Radiation Oncology

Contents

- General concept
- Impact on treatment decisions
  - Diagnostics
  - Radiation oncology
- Tracers
  - FDG
  - F-choline
  - F-MISO

Tumor cell biology

- Genetical basis
- Damage to DNA sequence
- Activation of oncogenes (4-6)

De-differentiation

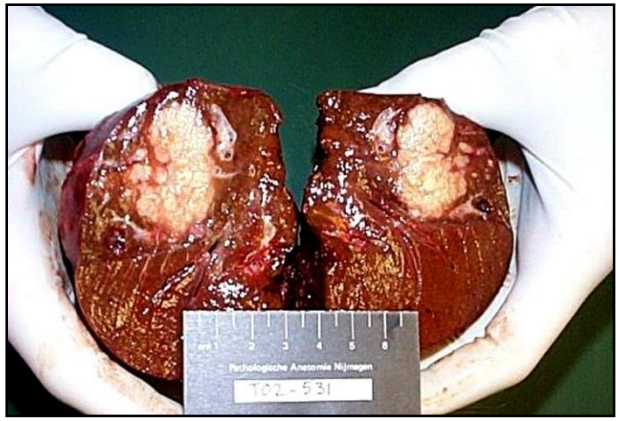
- Uncontrolled proliferation
- Loss of complex pathways
- Inefficient energy utilization

Adaptation

- Increased energy demand
- Activation of basic metabolic pathways
- Expression of primitive receptor sets

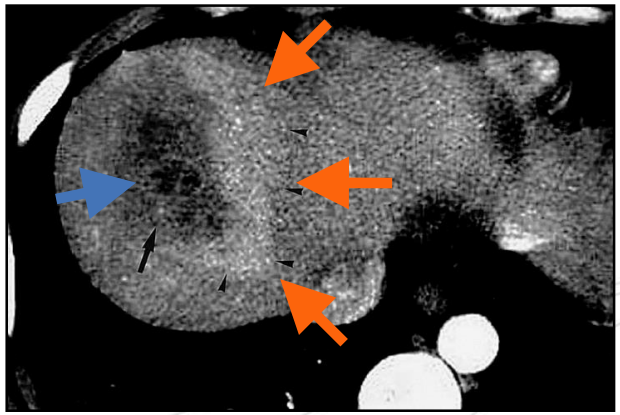
Subsequent tissue changes

- Local effects
- Destruction of tissue structure
- Expanding mass effects
- Increased tissue pressure
- Poor perfusion, hypoxia



Regional effects

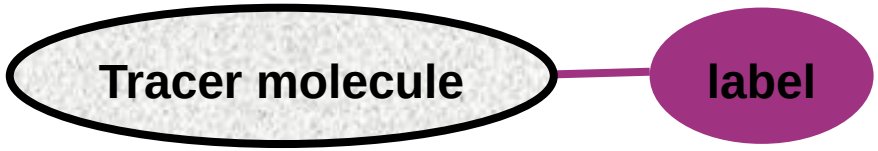
- Excretion of cytokines
- Inflammation
- Neovascularization



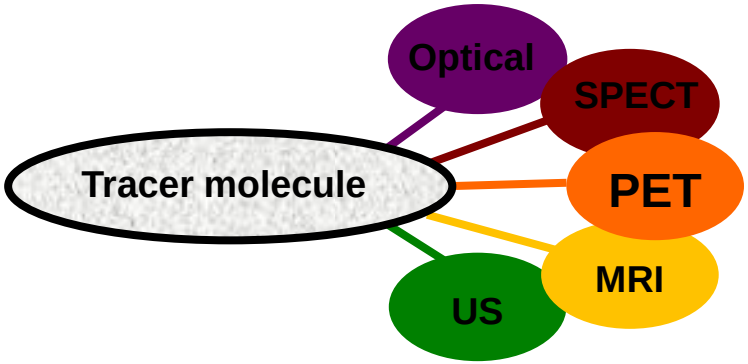
Cancer invokes many changes in functional and metabolic pathways, that can potentially be imaged

Metabolic tracers

- Specific molecules
- That are involved in a metabolic pathway of interest
- That can be delivered by perfusion
- That accumulate in the presence of a specific disease
- That are chemically feasible for stable „labeling“
- That are applicable for human use



Labels for molecular imaging



• CT	Dense label	Iodine, Barium
• Ultrasound	Echogenic label	Air bubbles
• Optical	Fluorescent label	Luciferine
• (f)MRI	Paramagnetic label	Iron particles
• NM/SPECT	Gamma emitters	Tc-99m, In-111, I-123
• PET	Positron emitters	F-18, Ga-68, I-124

Metabolic tracers

Example tracers

• Cell metabolism	Glucose - F18
• DNA synthesis	Thymidine - F18
• Cell membrane synthesis	Choline - C11 / F18
• Somatostatin receptor expression	Octreotate - Ga68
• Tissue hypoxia	Misonidazole - F18
• ...	

Highly specific tracers in nuclear medicine

Biological characteristics related to radiotherapy

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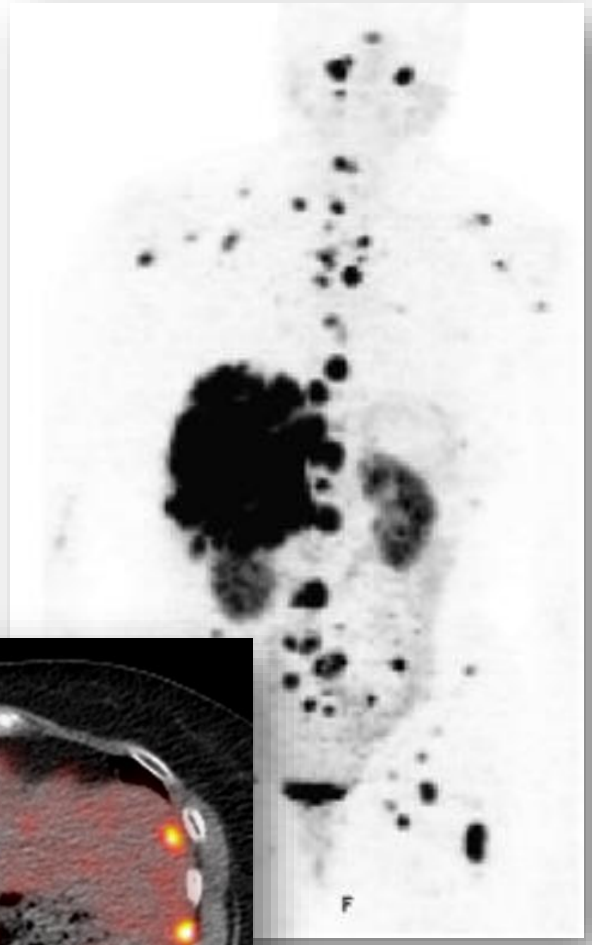
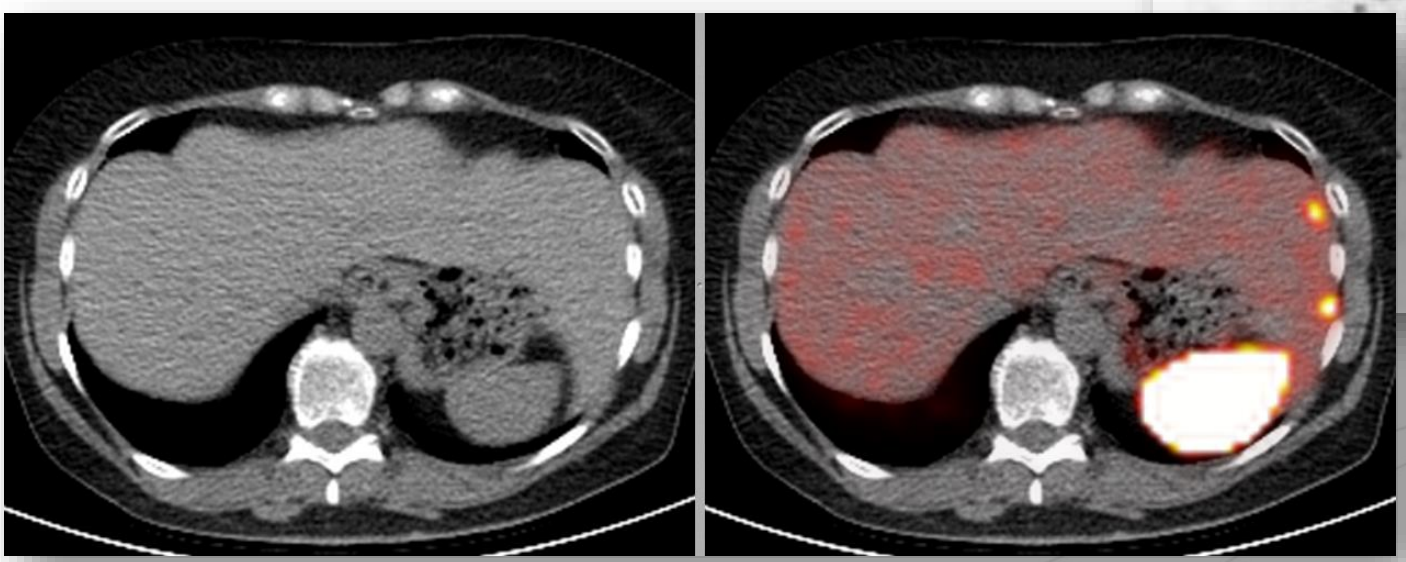
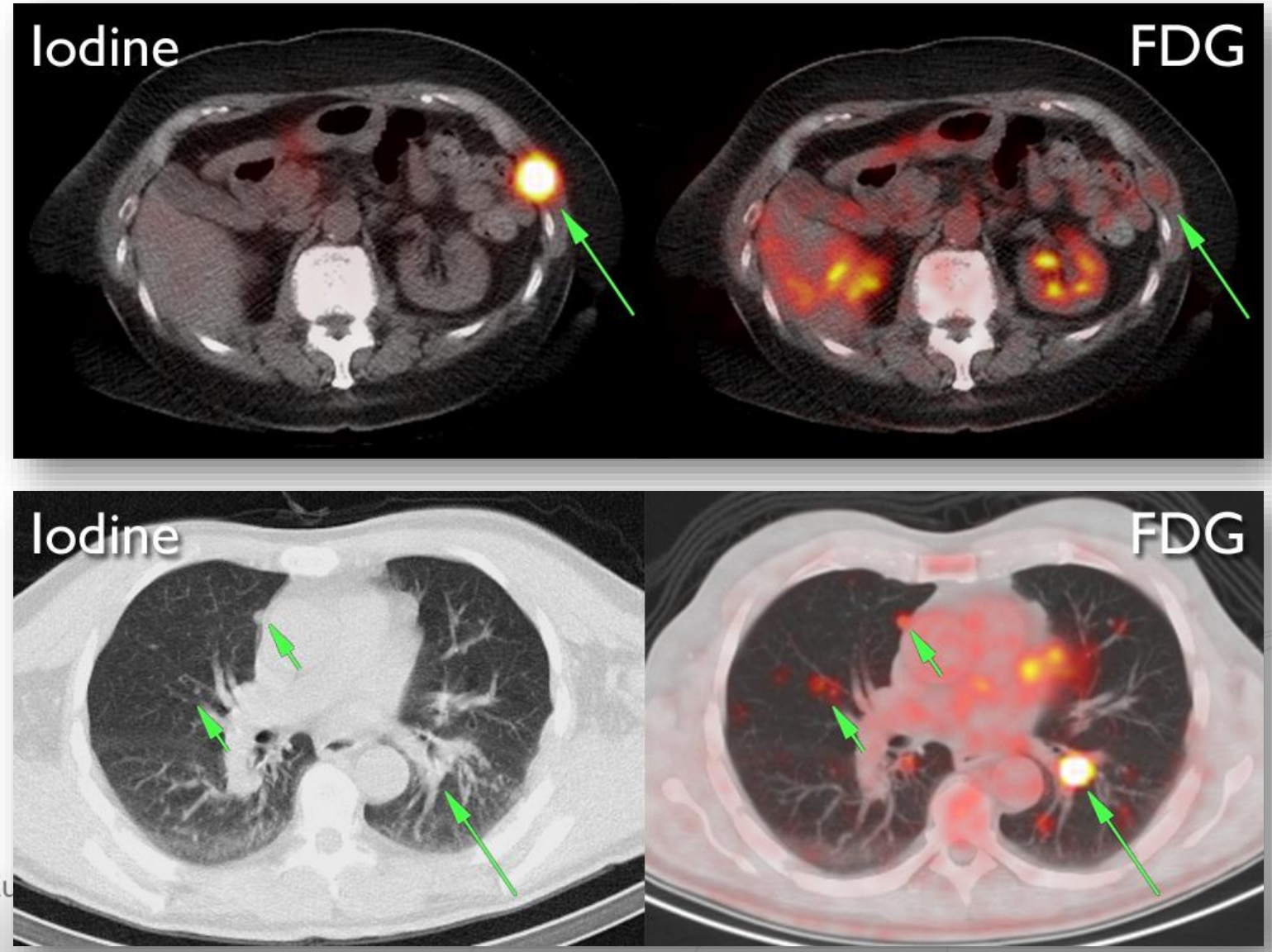
^{68}Ga-octreotate (NET)

Biological equivalent for treatment with Lutetium-octreotate





^{124}Iodine – Thyroid carcinoma



Treatment decisions

Nuclear medicine

- High diagnostic certainty
- Linear relation with treatment effect
- Direct impact in management

Radiation oncology

- Not so much…

FDG

Biological characteristics related to radiotherapy

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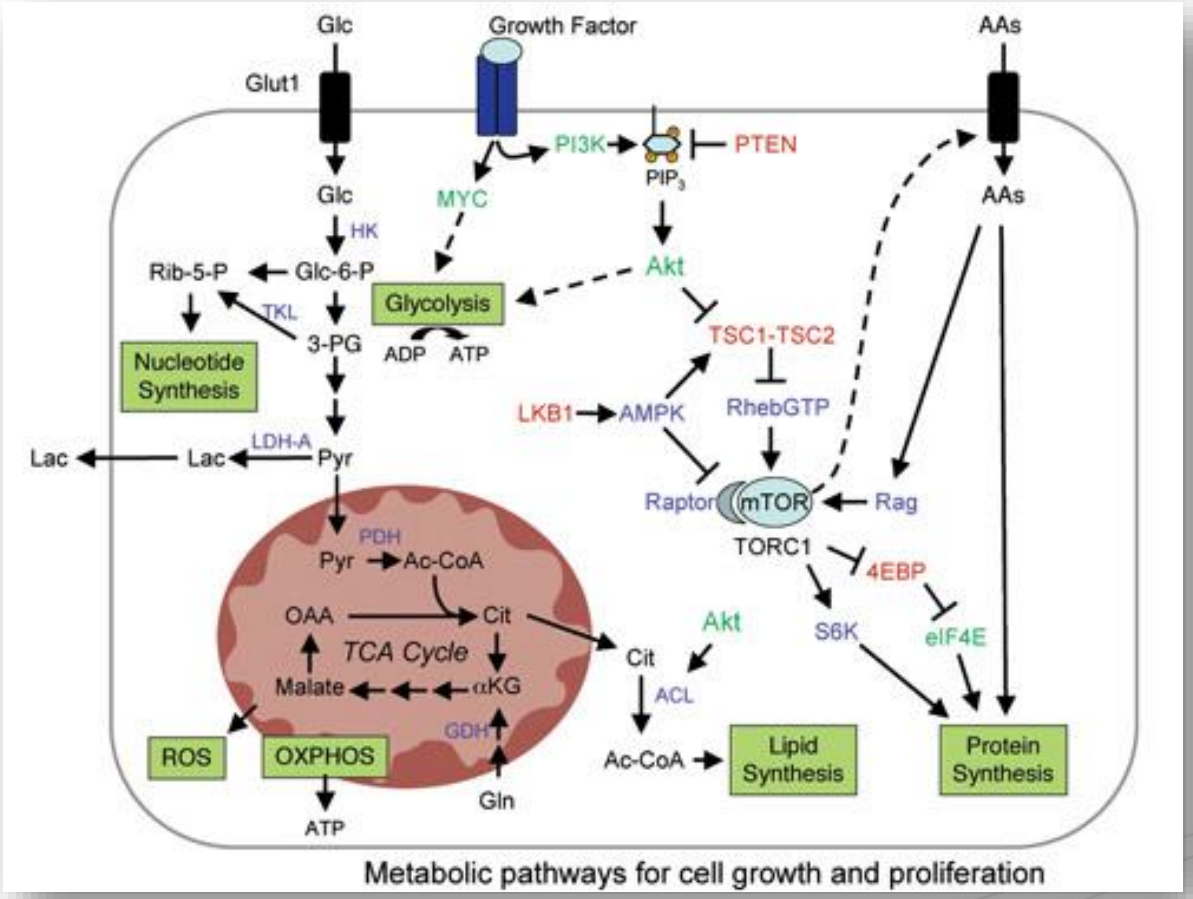
the FDG pathway



Is this essential knowledge?

Optimizing the FDG pathway

Maximum contrast between tumor and normal tissues

Tumor tissues ← **Just the way it is**

Patient / normal tissues ← **Can be optimized!**

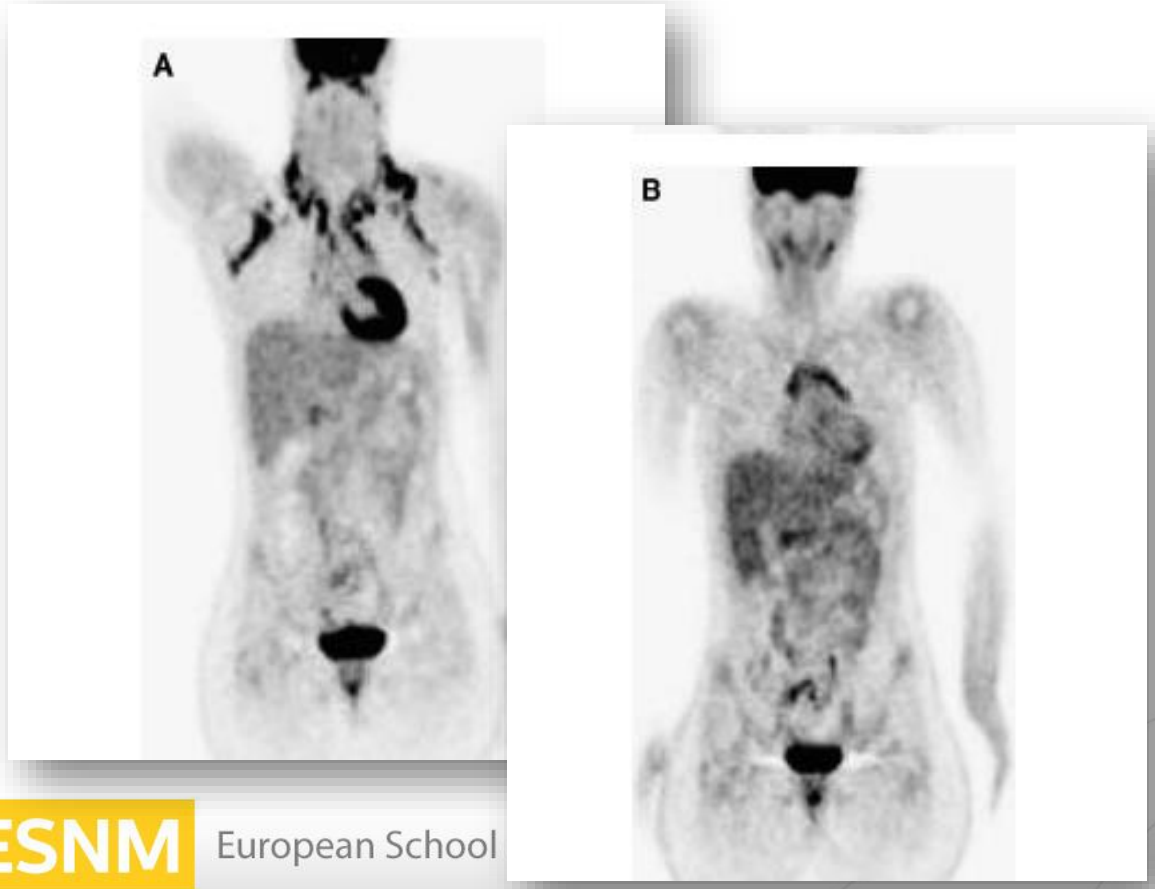
- Muscles
- Renal excretion
- Inflammation
- Diabetes mellitus

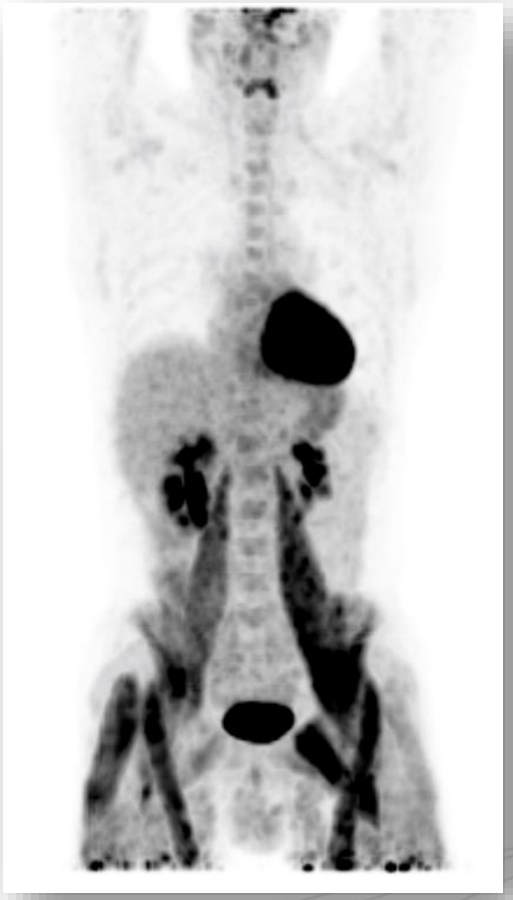
Patient preparation

- Inflammation
- Muscle activity

Diabetes

Fasting





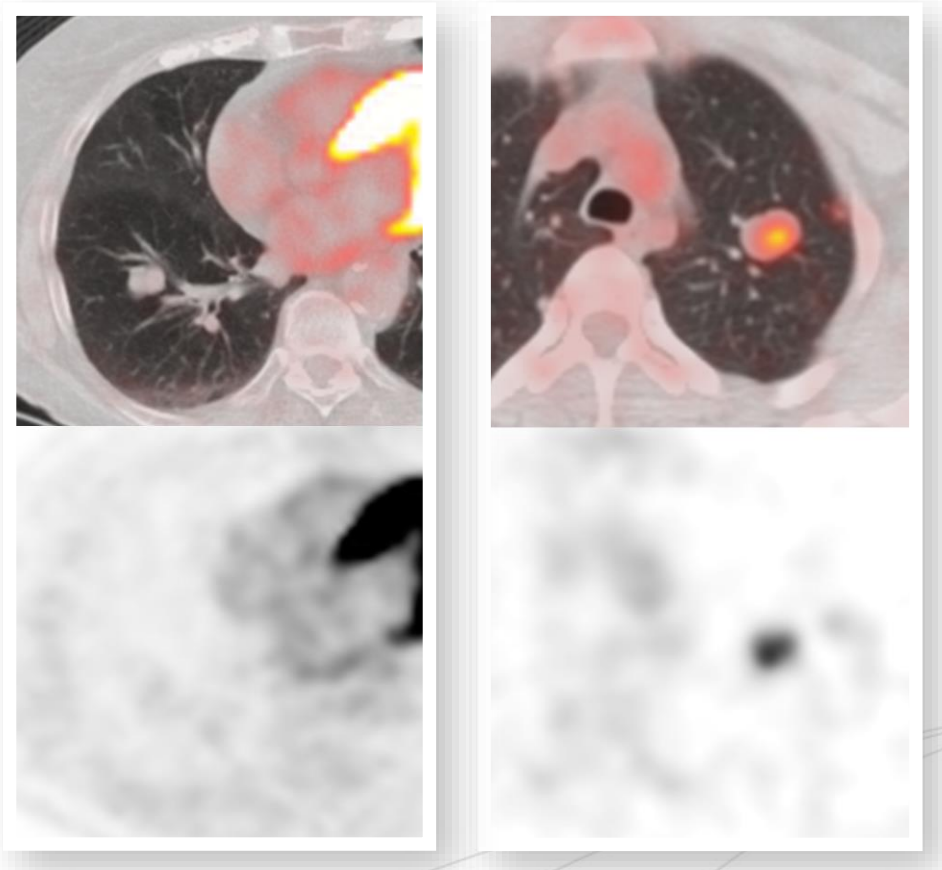
Excellent tumor identification (NSCLC)

Coin lesion

- Sensitivity 97%
- Specificity 79%

Impact on management

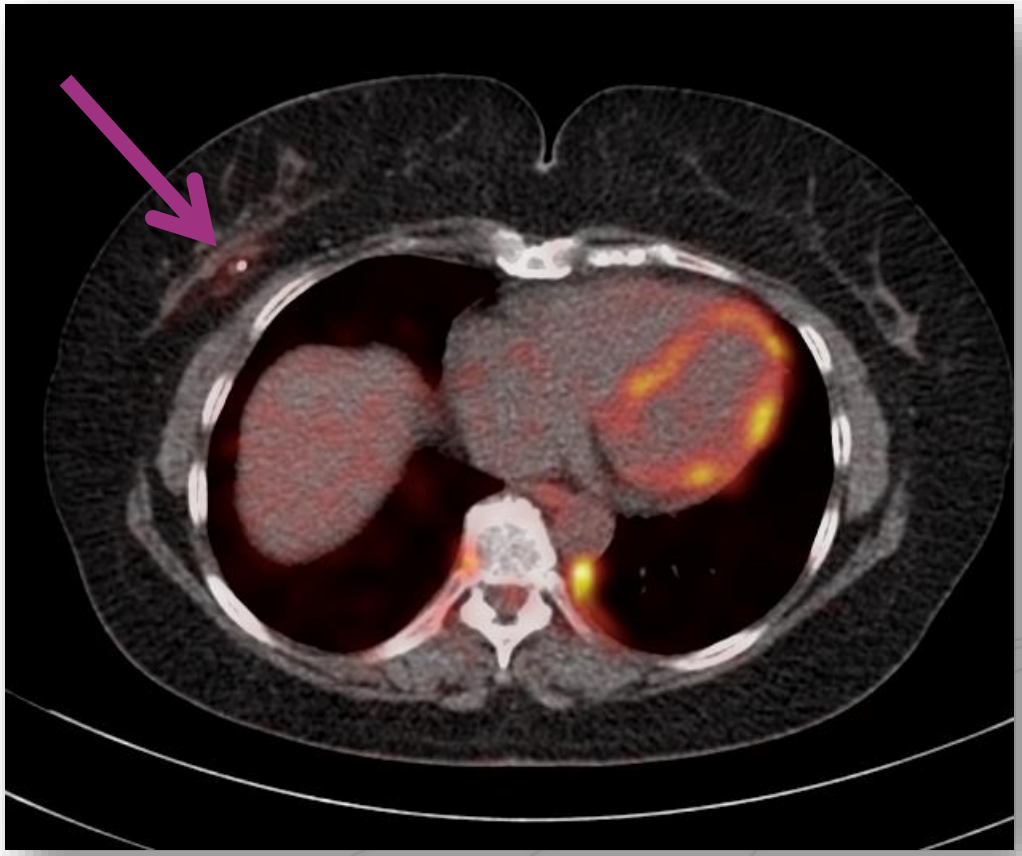
- Negative Follow-up
- Positive Biopsy **or direct treatment**



Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care 18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review.
Ung et al. J Natl Cancer Inst. 2007 Dec 5;99(23):1741-3.

Poor tumor identification (breast)

Diffuse grade I invasive lobular carcinoma



What does FDG show ?

Signal comes from

- Cells that proliferate
- Cells that de-differentiated
- Cells that show Glut-1 expression
- Cells that are hypoxic

PET shows voxels containing

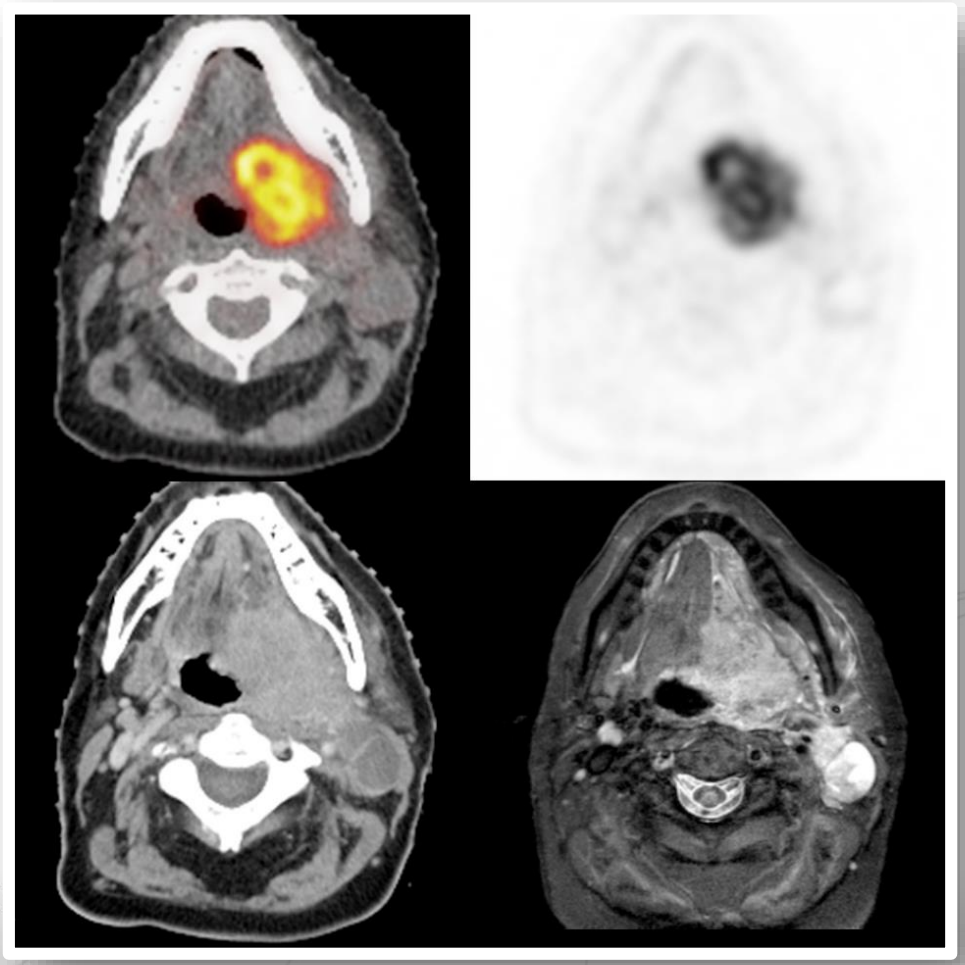
- Many tumor cells
- Aggressive biology
- Likely to be radioresistant

PET positive areas contribute to GTV definition

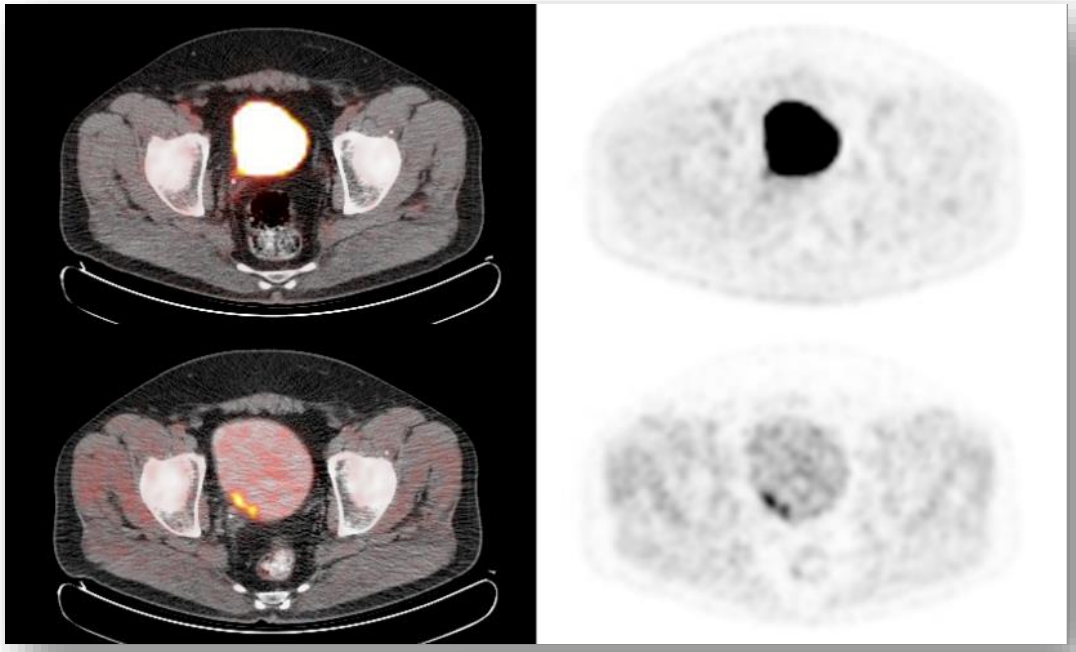
FDG may miss tumor

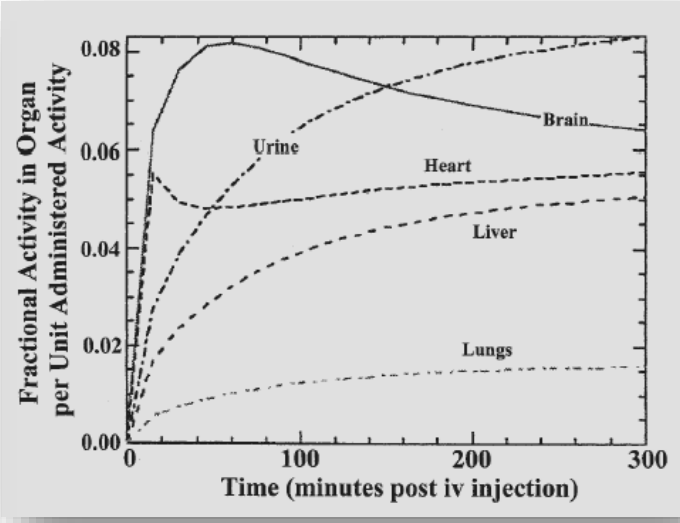
But not

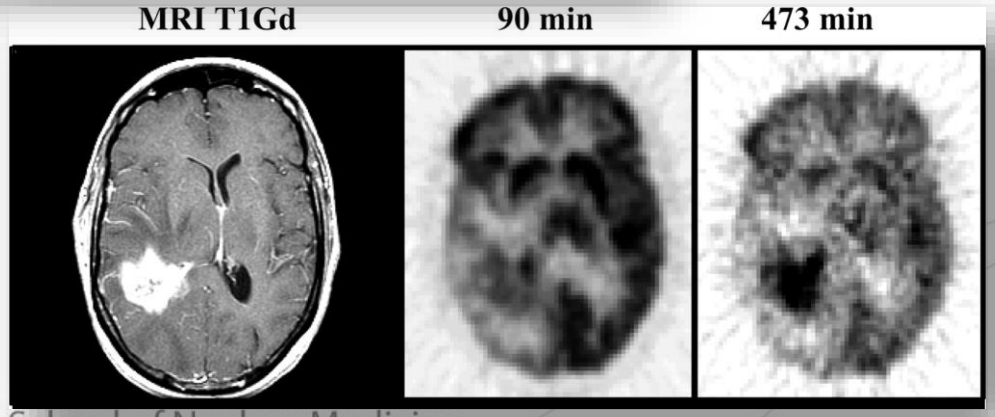
- Microscopic extentions
- Superficial spread
- Diffuse infiltration
- Necrotic parts
- Well differentiated tumor parts



Longer biodistribution?







Biological consequences

Properly applied FDG PET

- Has a relation with tumor biology

- **Contributes to GTV definition**
- **Can define biological boost definition**

F-choline

Biological characteristics related to radiotherapy

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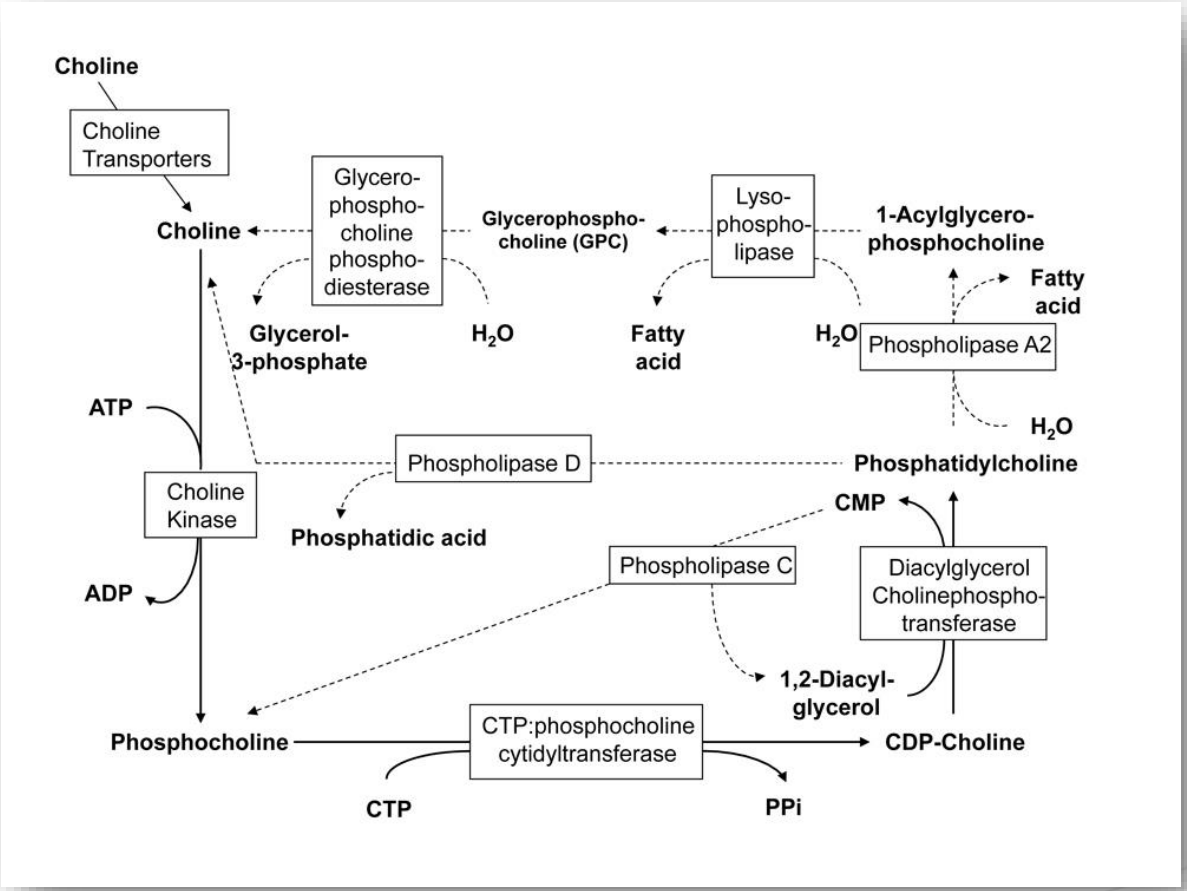
the choline pathway



Is this essential knowledge?

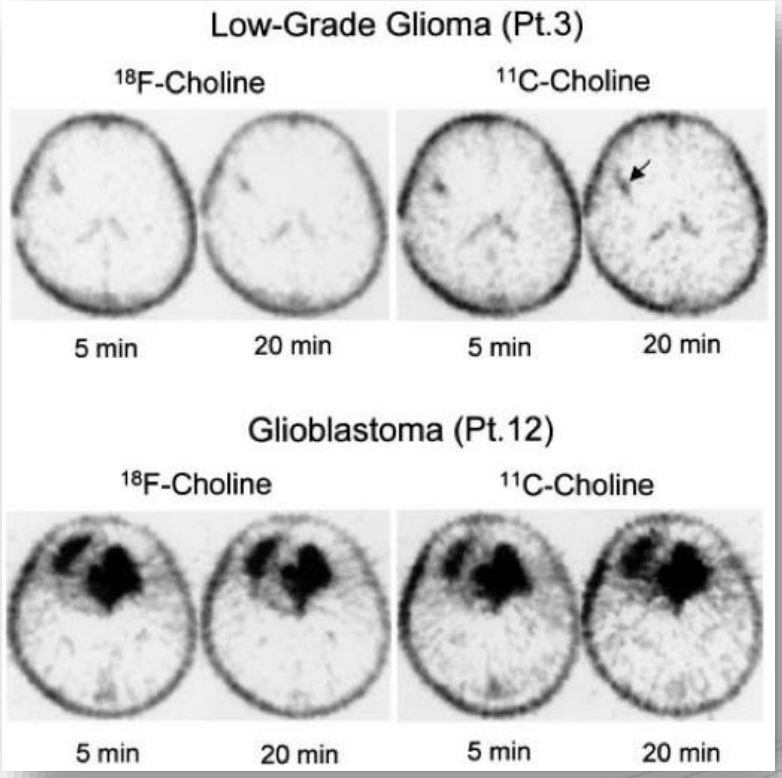
Timing and radionuclide?

^{11}C-choline

- On-site cyclotron required
- Short halflife (20 min)
- No renal excretion

^{18}F-(m)ethyl-choline

- No cyclotron required
- Road transport possible
- Renal excretion



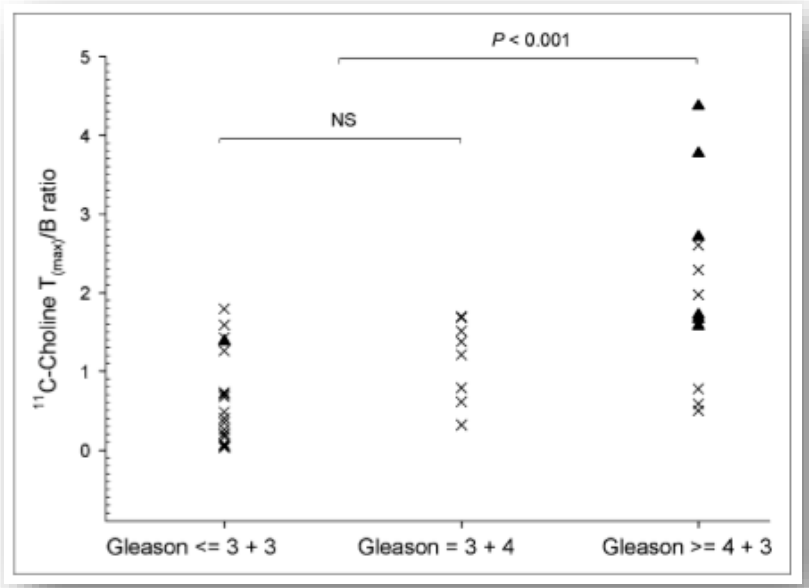
- No relevant differences for detection of glioma

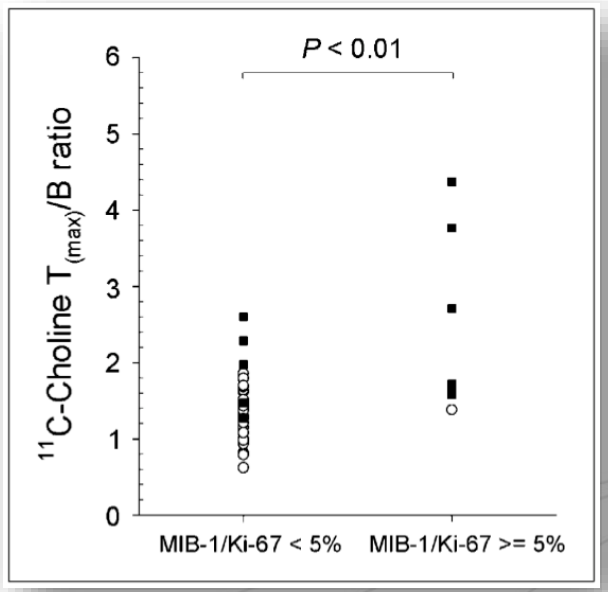
J Neurosurg. 2003 Sep;99(3):474-9. Use of 18F-choline and 11C-choline as contrast agents in positron emission tomography imaging-guided stereotactic biopsy sampling of gliomas. Hara T, et al.

Relation with tumor proliferation

Conflicting evidence

- Correlates with proliferation in cell culture (1)
- Does not correlate with Ki-67 in human prostate ca in vivo (2)

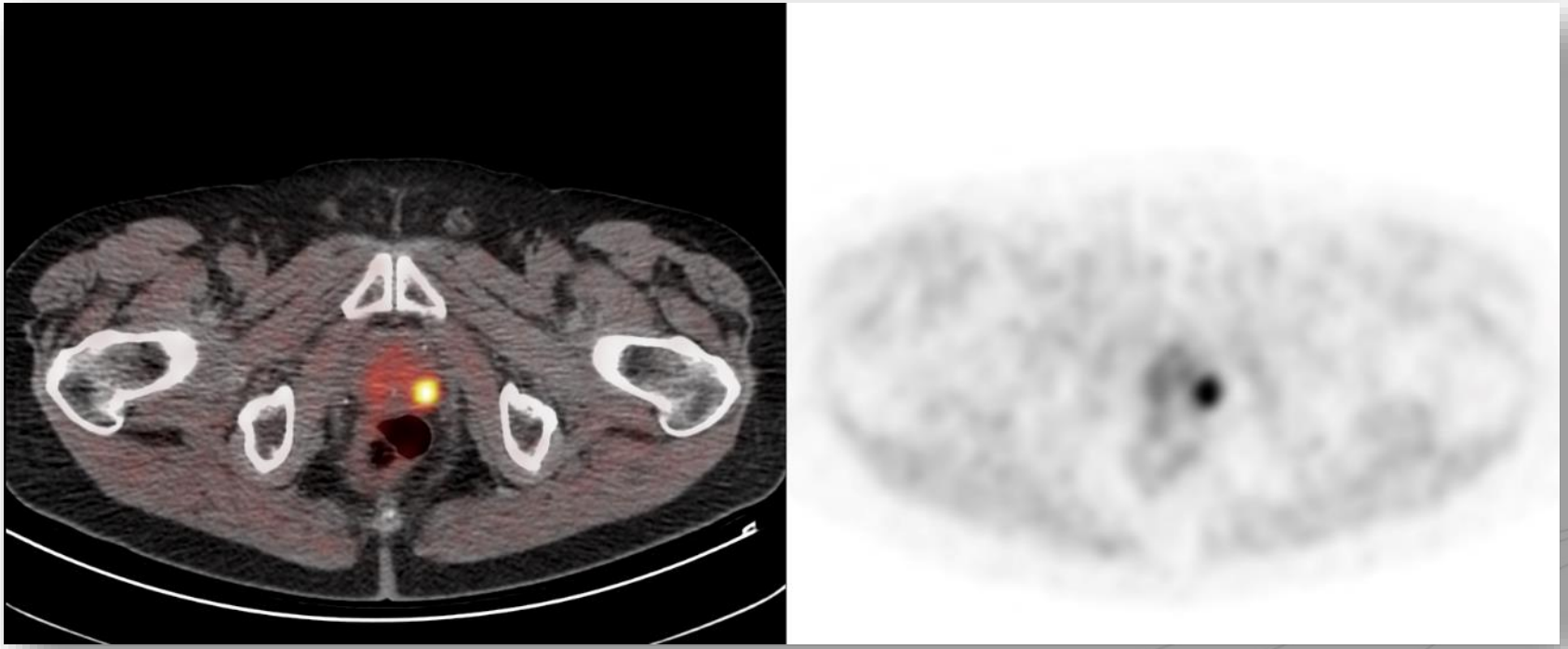




- (1) Al-Saeedi F et al. Eur J Nucl Med Mol Imaging. 2005 Jun;32(6):660-7.
- (2) Breeuwsma AJ et al. Eur J Nucl Med Mol Imaging. 2005 Jun;32(6):668-73
- (3) Piert et al 2009

Example

Is this the whole tumor?



Biological consequences

Properly applied Choline PET

- Has a relation with tumor biology

- **Contributes to GTV definition**
- **Can define biological boost definition**

F-MISO

Biological characteristics related to radiotherapy

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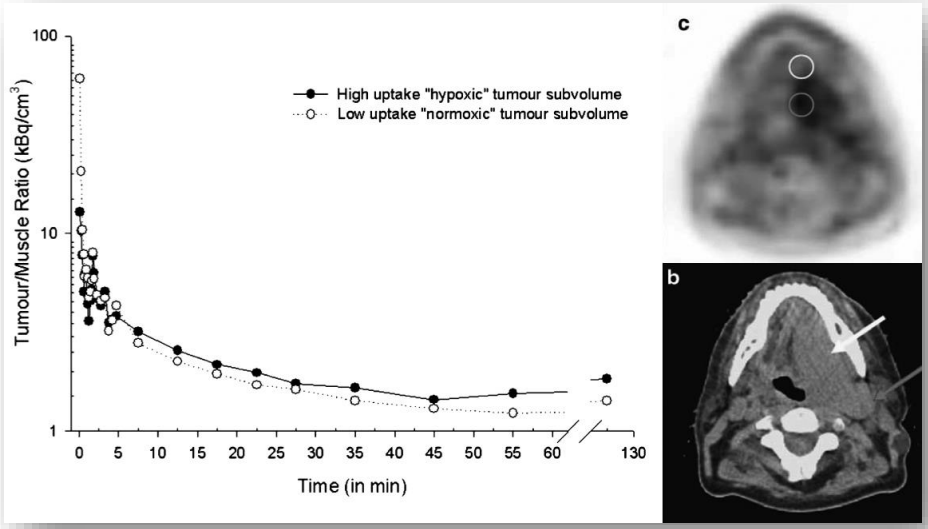
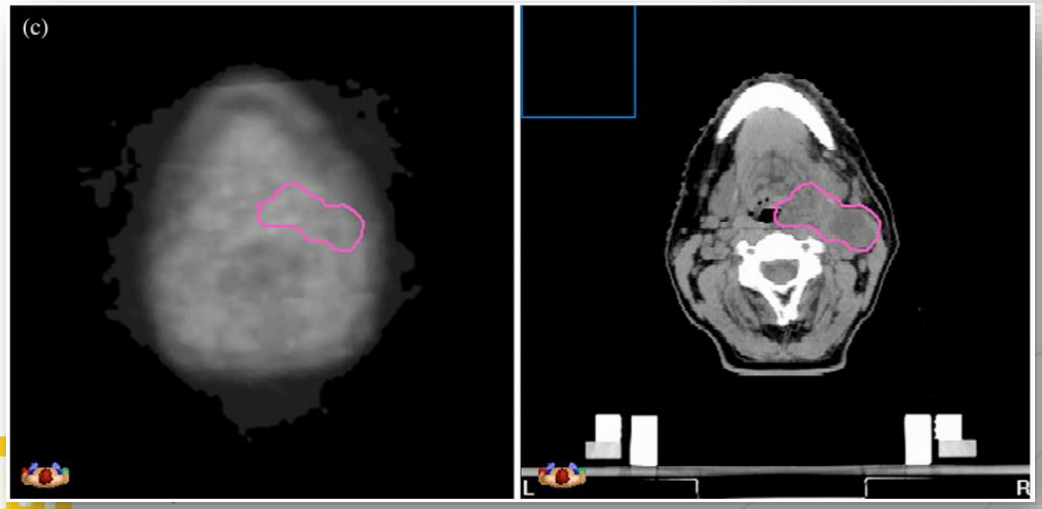
F-MISO biodistribution

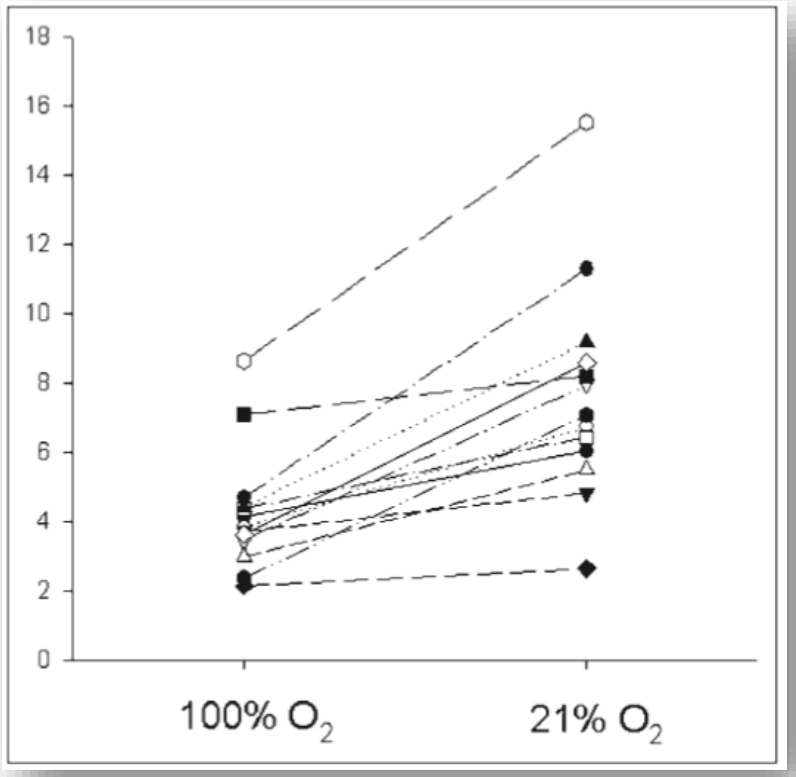
- Perfusion
- Vascular permeability
- Activated anaerobic enzyme path binding

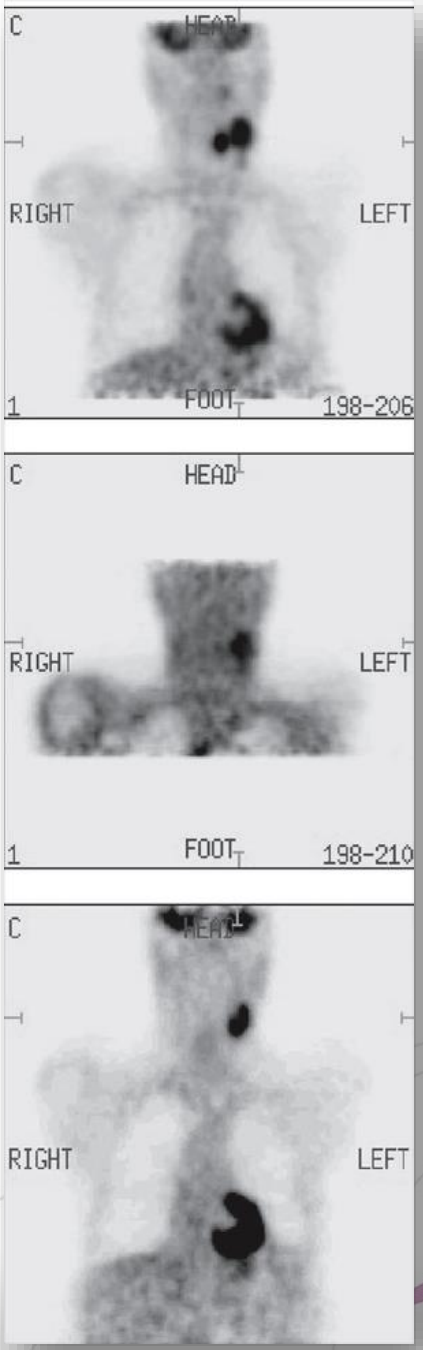




Biological relevance

- Identification of radioresistent tumor subvolume





Biological consequences

Properly applied FMISO PET

- Has a relation with tumor biology

- **Can NOT contribute to GTV definition**
- **Can define biological boost definition**

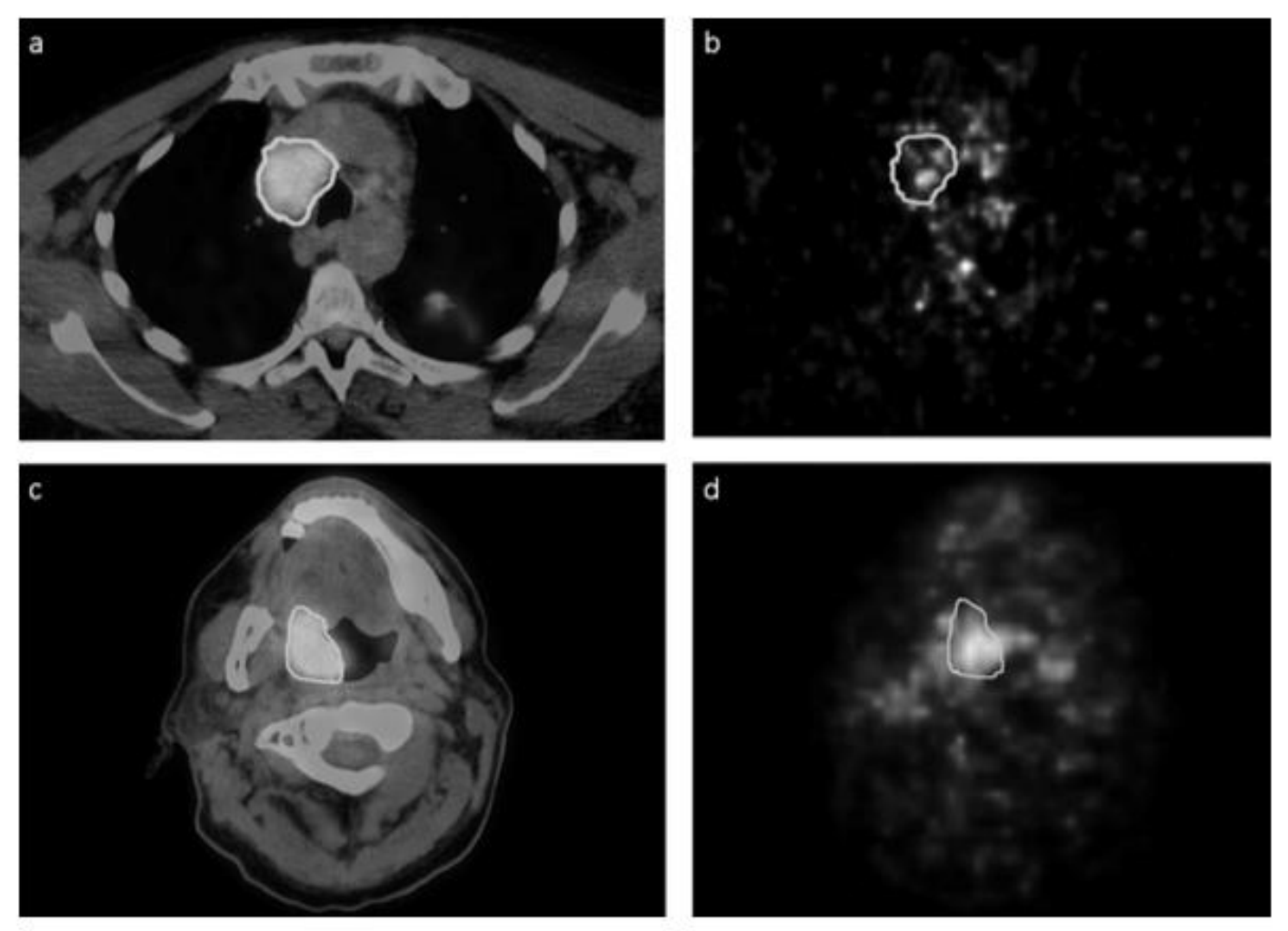
Zr-cetuimab

Biological characteristics related to radiotherapy

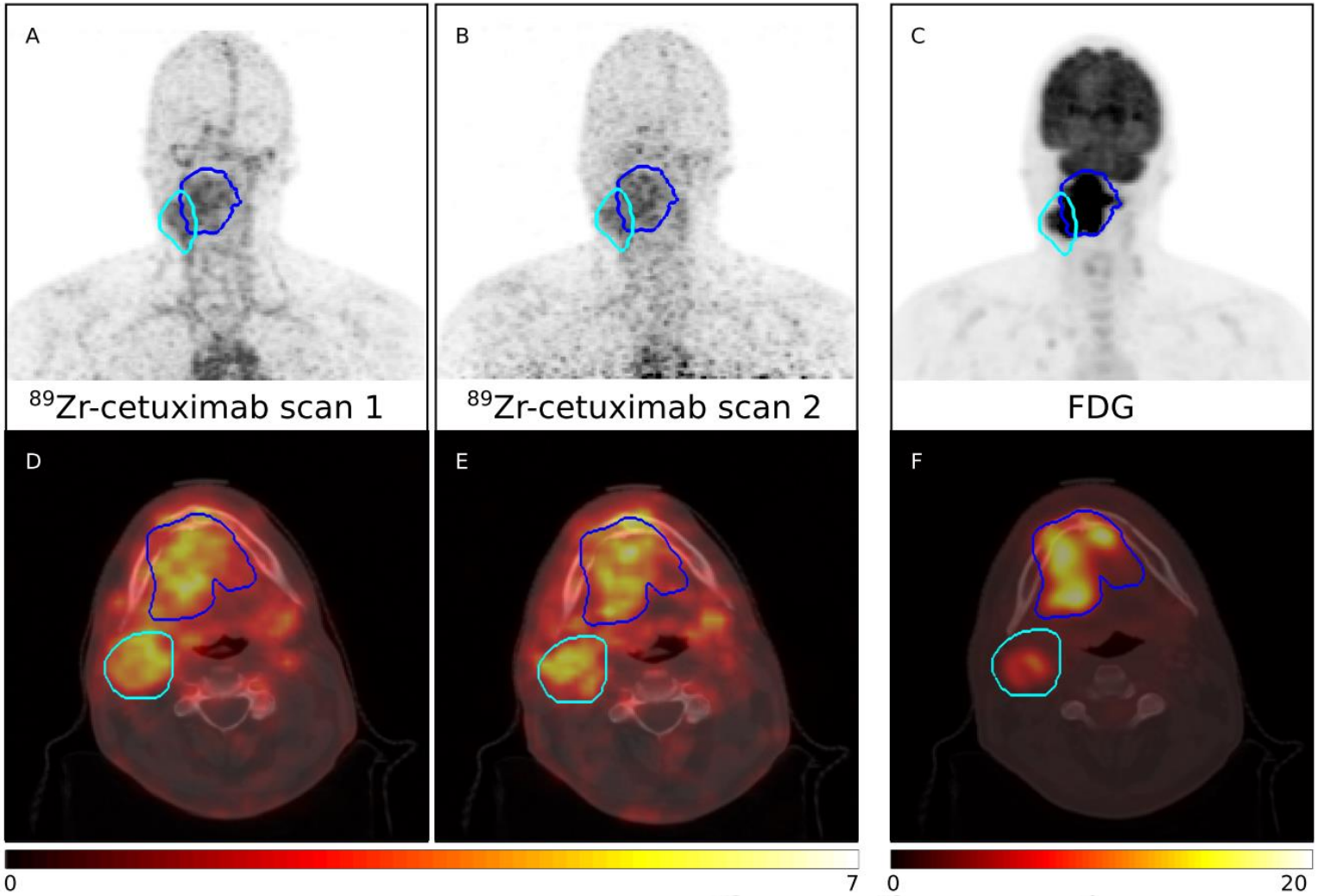
May 2016, Lisbon

Course on Molecular Imaging and Radiation Oncology

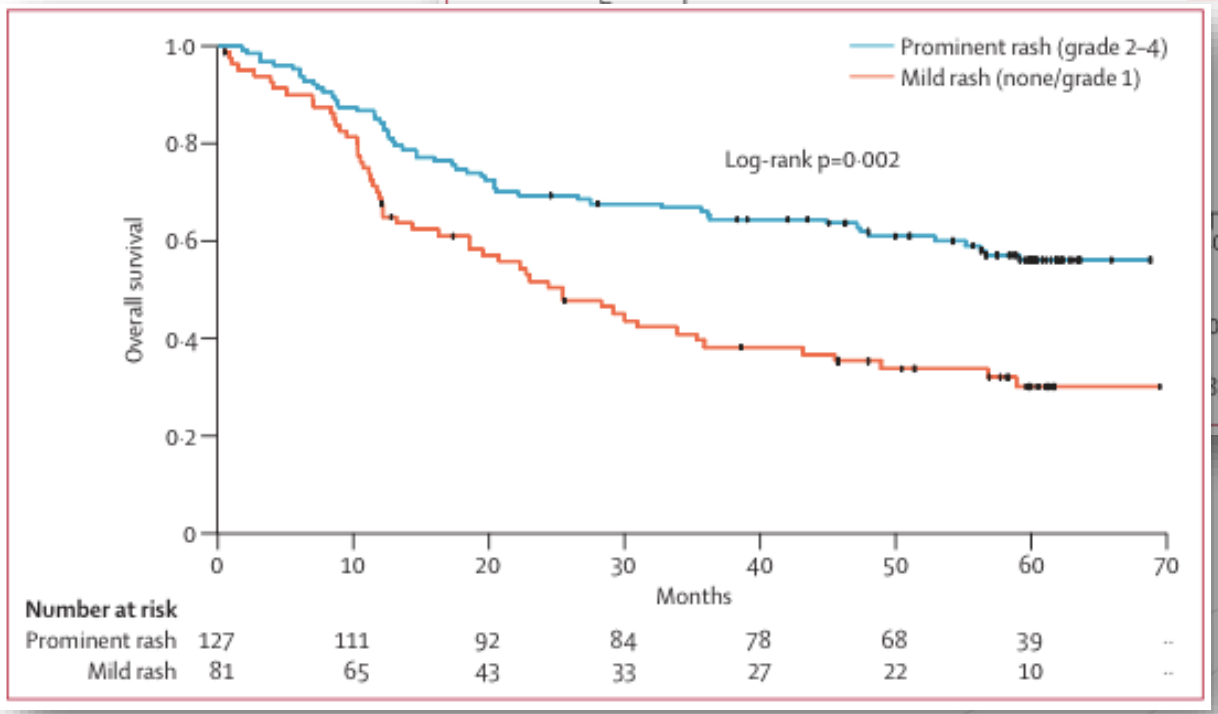
Local effect identified by uptake?

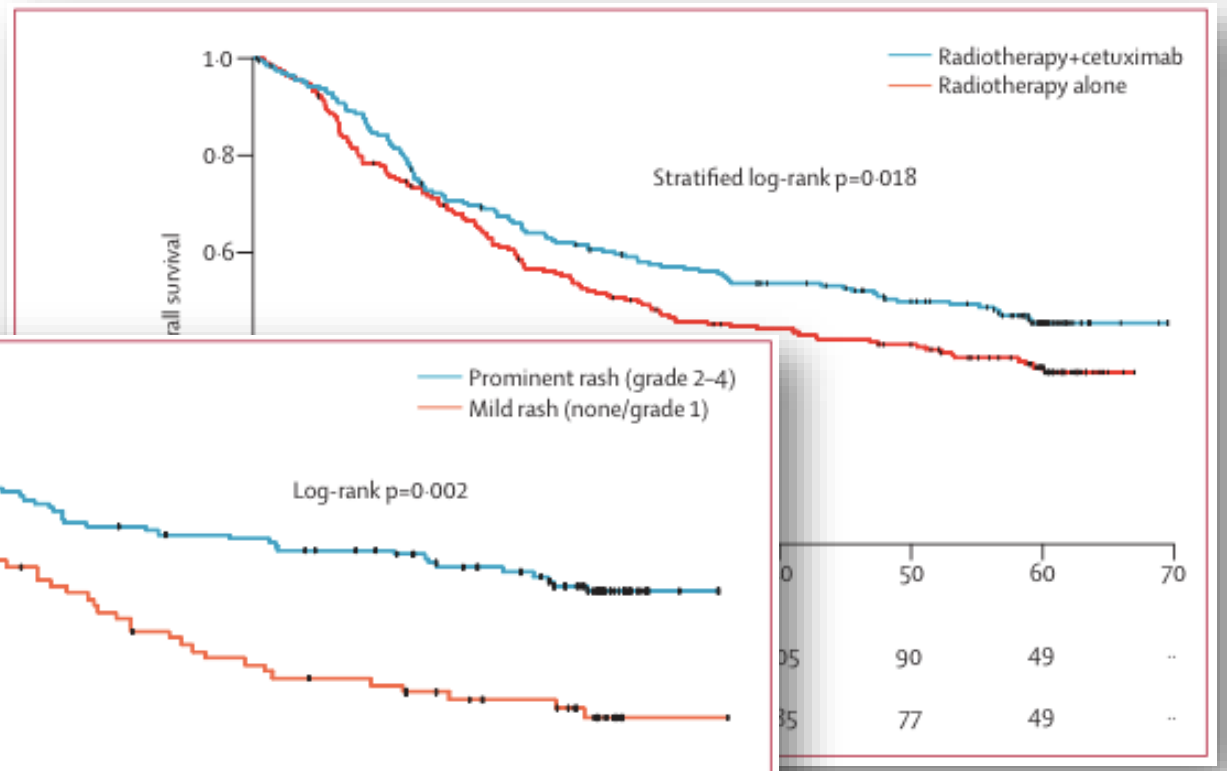


Local effect identified by uptake?



Systemic effect identified by rash





Bonner et al, Lancet oncology 2010

Biological consequences

Properly applied Zr-cetuimab PET

- Has a relation with tumor biology

- **Does NOT have a relation with systemic effects**
- **Can NOT contribute to GTV definition**
- **Can NOT define biological boost definition**

Overall conclusions

The meaning of PET tracer uptake depends on

- The tracer
- Timing
- Patient preparation
- Tumor type
- Clinical question

This means that

- PET evaluation must be validated for each tracer, tumor type and clinical question separately

Thank you for your attention

Questions ?

MRI basics: physics

Uulke van der Heide

NETHERLANDS CANCER INSTITUTE
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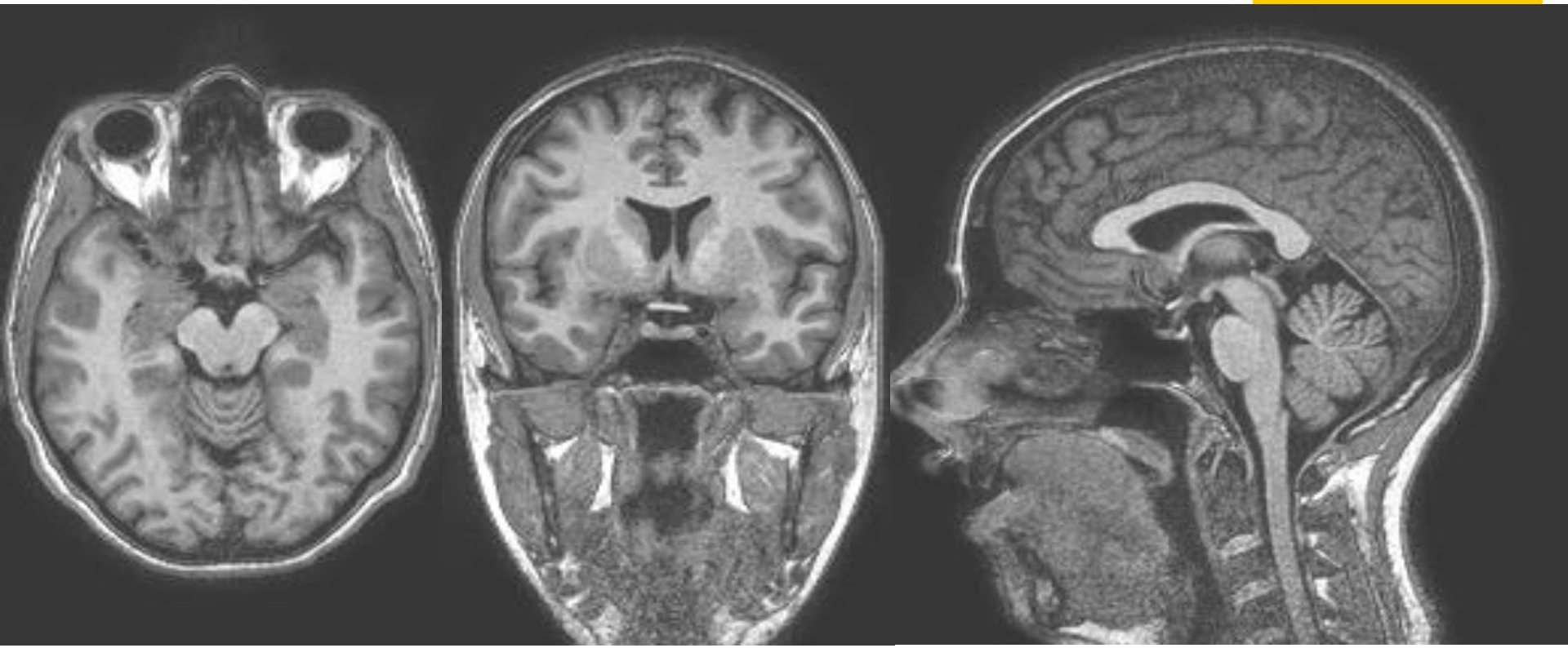
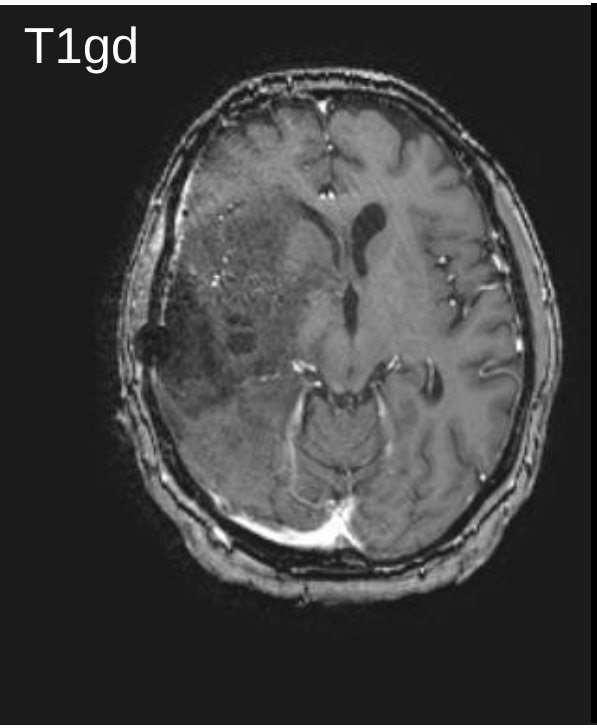
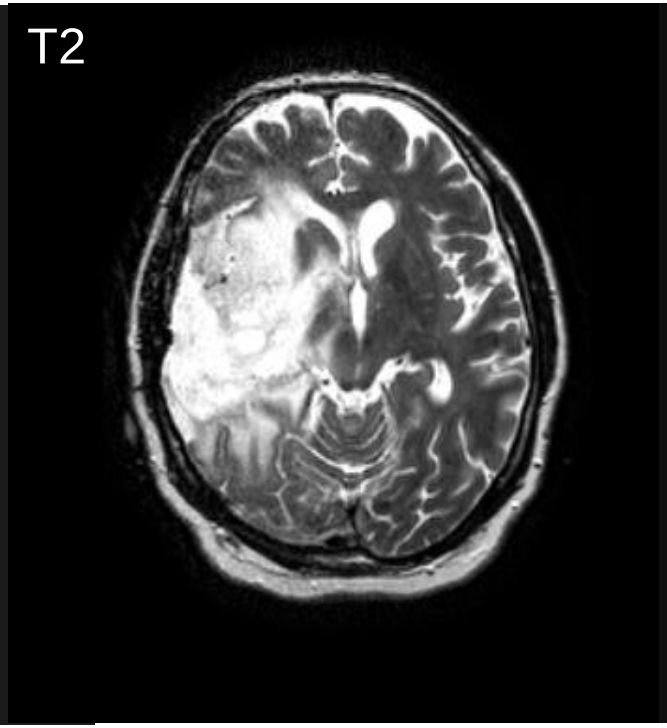
MRI has exquisite soft tissue contrast

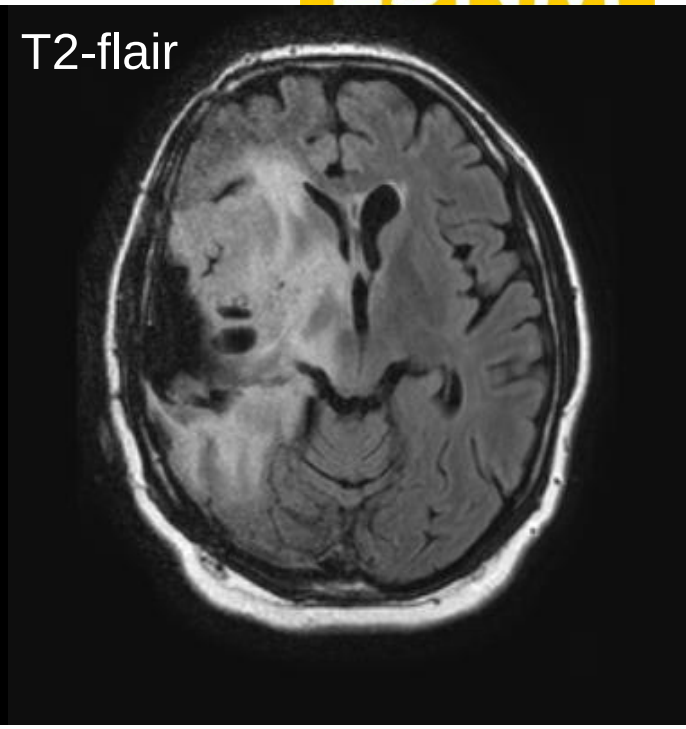


T1 3D-TFE sequence of healthy volunteer

A variety of contrasts







T1-weighted
T1-weigthed + Gd
T2-weighted
Fat suppression (SPIR, SPAIR, STIR)
T2-FLAIR
…

patient with glioblastoma multiforme

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functional imaging with MRI

Cell density, microanatomy

- **DWI, DTI**

Perfusion, permeability of microvasculature

- **DSC-MRI, DCE-MRI**

Cell membrane synthesis

- **MRSI (choline)**

Metabolism

- **^{31}P-MRSI**

Hypoxia

- **R2* (BOLD), MRSI (lactate)**

Mechanical rigidity

- **MR elastography (Young's modulus)**

pH

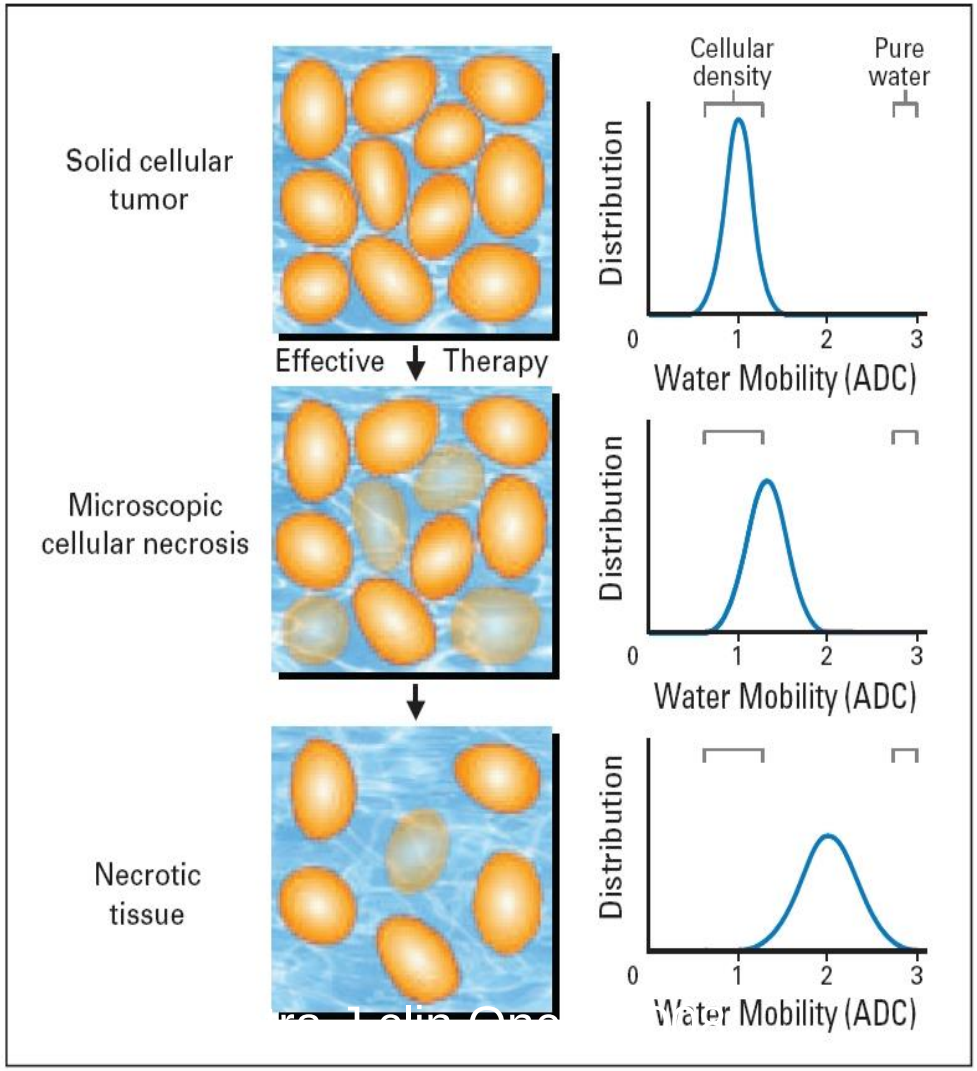
- **Chemical exchange saturation transfer (CEST) MRI**

Temperature

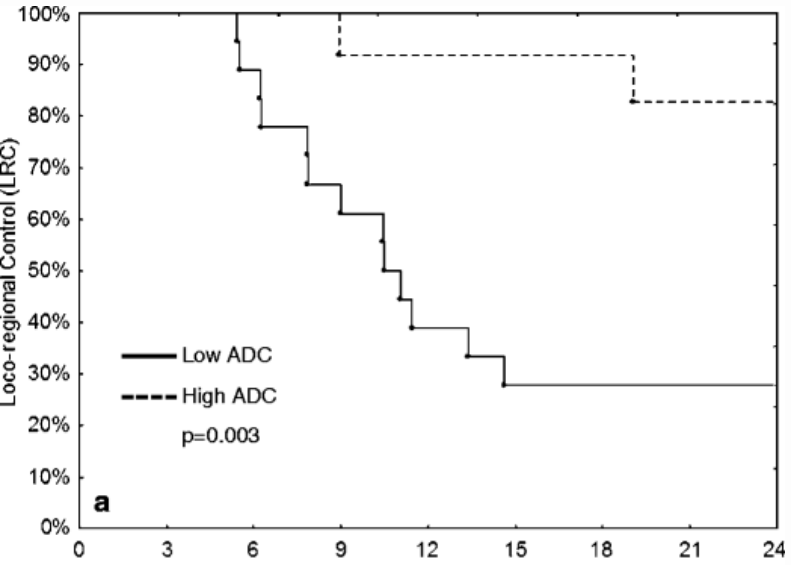
- **Proton resonance frequency shift imaging**

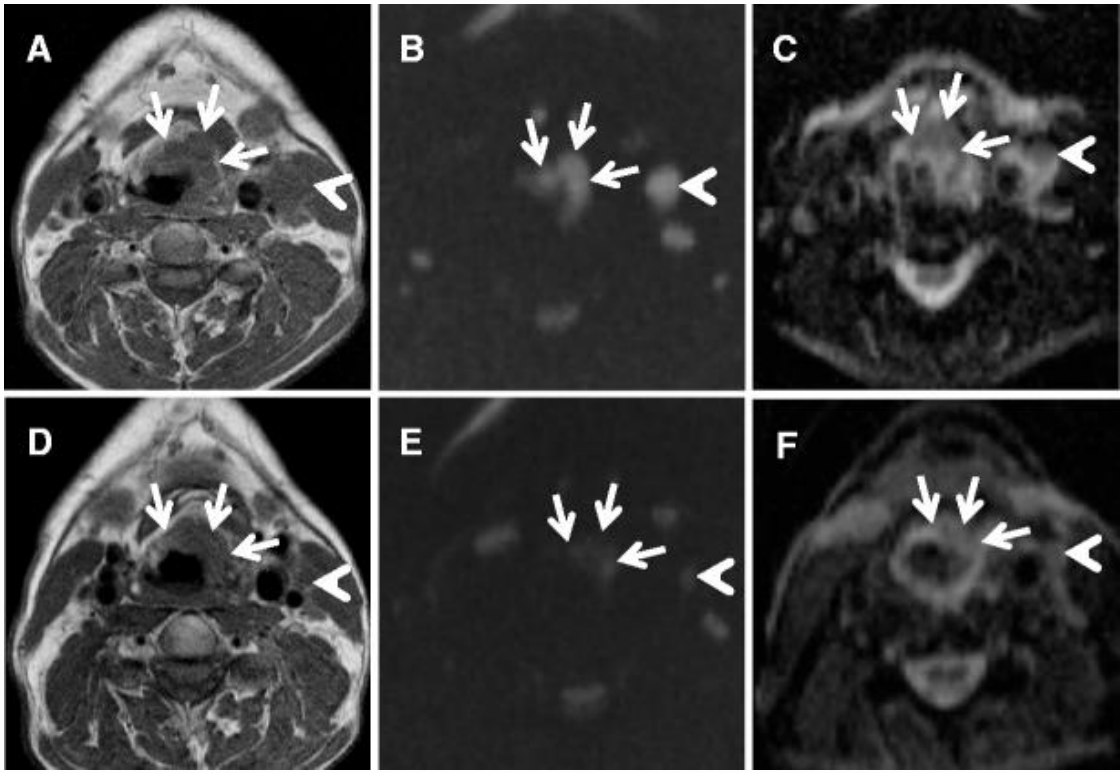
Diffusion-Weighted MRI (DWI)

- Measures the mobility of water
  - Apparent Diffusion Coefficient (ADC)
- Tissue characterization
  - high cellularity, tissue disorganisation, high extracellular space tortuosity
- Monitoring treatment response
  - vascular changes and cellular death ↑ ADC



DWI as biomarker for response to treatment



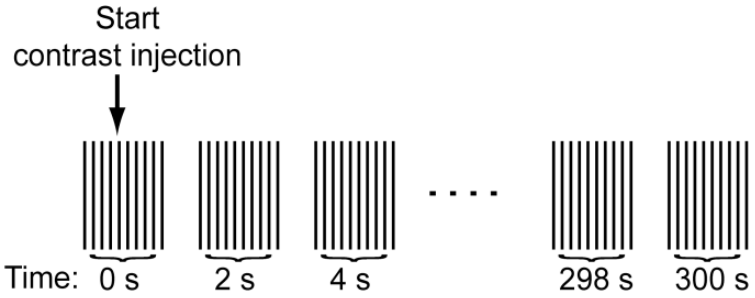


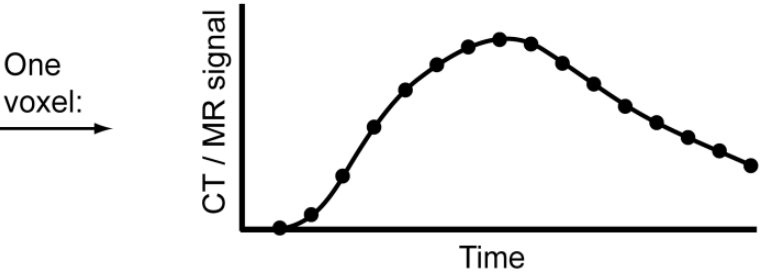
Head-neck cancer

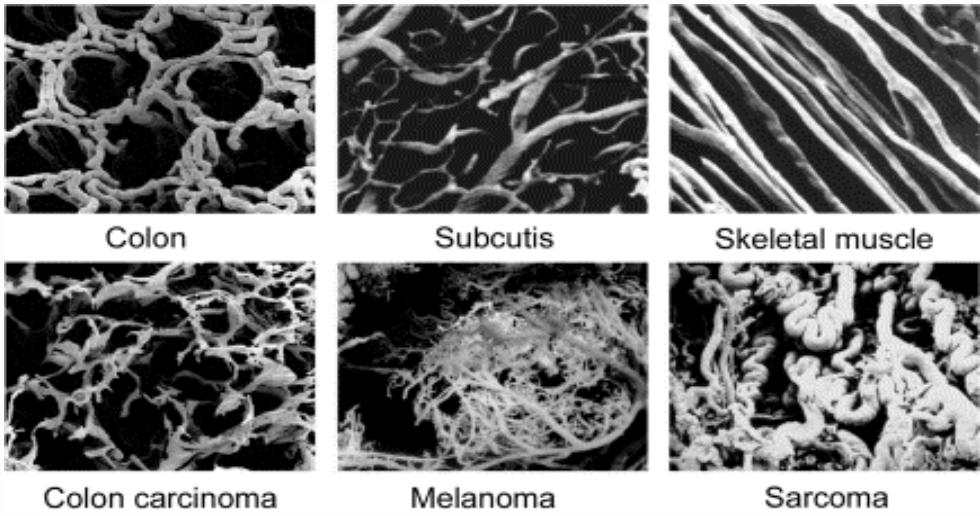
- >25% increase in ADC after 2 weeks of chemoradiation is associated with good loco-regional control

Vandecaveye et al. 2010; Eur. Radiol. 20:1703-14

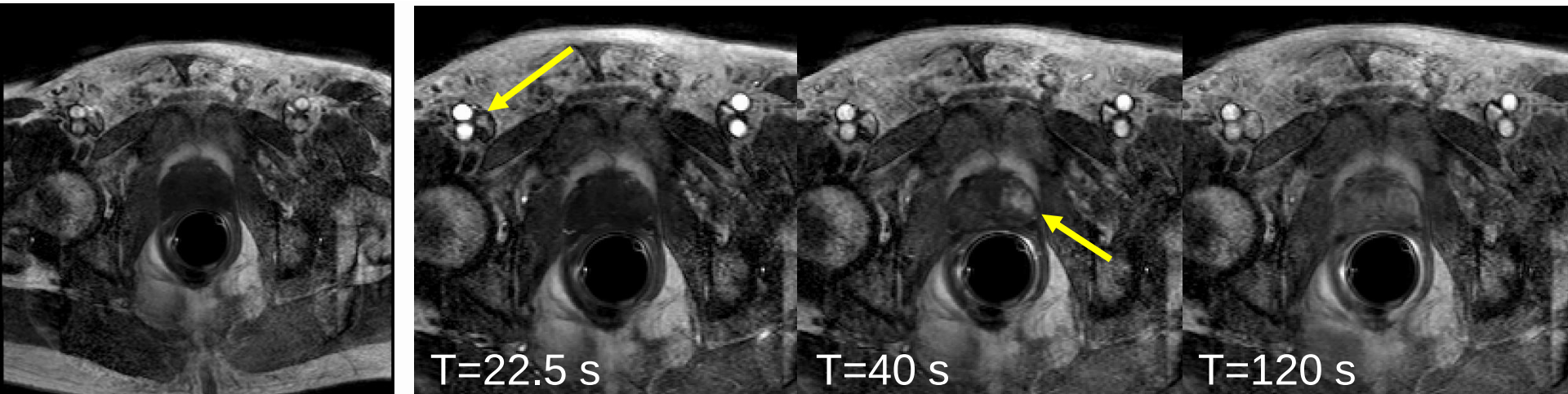
Dynamic Contrast-Enhanced (DCE) MRI



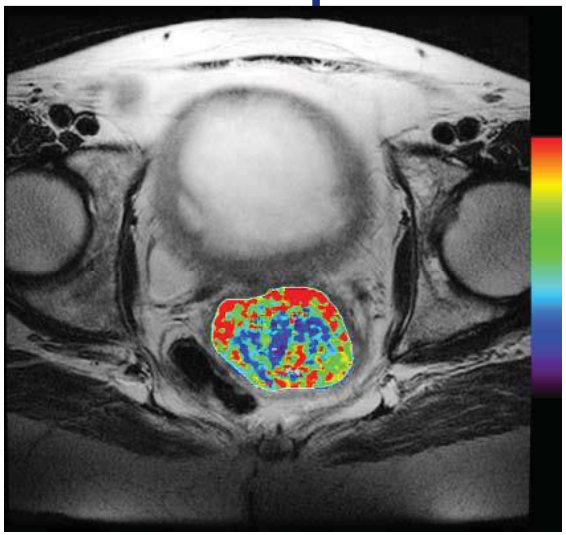


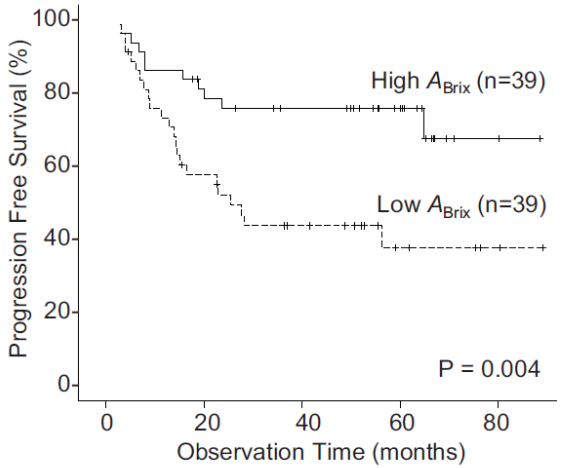


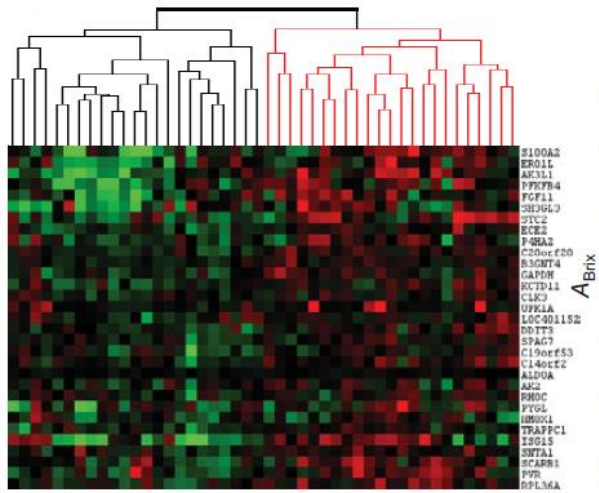
Vaupel, 2004; Semin. Radiat. Oncol. 14:198-206

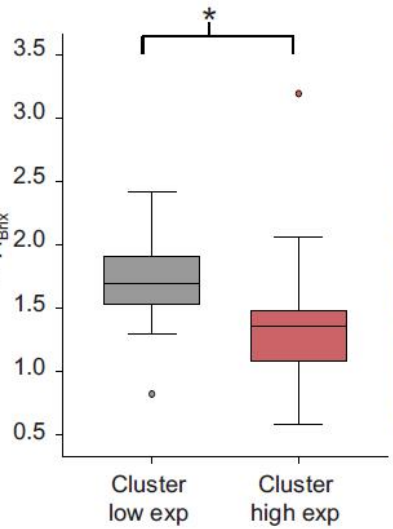


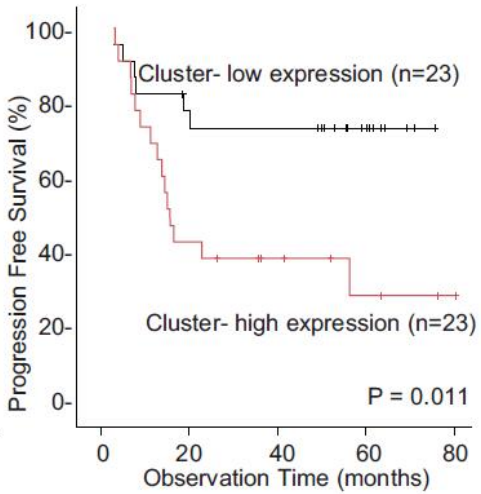
Correlate DCE-MRI with gene expression in cervix cancer











Halle et al. 2012; Cancer Res. 72:5258-5295

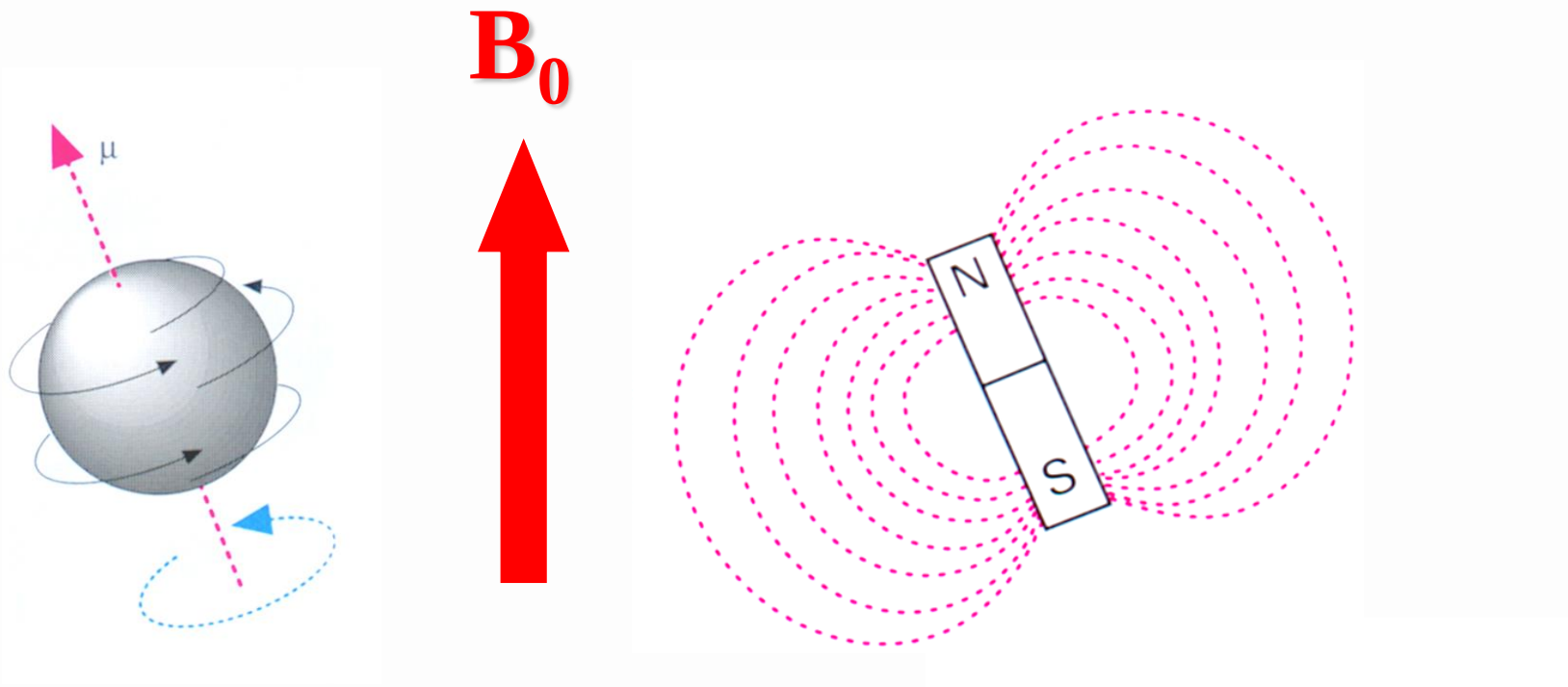
MRI for radiotherapy

- MRI is a versatile technique
  - different types of anatomical contrast
  - functional techniques
- Multiple sequences can be scanned within a single exam
- It is non-invasive and therefore quite suitable for response monitoring

MRI basics: physics

- T1 and T2-weighted contrast
- Image formation
- Challenges of MRI for use in radiotherapy

Hydrogen atoms behave as magnets

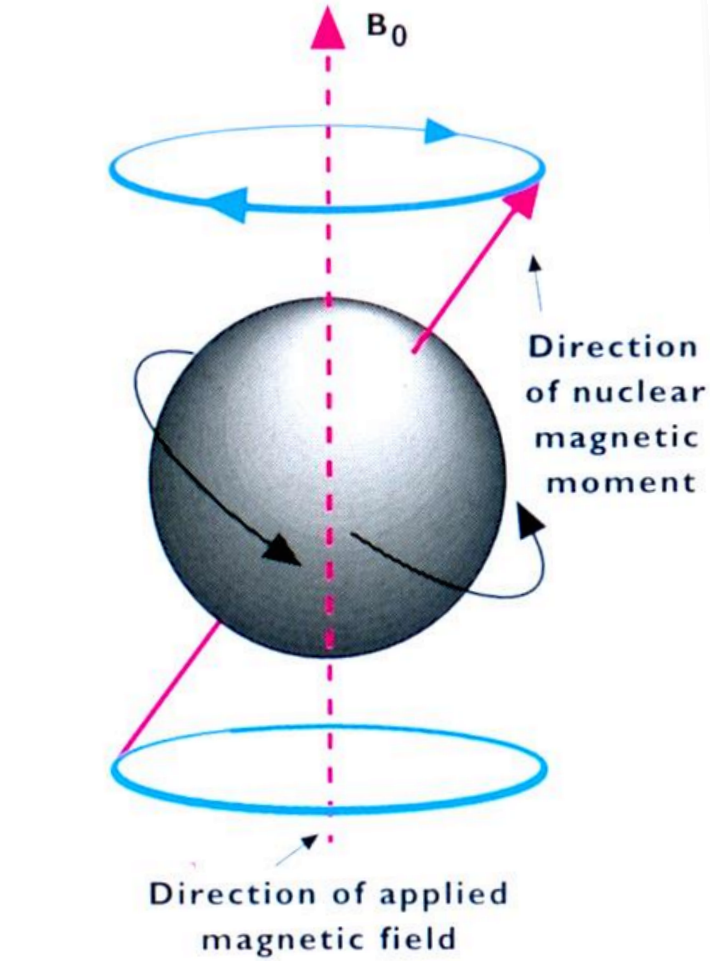


A positive charge, spinning at the Larmor frequency ω_0

$$\omega_0 = \gamma \cdot B_0$$

64 MHz @ 1.5T
128 MHz @ 3.0T

Excitation with resonant RF

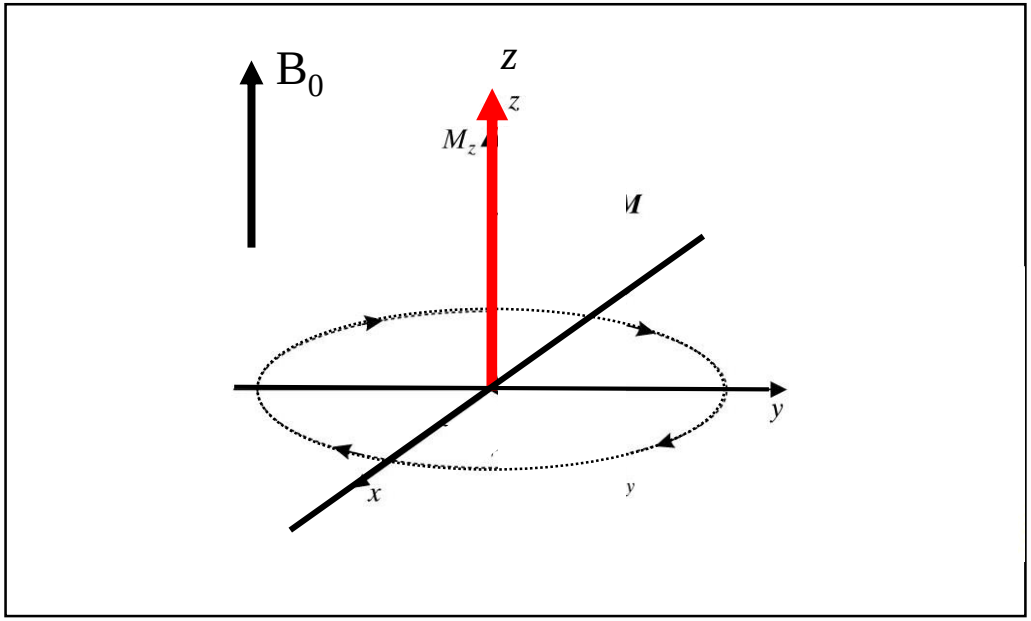


Magnetisation vector precesses around B_0 with the **Larmor** frequentie ω_0

The magnetization axis will flip

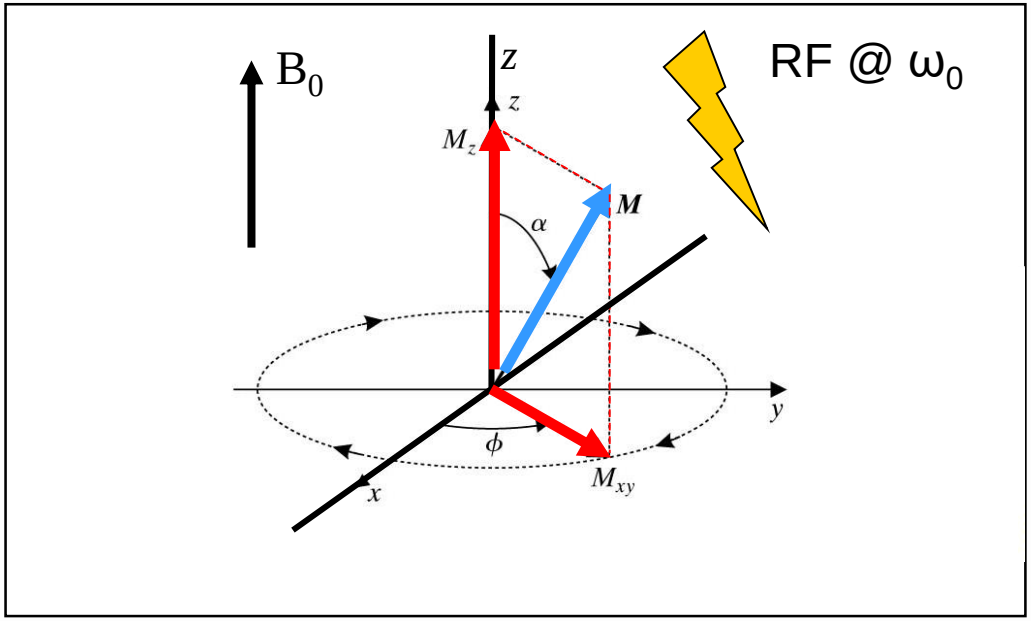
This produces a magnetization component in the transversal plane

Excitation with resonant RF



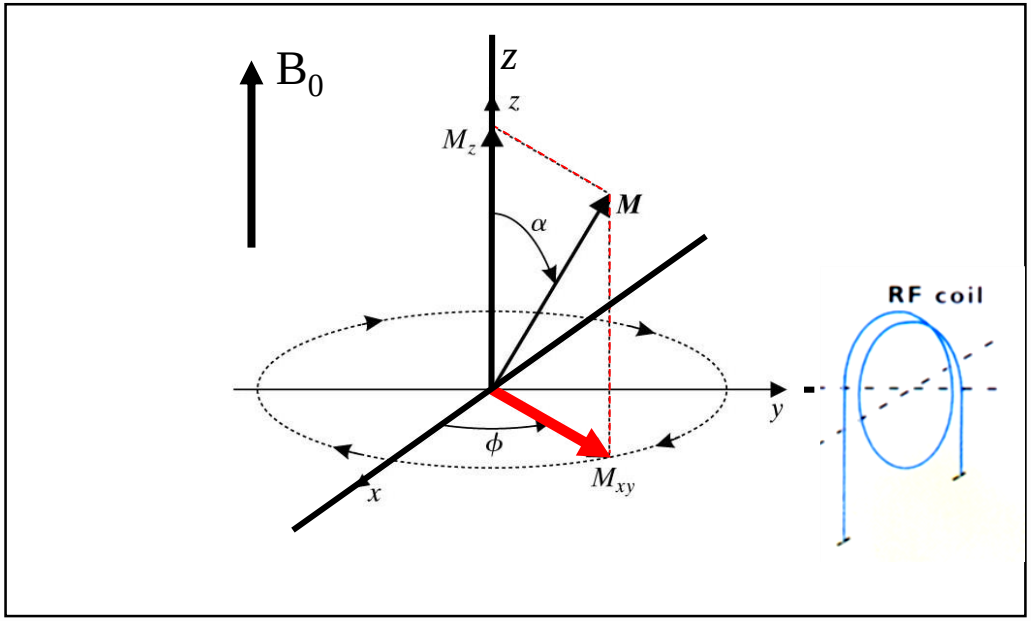
- If the spins are excited with RF at the larmor frequency ω0, the magnetization is flipped to an angle α

Excitation with resonant RF



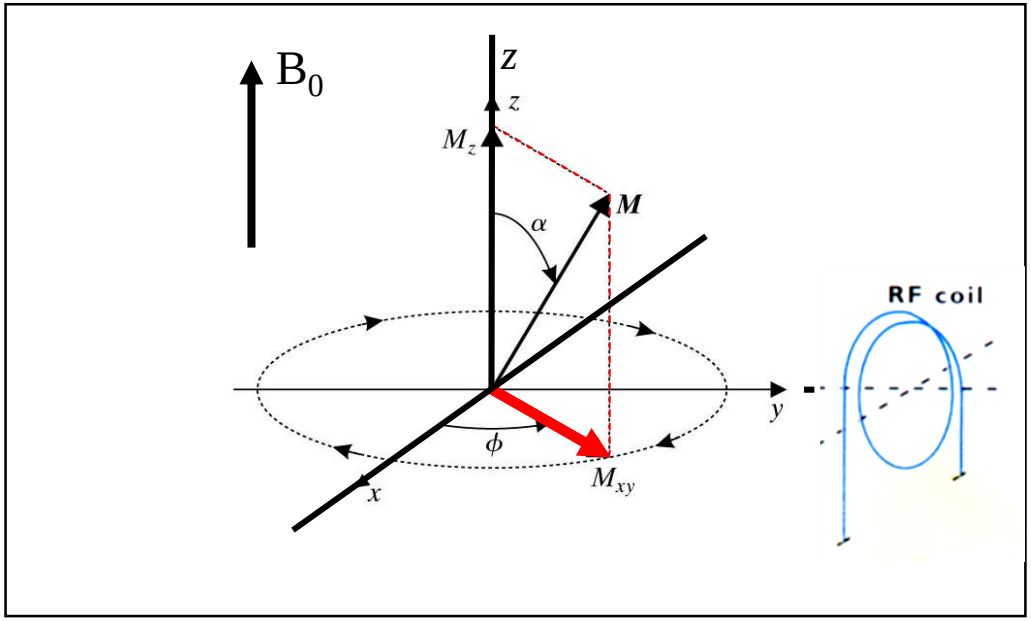
- If the spins are excited with RF at the larmor frequency ω0, the magnetization is flipped to an angle α
- This reduces the magnetization component along the longitudinal axis (z)
- It creates a magnetization component in the transversal plane

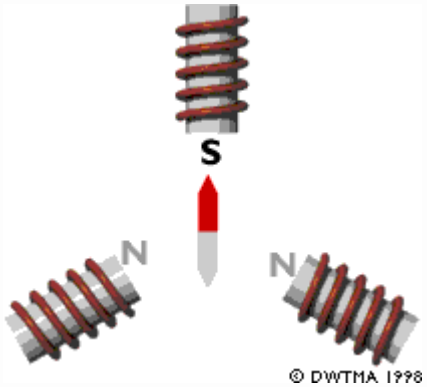
Detecting the MR signal



- Magnetization in the transversal plane behaves like a rotating magnet (like in a power generator)
- It produces a RF signal that can be detected with a coil

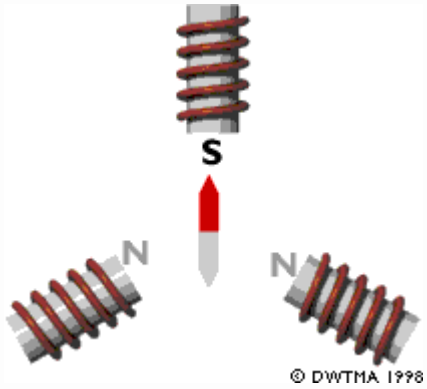
Detecting the MR signal

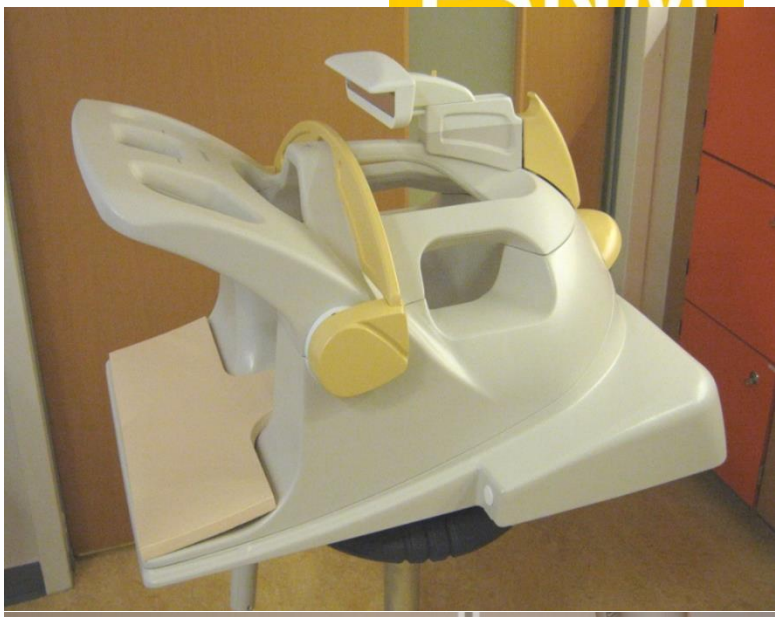


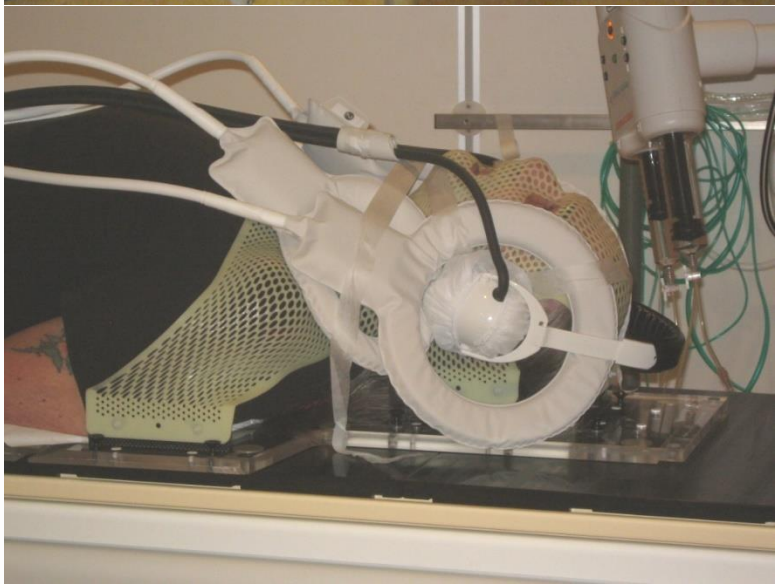


- Magnetization in the transversal plane behaves like a rotating magnet (like in a power generator)
- It produces a RF signal that can be detected with a coil

Receive coils picking up the MR signal



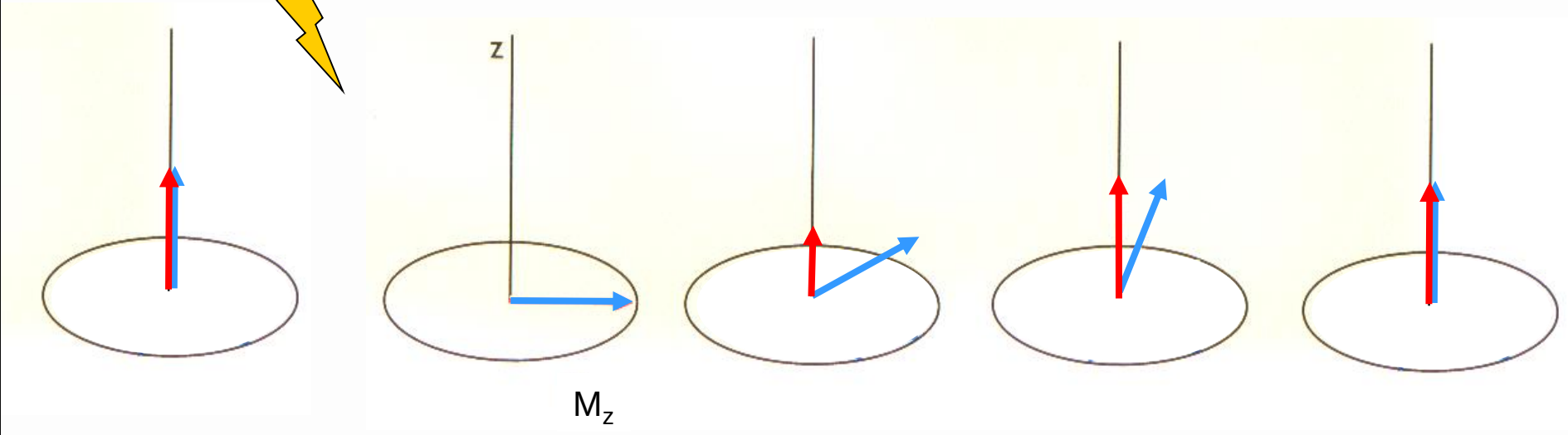




T_1-relaxation

RF @ ω_0

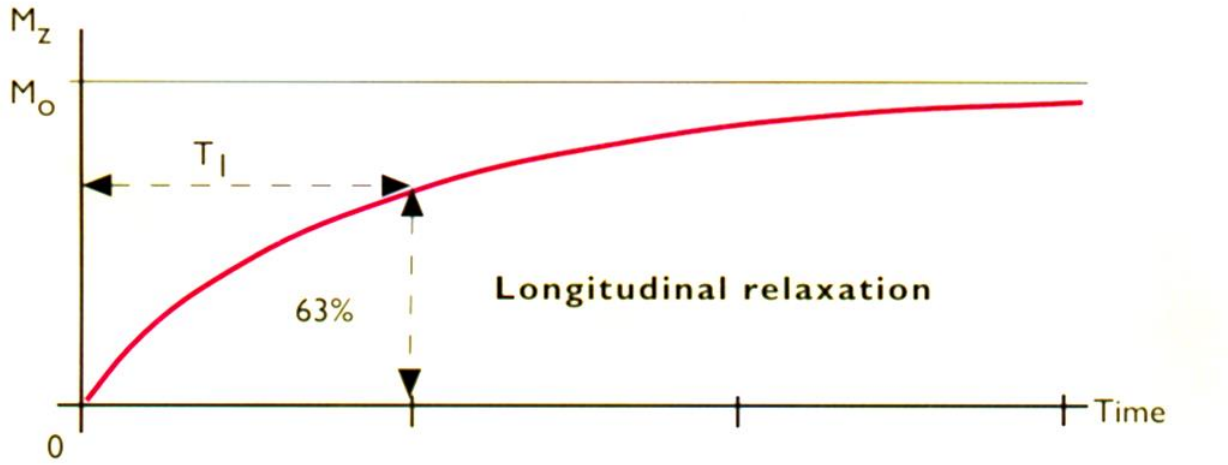
t=0



Longitudinal magnetisation recovers with time constant T_1:

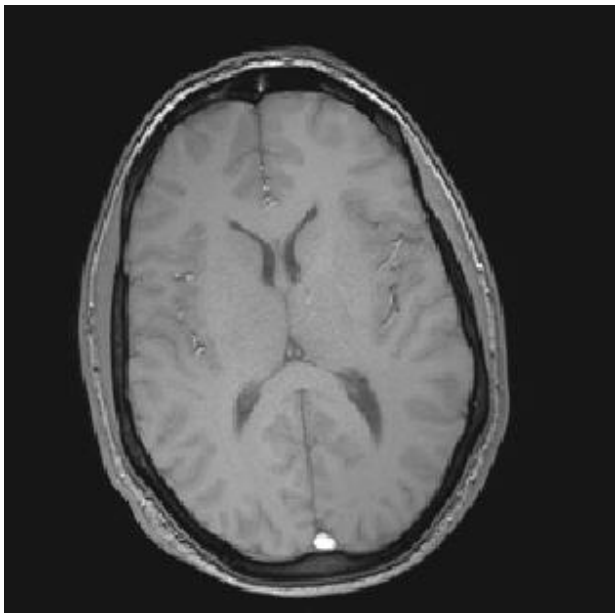
$$M_z(t) = M_z(0) \cdot \left(1 - e^{-t/T_1}\right)$$

T_1-relaxation (longitudinal)



At $t=T_1$ 63% of M_z is restored

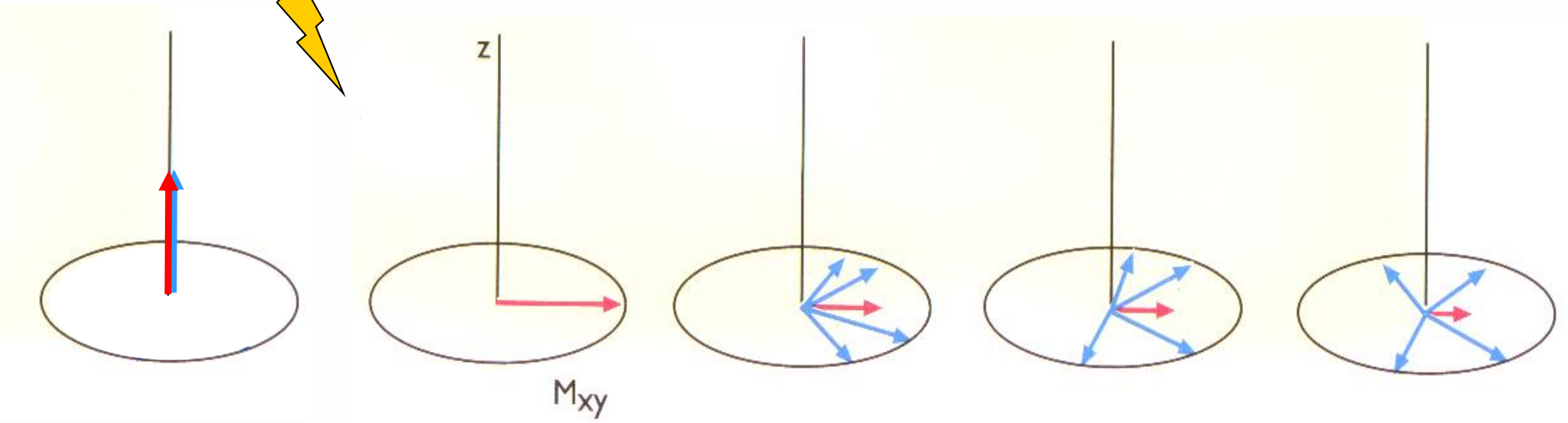
- Adipose tissue – 240ms
- Spinal fluid – 4300ms
- Gray matter – 980ms
- White matter – 780ms
- Muscles – 880ms



T_2-relaxation

RF @ ω_0

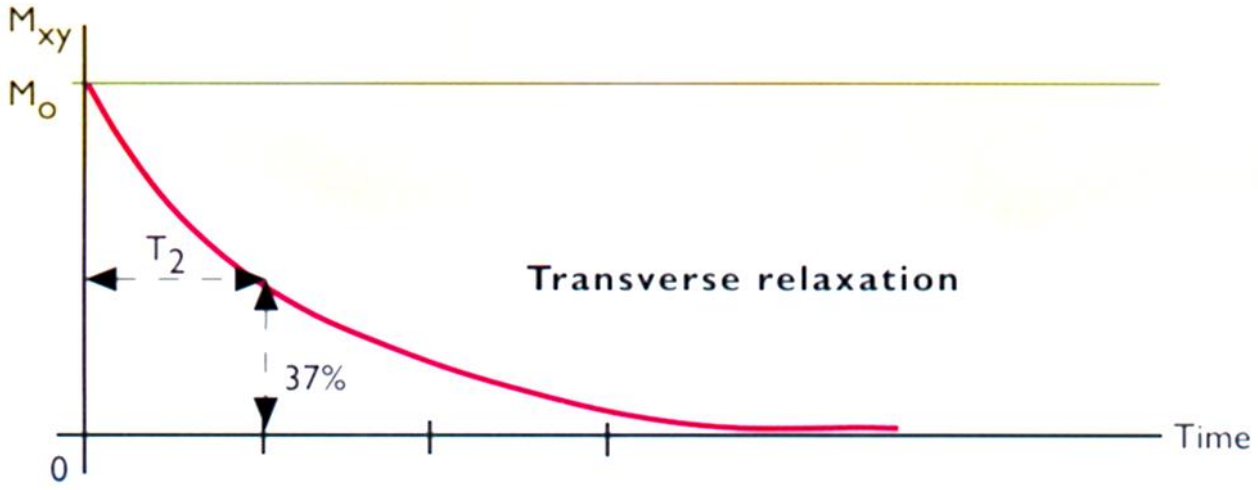
t=0



Transversal magnetisation decays with time constant T_2:

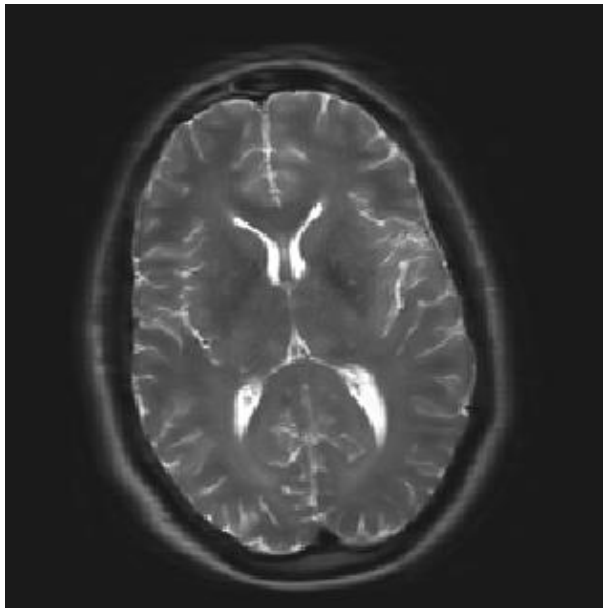
$$M_{xy}(t) = M_{xy}(0) \cdot e^{-t/T_2}$$

T_2-relaxation (transversal)

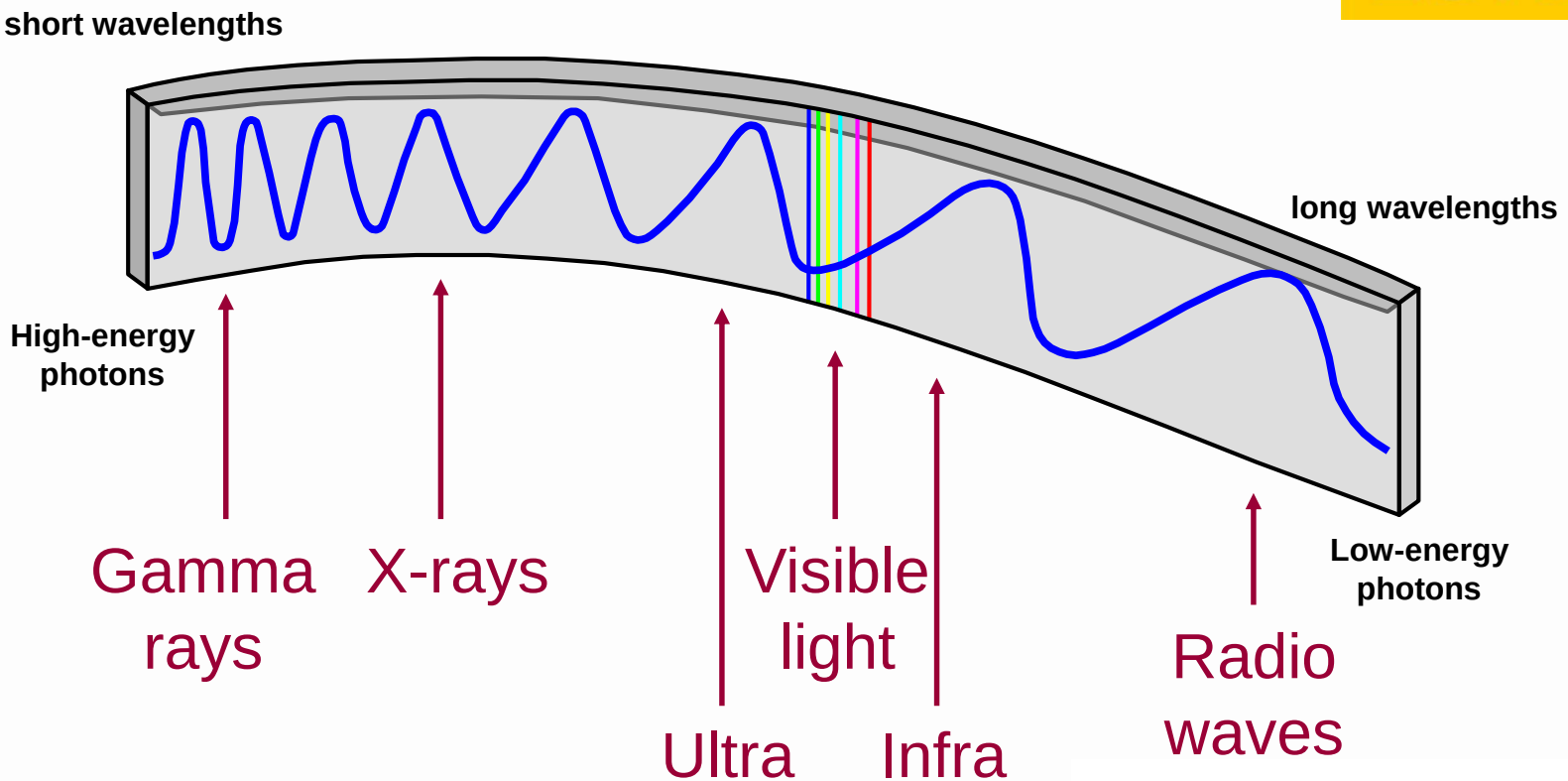


At $t=T_2$ only 37% of M_{xy} remains

- Adipose tissue – 70ms
- Spinal fluid – 2200ms
- Gray matter – 100ms
- White matter – 90ms
- Muscles – 50ms



MRI operates at radiofrequencies (RF)



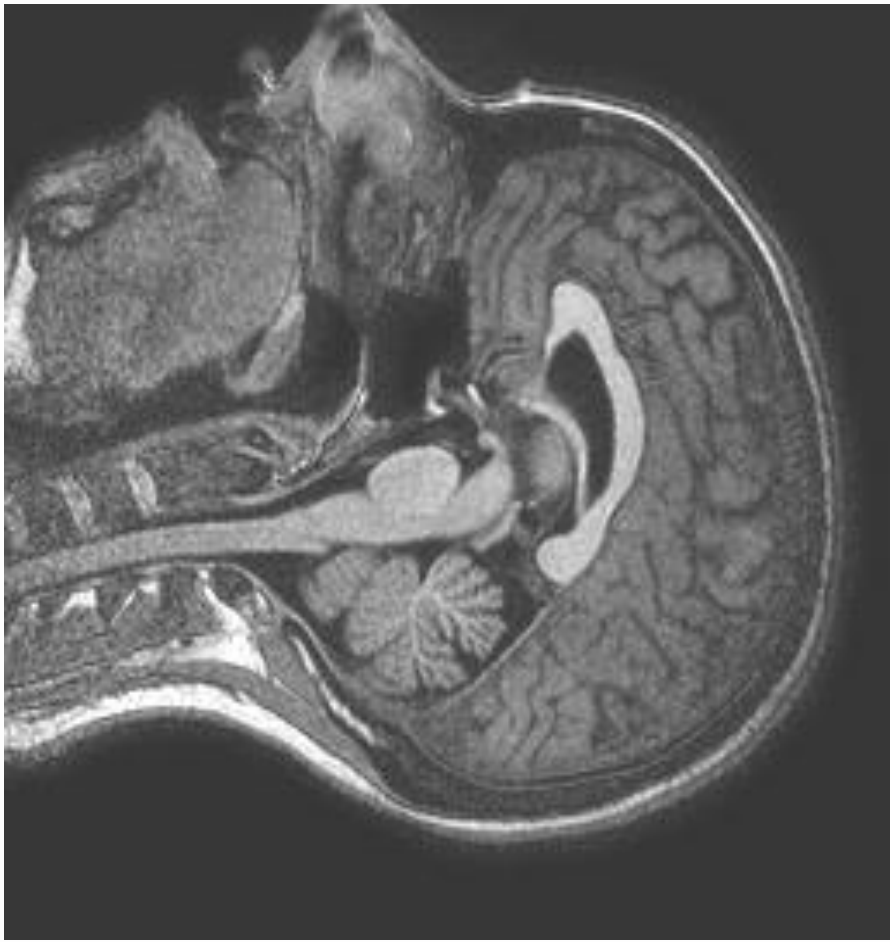
64 MHz @ 1.5T
128 MHz @ 3.0T

Spatial encoding

- Wavelength of RF is long (~meters)
- Imaging must use a different principle

- Use the Larmor relation:

$$\omega_0 = \gamma \cdot B_0$$



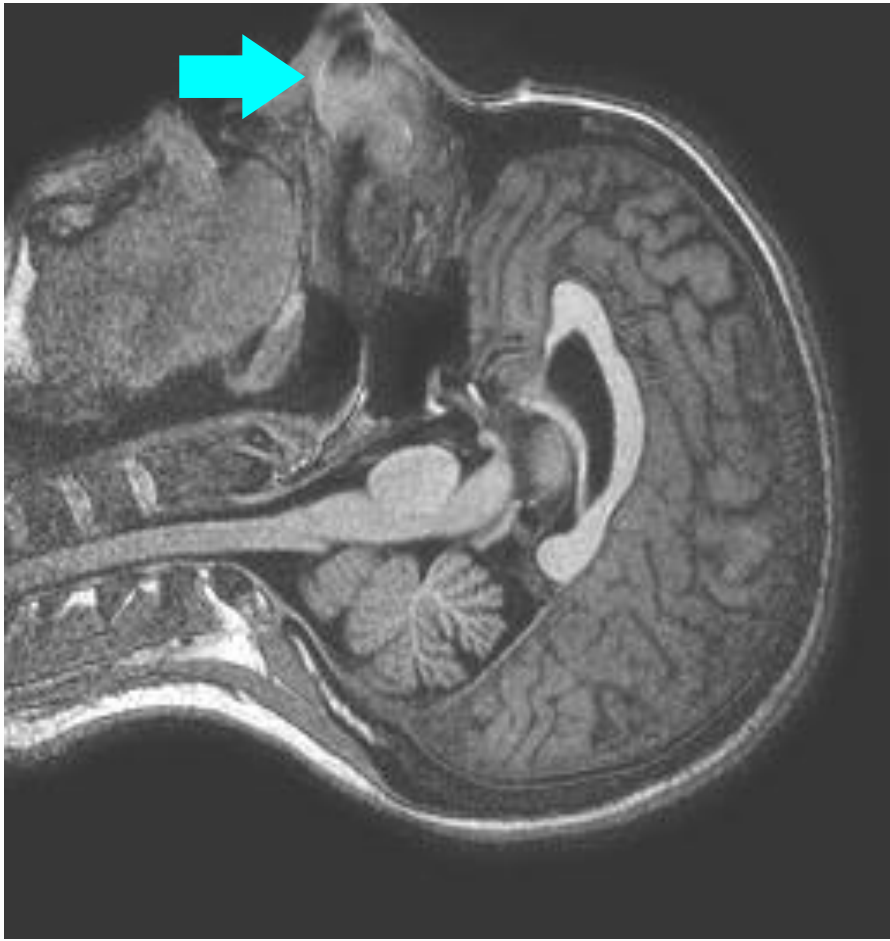
Spatial encoding

- Wavelength of RF is long (~meters)
- Imaging must be done based on a different principle

B_0

- Use the Larmor relation:

$$\omega_0 = \gamma \cdot B_0$$

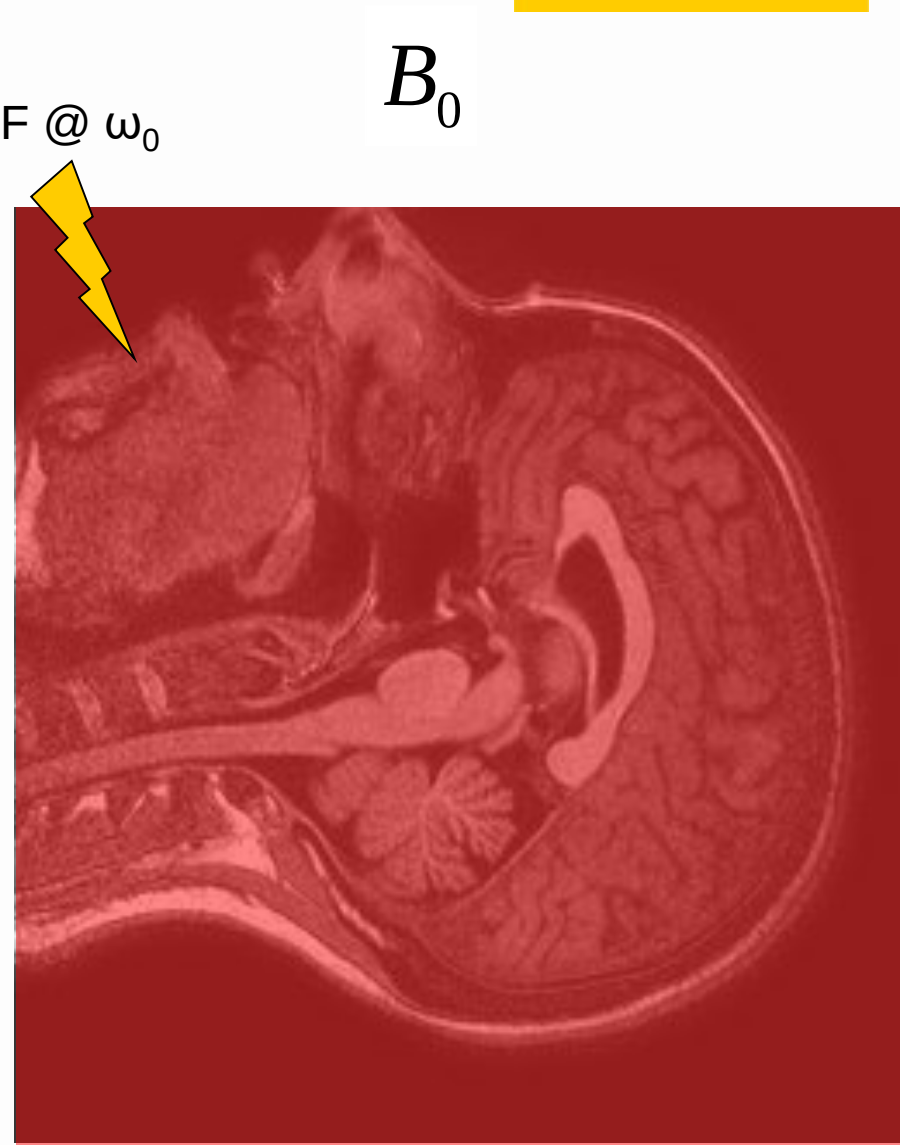


Spatial encoding

- Wavelength of RF is long (~meters)
- Imaging must be done based on a different principle

- Use the Larmor relation:

$$\omega_0 = \gamma \cdot B_0$$



Spatial encoding

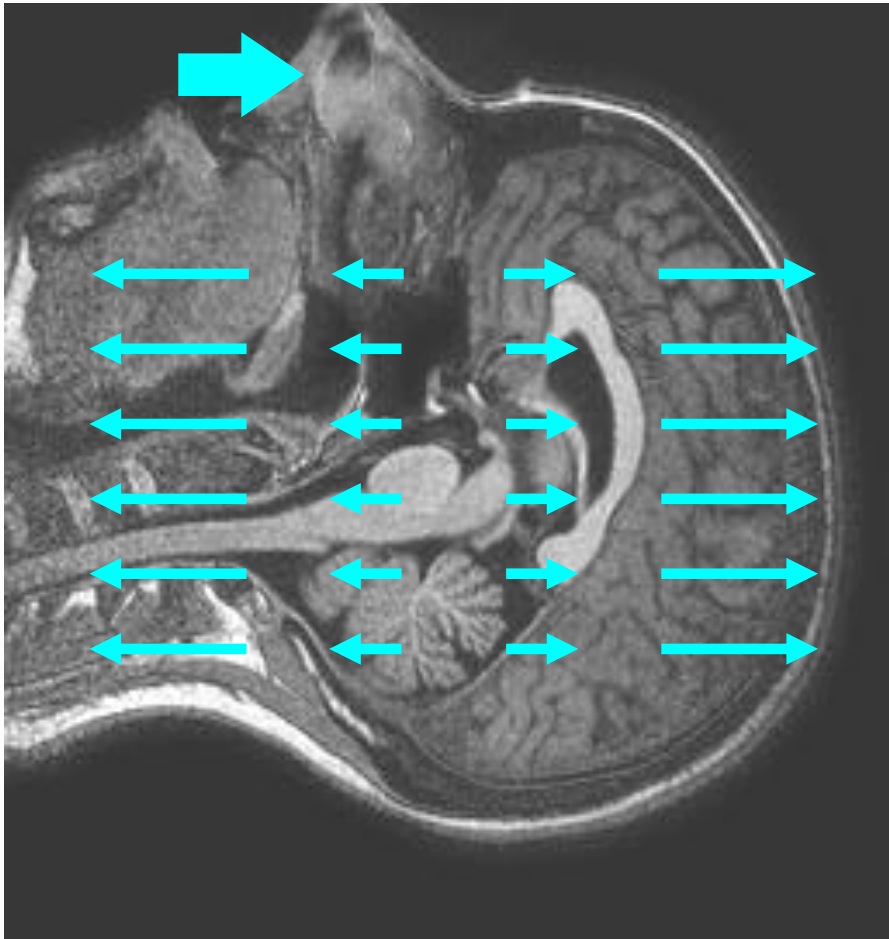
- Wavelength of RF is long (~meters)
- Imaging must be done based on a different principle

$$B = B_0 + zG_z$$

- Use the Larmor relation:

$$\omega_0 = \gamma \cdot B_0$$

- Apply a gradient in the magnetic field



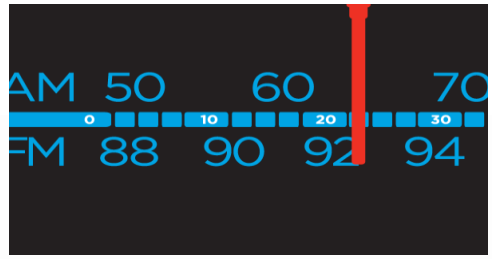
Spatial encoding

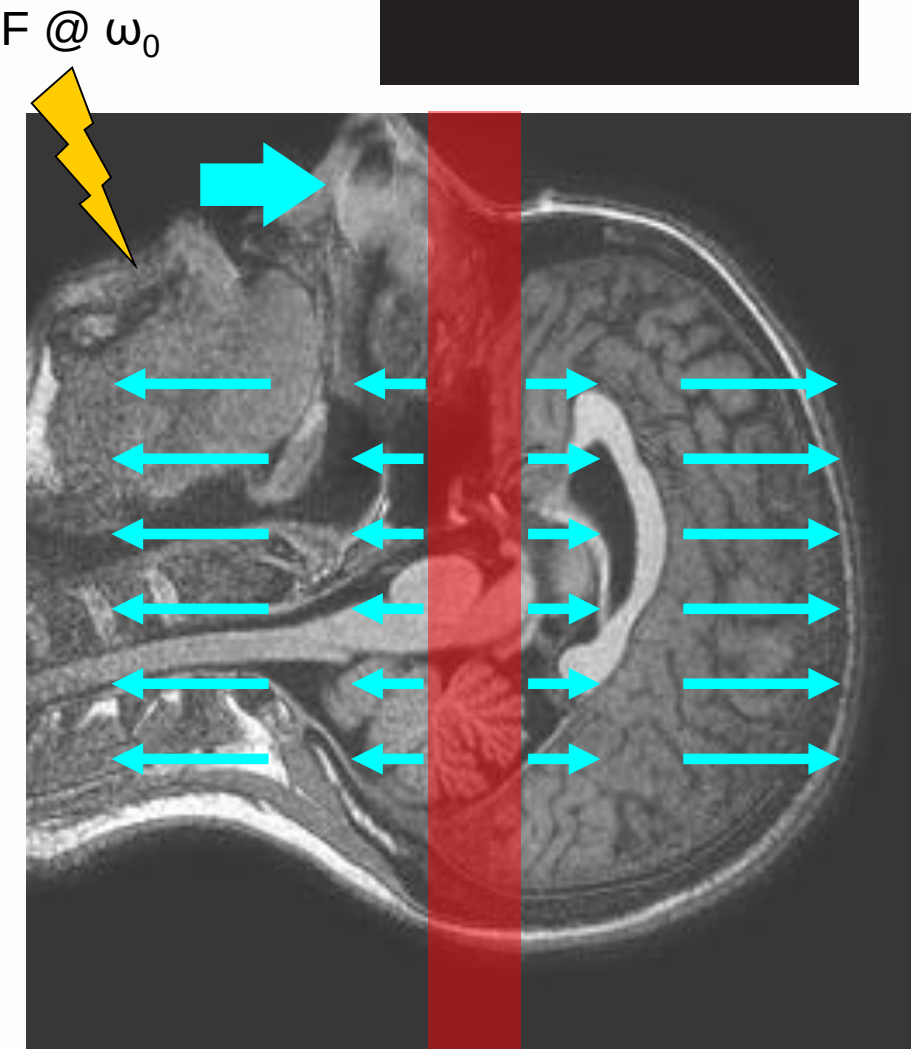
- Wavelength of RF is long (~meters)
- Imaging must be done based on a different principle

- Use the Larmor relation:

$$\omega_0 = \gamma \cdot B_0$$

- Apply a gradient in the magnetic field





Spatial encoding

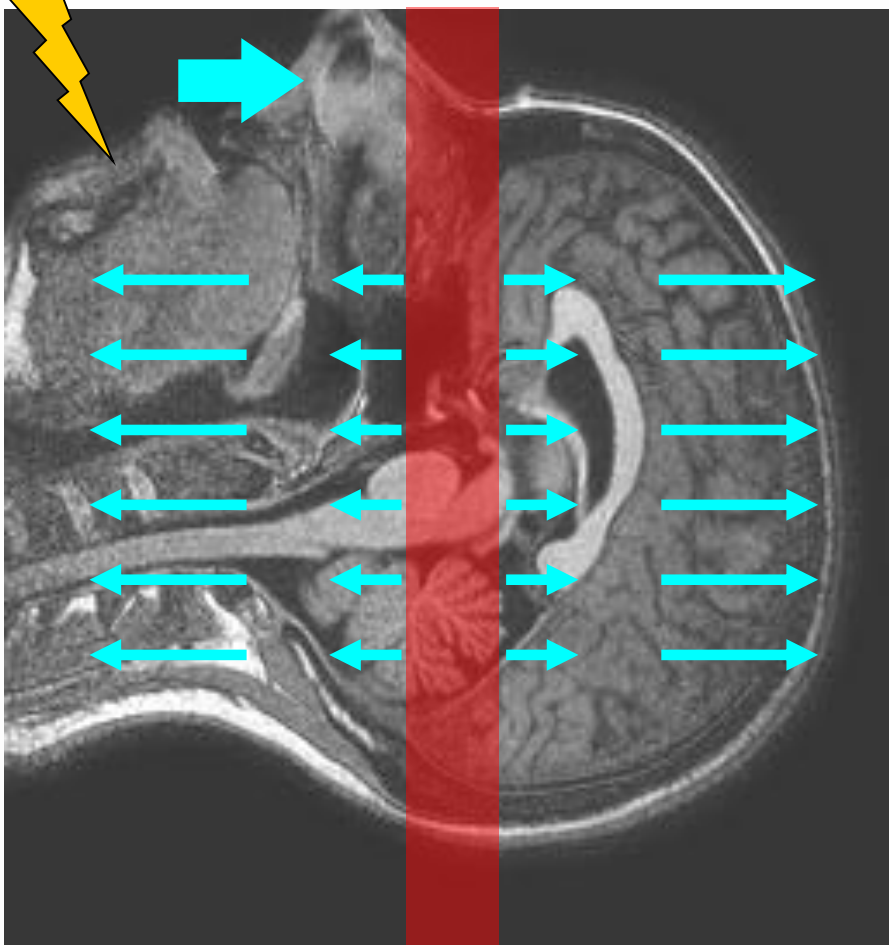
- Wavelength of RF is long (~meters)
- Imaging must be done based on a different principle

- Use the Larmor relation:

$$\omega_0 = \gamma \cdot B_0$$

- Apply a gradient in the magnetic field

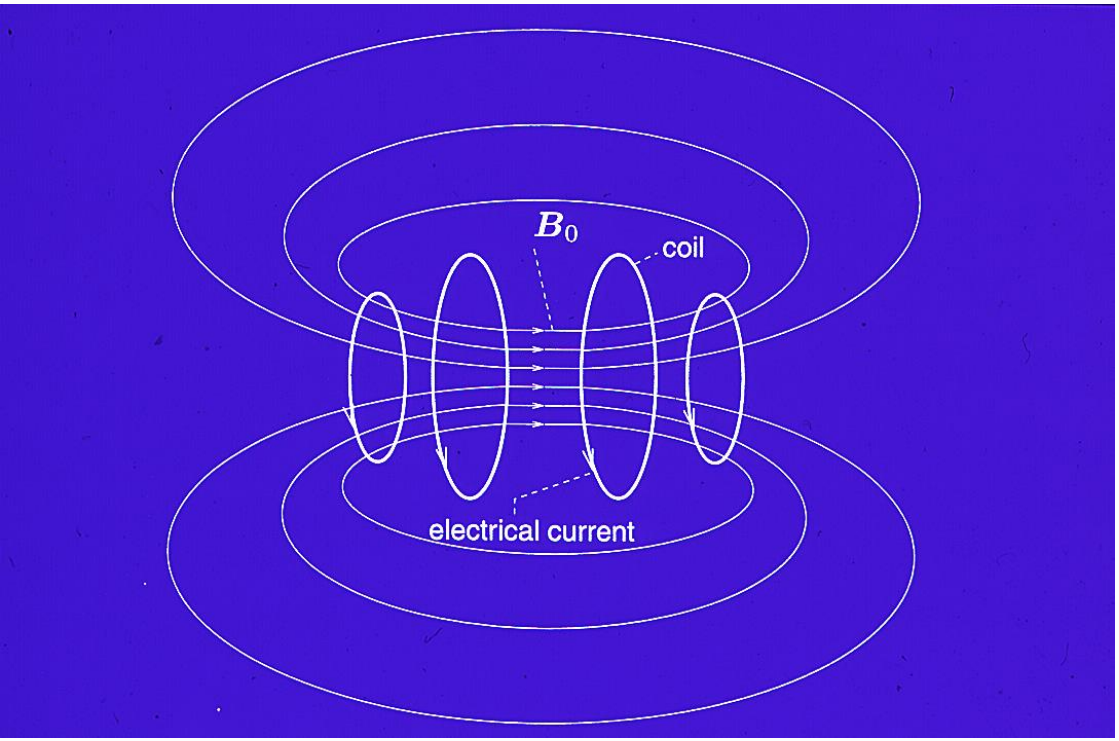
RF @ $\omega_0 + \Delta\omega$

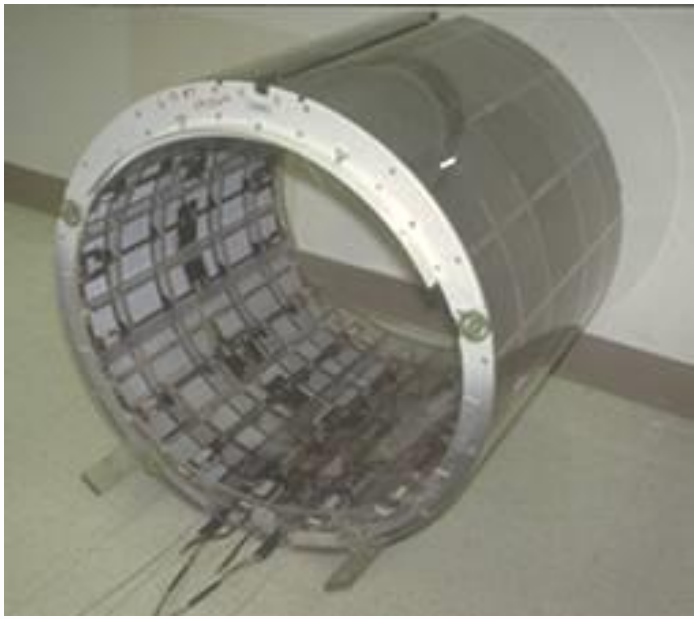


MRI basics: physics

- Hydrogen atoms are spins that precess when a magnetic field is applied
- Spins precess at the Larmor frequency: $\omega_0=\gamma \cdot B_0$
- Spatial encoding is done with magnetic field gradients and variation of the RF frequency
- Tissues have a characteristic T1 and T2 relaxation rate

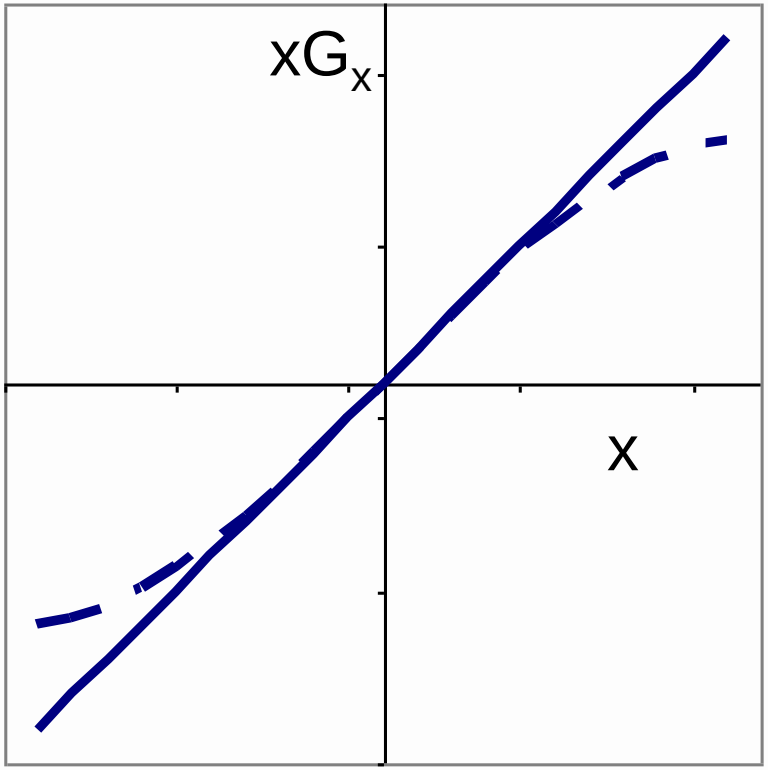
Imperfections of B_0 and gradient fields



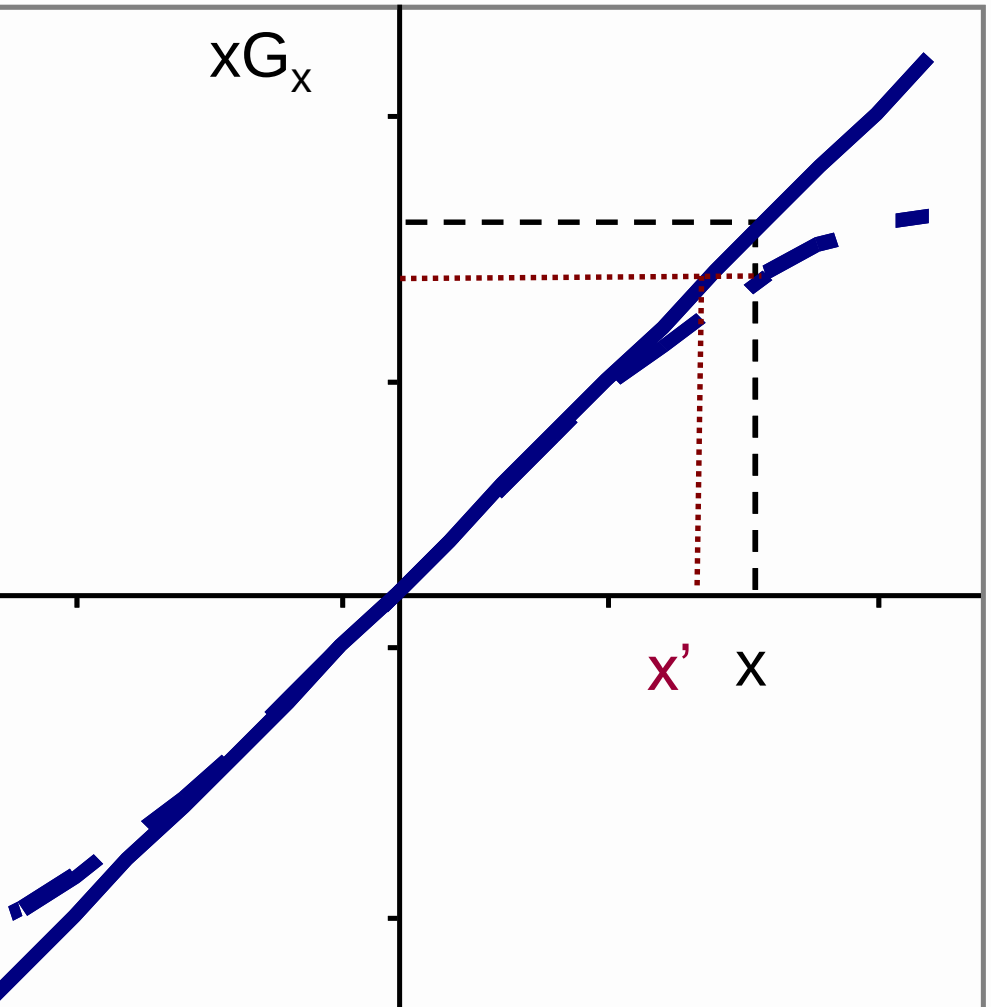


- Imperfect magnetic field homogeneity:
- divergence of the magnetic field lines at the end of the coil
- imperfect winding of the superconducting wire
- variations of current densities in the wire
- Distortion of the magnetic field by metal close to the scanner

Imperfect magnets cause non-linear gradients



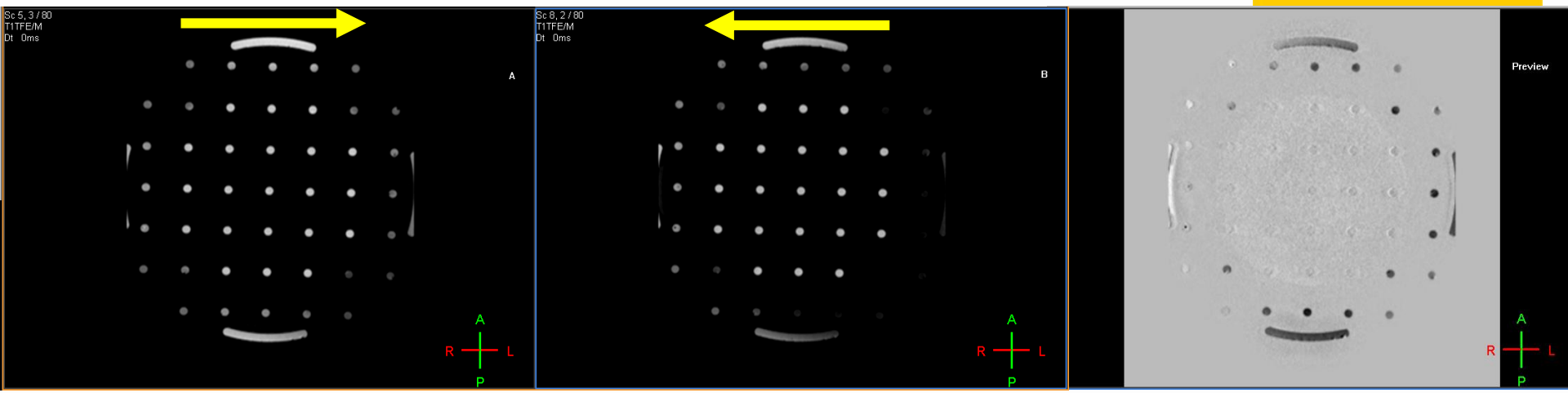
Non-linear gradients cause position distortions



- As the field strength at a position deviates from the correct value, position encoding is distorted
- This is a static property of each scanner
- It can be corrected
- However:

  it often isn't

Impact of gradient distortions



- Distortions can be measured by switching the gradient direction
- Subtraction shows distortions that are more severe towards the outside of the image

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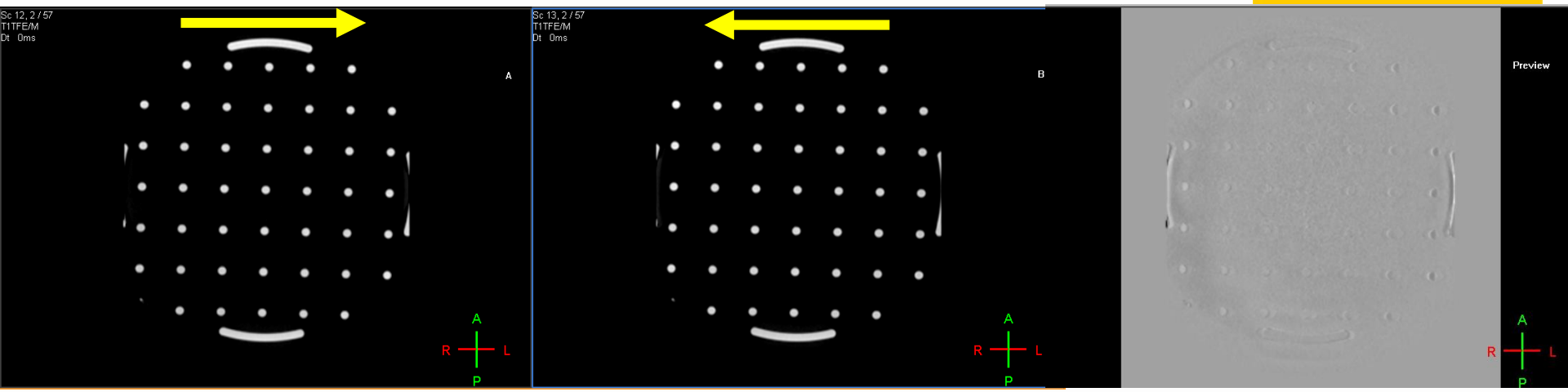
Impact of gradient distortions



- Distortions can be measured by switching the gradient direction
- Subtraction shows distortions that are more severe towards the outside of the image
- Correction is possible and a standard option on every scanner

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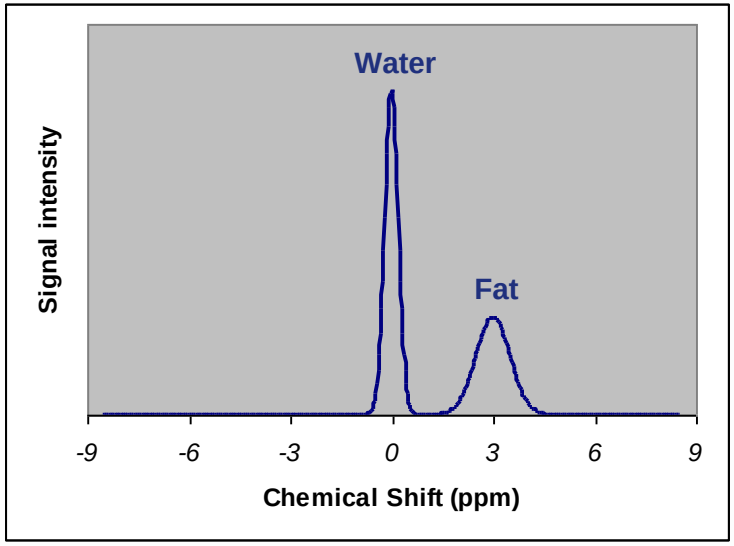
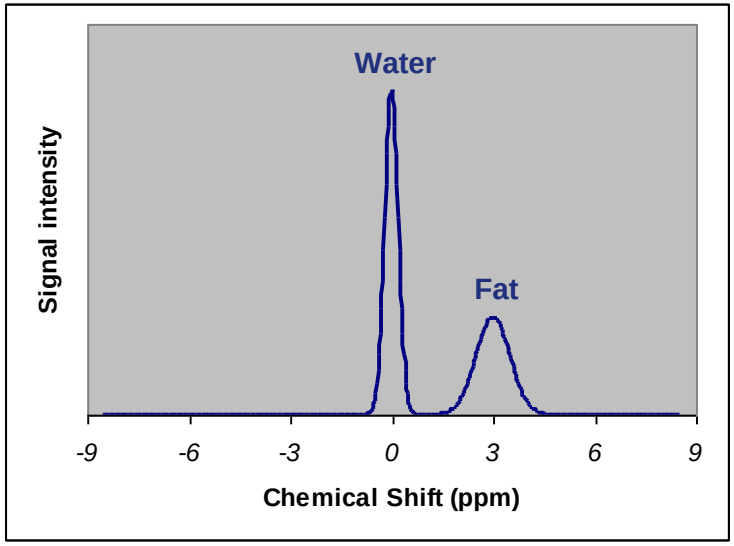
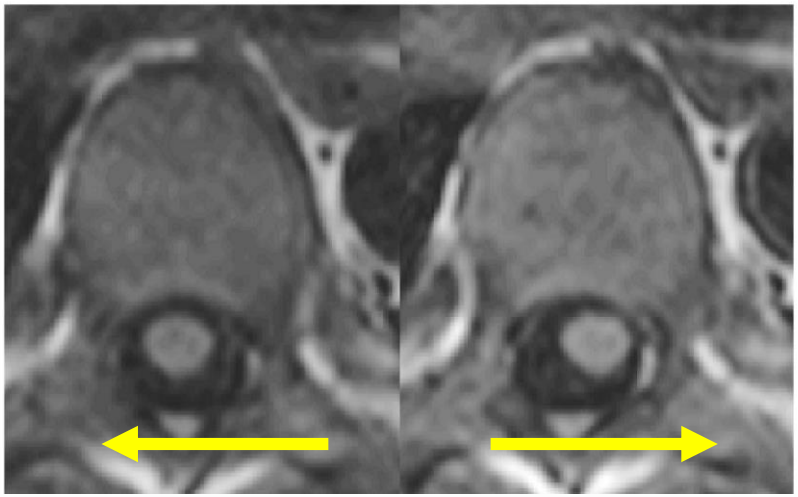
Water-fat shift



- Magnetic field at the nucleus depends on magnetic shielding of surrounding electron clouds, depends on molecular environment
- resonant frequencies of protons in fat and water differ by 3.4 ppm

Water-fat shift





- Magnetic field at the nucleus depends on magnetic shielding of surrounding electron clouds, depends on molecular environment
- resonant frequencies of protons in fat and water differ by 3.4 ppm

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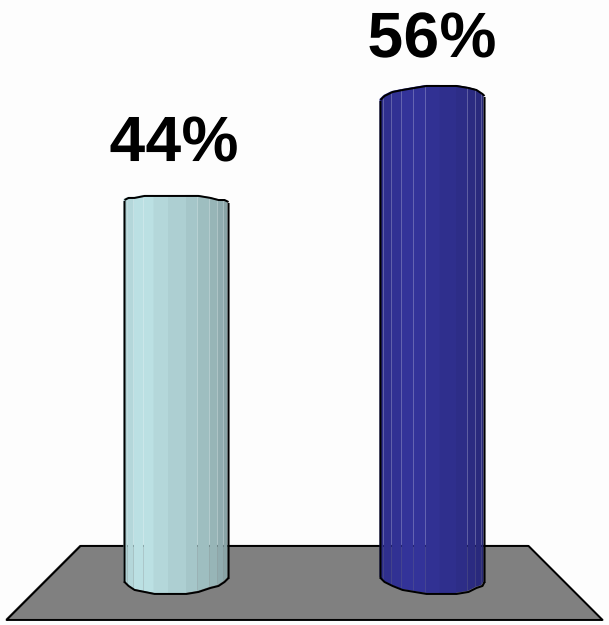
The water-fat shift is related to the strength of the magnetic field gradients. How can you reduce the WFS?

ESTRO School

ESNM

✓ a. Increase the gradient strength

b. Decrease the gradient strength



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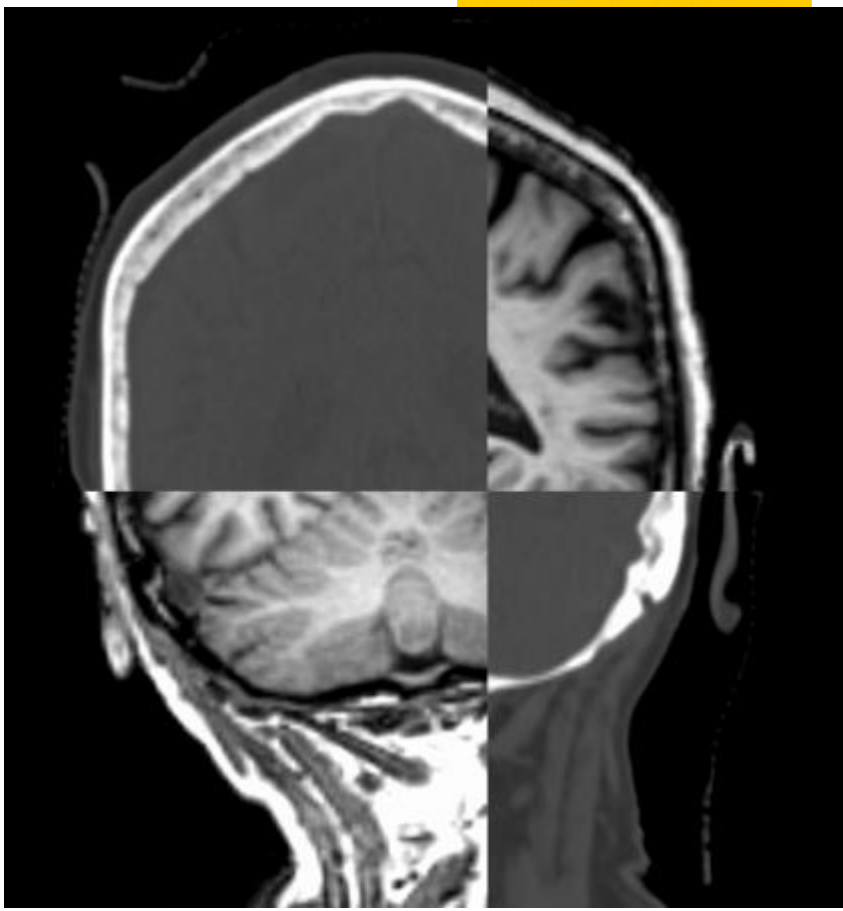
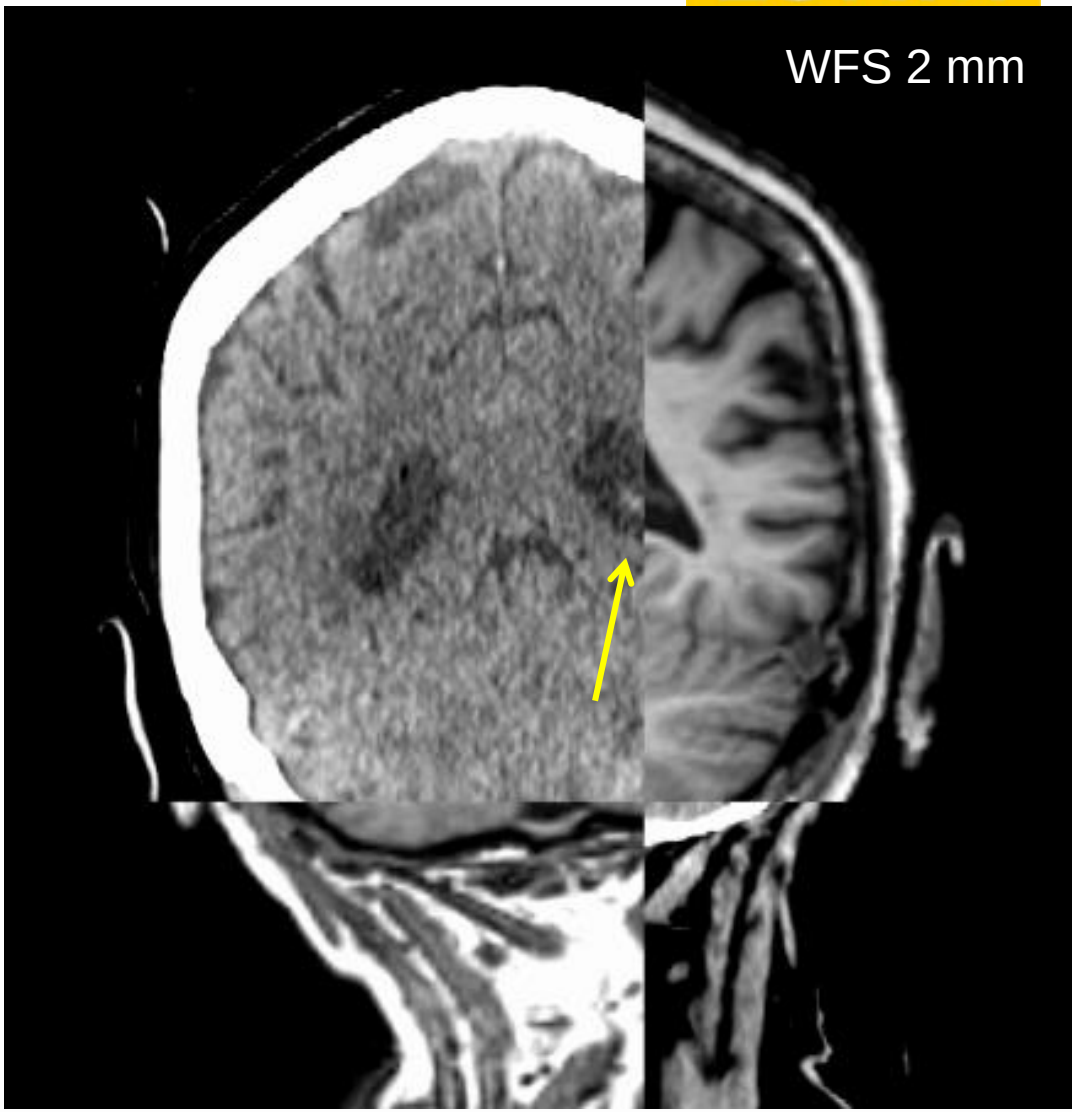
MRI and CT of brain

- Cortical bone:
  - CT: bright
  - MRI: dark
- Bone marrow
  - CT grey
  - MRI: grey
- skin
  - CT: dark grey
  - MRI bright



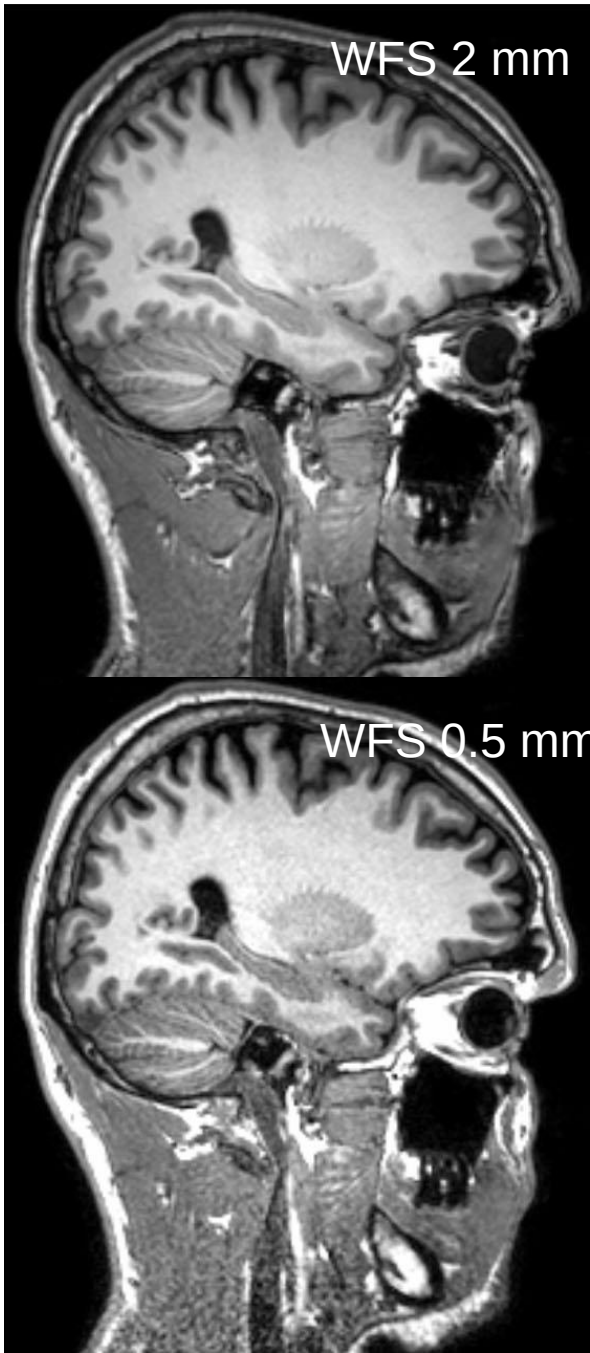
MRI and CT of brain

- Water-fat shift (WFS)
  - The water and fat are shifted relative to each other.
  - The WFS is a parameter that can be tuned;

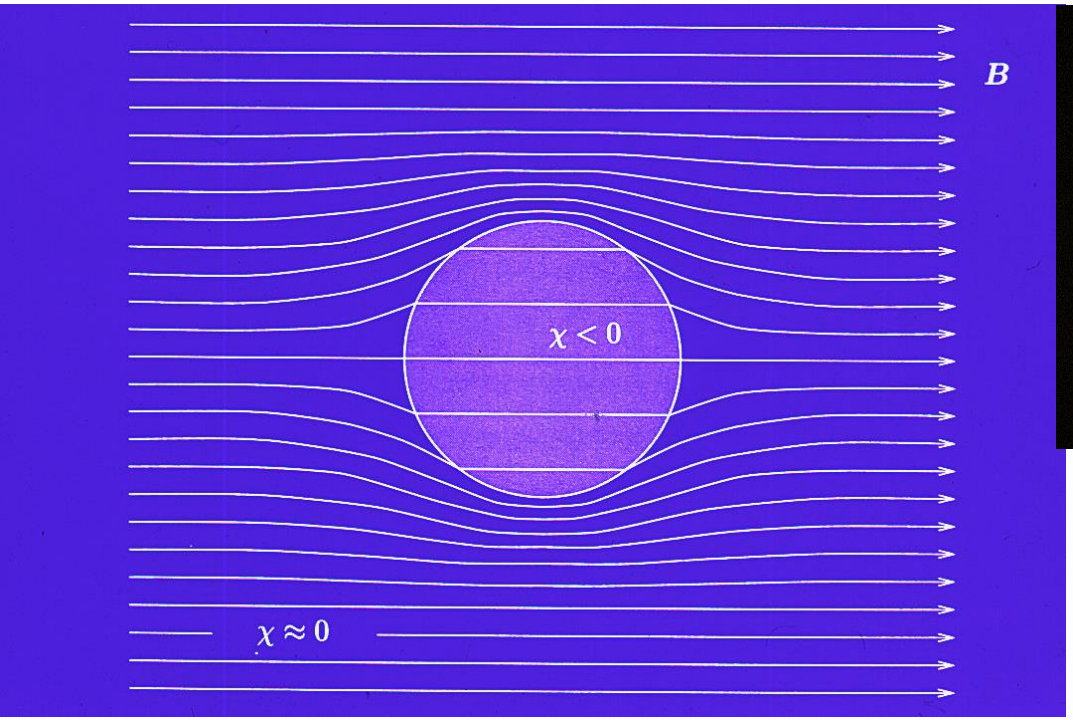


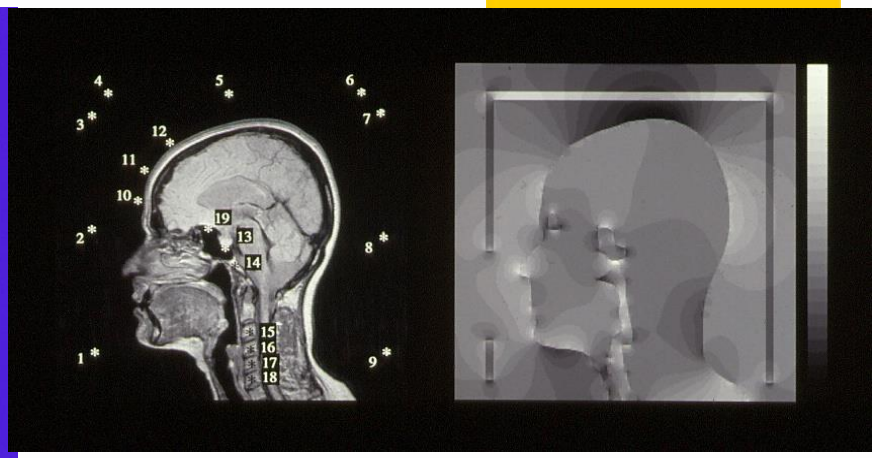
Water-fat shift

- Water-fat shift can be reduced, at the expense of signal
- Typically, diagnostic protocols use large WFS, to enhance signal (SNR)
- For radiotherapy, it is preferable to reduce the WFS to less than 1 pixel.



Magnetic susceptibility





- Magnetic susceptibility χ : $M=\chi H$
- A patient distorts the magnetic field
- Air cavities distort the magnetic field
- This compromises geometrical accuracy
- It can be minimized by reducing the water-fat shift

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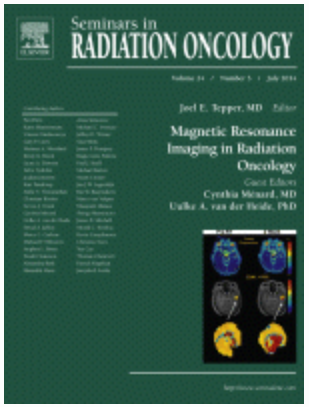
Summary

- MRI is a versatile technique
  - different types of anatomical contrast: T1 and T2
  - functional techniques: DWI, DCE-MRI
- Multiple sequences can be scanned within a single exam
- Spins precess at the Larmor frequency: $\omega_0=\gamma \cdot B_0$
- Gradient magnets are used for spatial encoding
- Non-linearities in gradients and distortions in magnetic field result in geometrical distortions
- Reducing water-fat shift improves geometrical integrity at the cost of SNR

Literature

- Seminars in Radiation Oncology; July 2014



ESNM/ESTRO COURSE
MOLECULAR IMAGING & RADIATION ONCOLOGY
10-13 APRIL BORDEAUX

MRI: Clinical Perspective

Professor Vicky Goh

Division of Imaging Sciences & Biomedical Engineering, Kings College London

Department of Radiology, Guy's & St Thomas' NHS Trust

London, UK

Email: vicky.goh@kcl.ac.uk

Learning Objectives

- To appreciate the advantages of MRI
- To illustrate the role of MRI for imaging cancer
  - Diagnosis
  - Characterisation
  - Staging
  - Therapy guidance
  - Response assessment
- To understand the challenges of integrating MRI into hybrid PET/MRI

MRI in Clinical Medicine

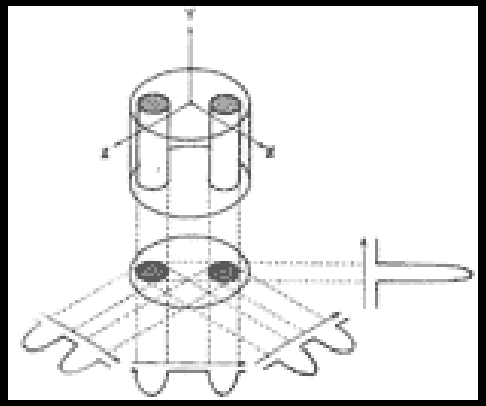
Paul Lauterbur

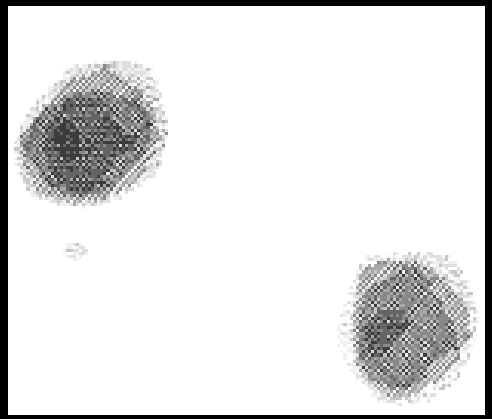
Peter Mansfield

- Awarded the 2003 Nobel Prize for medicine for contributions to the field of MRI

<http://www.nobelprize.org/educational/medicine/mri/>

MRI in Clinical Medicine





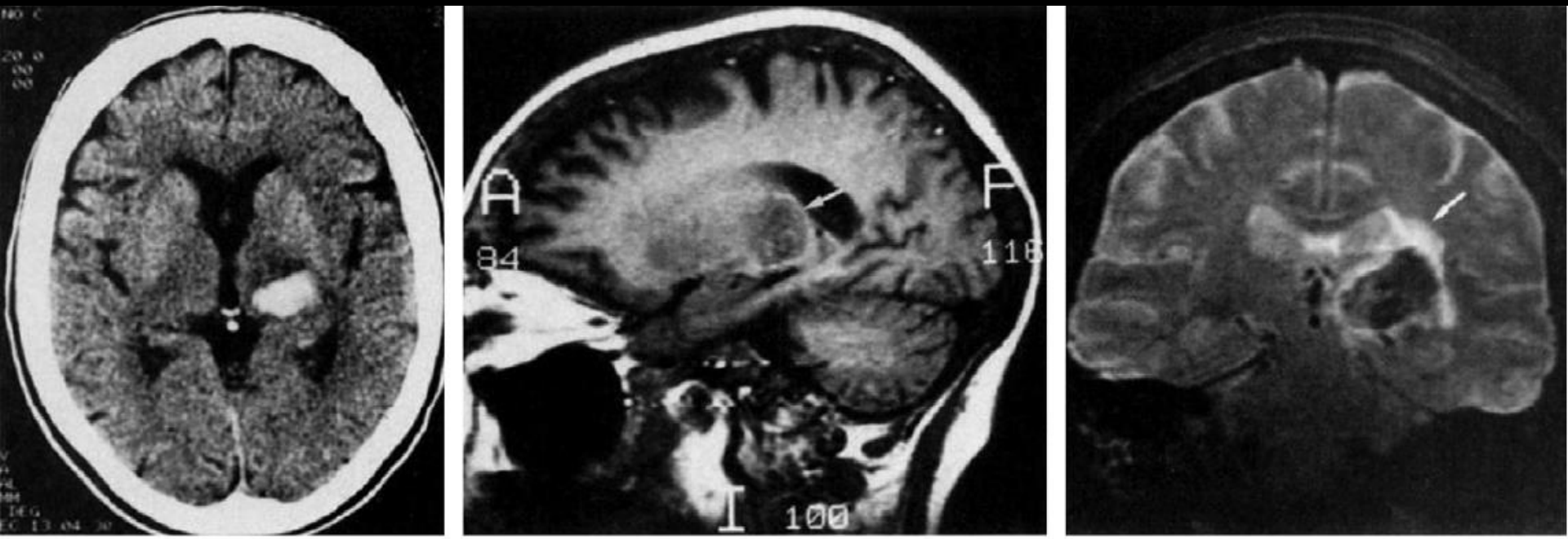
- Use of 2 fields: one interacting with the object under investigation, the other restricting this interaction to a small region
- Rotation of the fields relative to the object produced a series of 1-D projections of the interacting regions, from which 2- or 3-D images of their spatial distribution could be reconstructed.

Lauterbur PC. Nature 1973;242(5394):190–1

http://www.nature.com/physics/looking-back/

Edelman RR . Radiology 2014.
Special Centennial Issue.

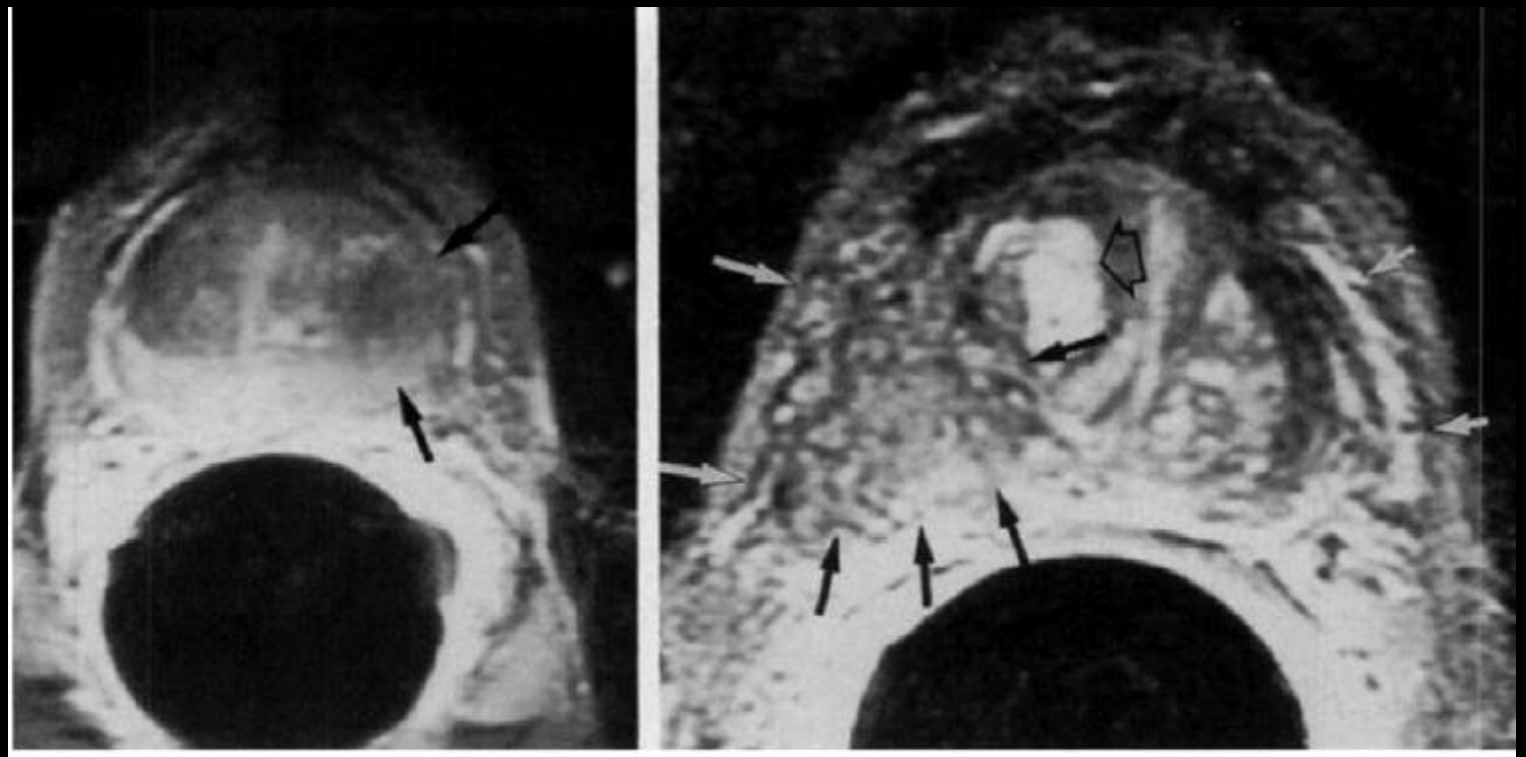
First reports in Radiology:
1980 – only 7 years after MRI shown to be feasible



a. b. c.

Figure 1: **(a)** Axial CT image, **(b)** sagittal T1-weighted MR image, and **(c)** coronal T2-weighted MR image of hypertensive intracranial hemorrhage (arrow in **b**). Perihematoma hyperintensity (arrow in **c**) is consistent with edema (images from reference 13).

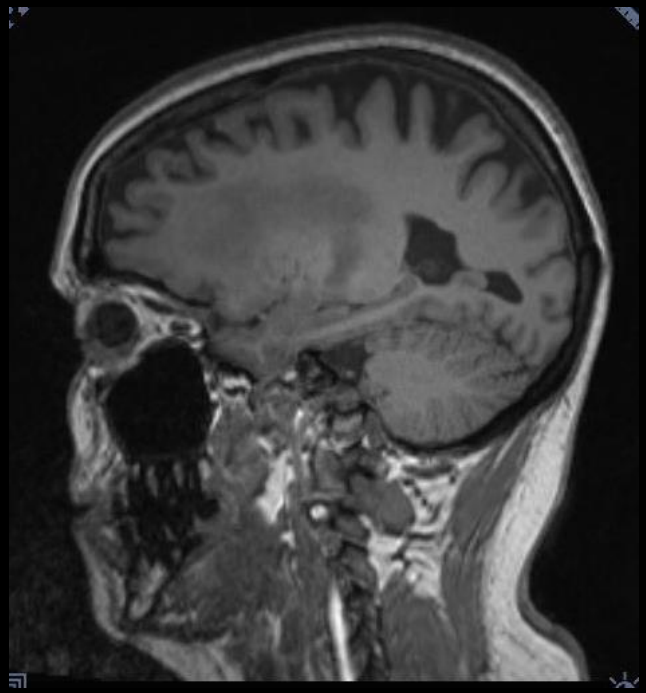
Gomori JM et al. Intracranial hematomas: Imaging by high-field MR. Radiology 1985; 157(1): 87-93



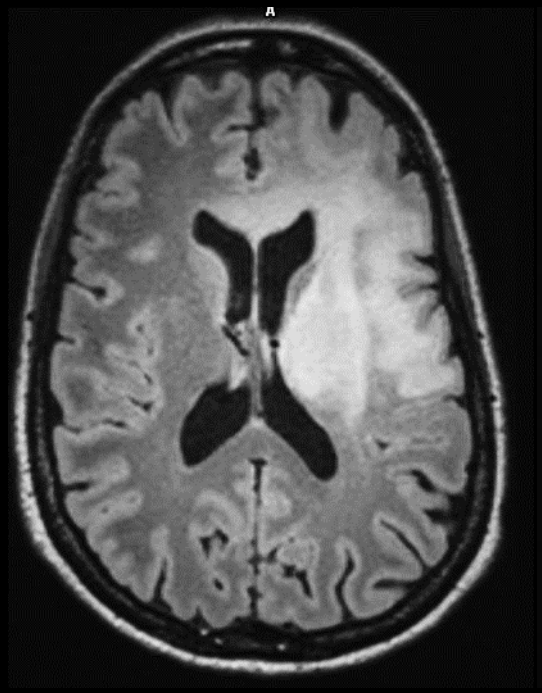
a. b.

Figure 4: MR images in two patients with prostatic carcinoma. **(a)** Low-intensity lesion in left peripheral zone is in region with positive biopsy findings (arrows). **(b)** Low-intensity lesion in right side of the prostate extends into the periprostatic fat (large solid arrows). High-signal-intensity glandular benign prostatic hypertrophy is seen in the central gland (open arrow) (images from reference 30).

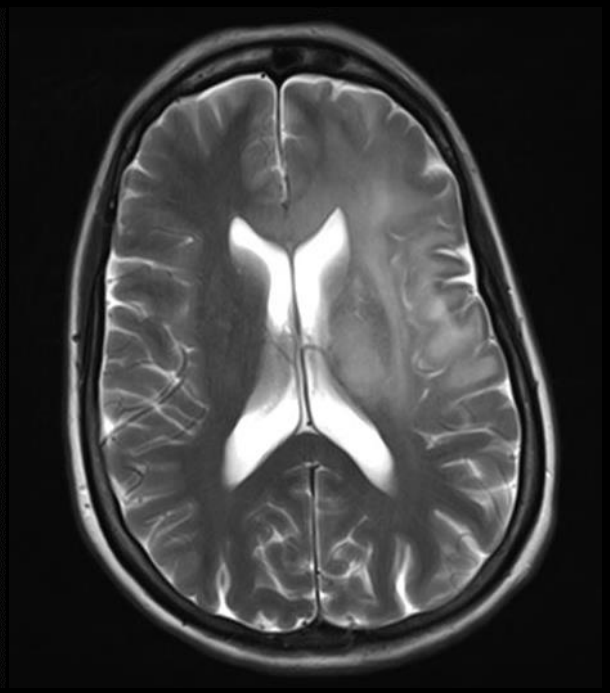
Schnall MD et al. Prostate: MR imaging with an endorectal surface coil. Radiology 1989;172: 570-4



T1 sagittal isotropic

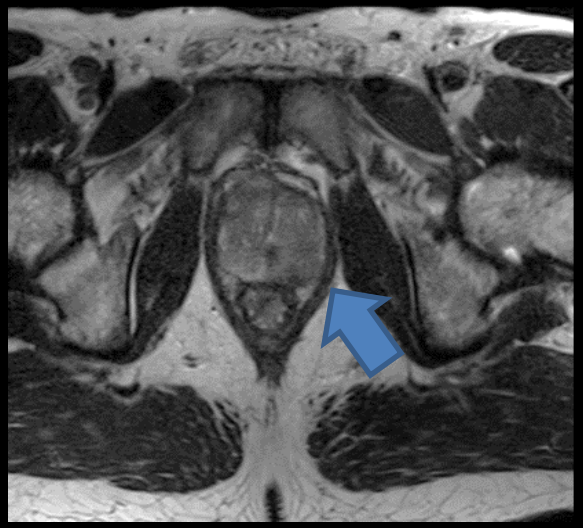


FLAIR

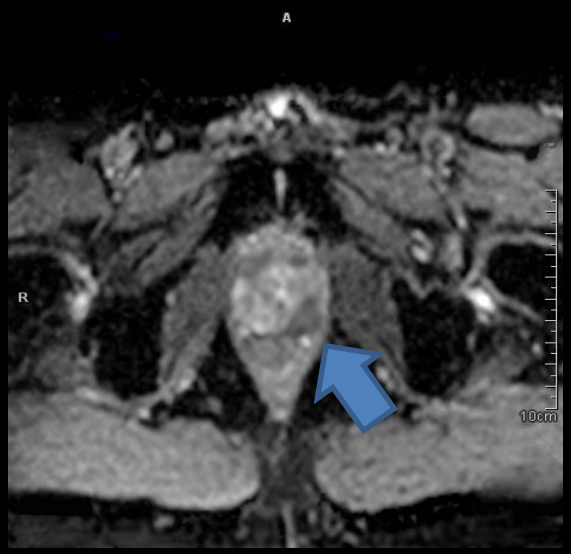


T2 axial

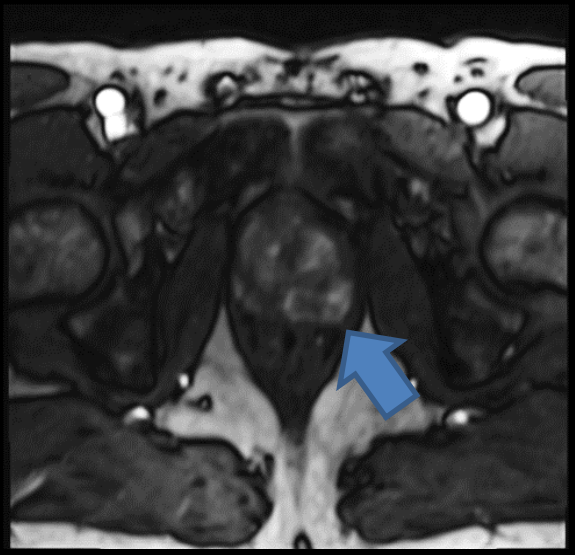
Low grade glioma



T1 axial

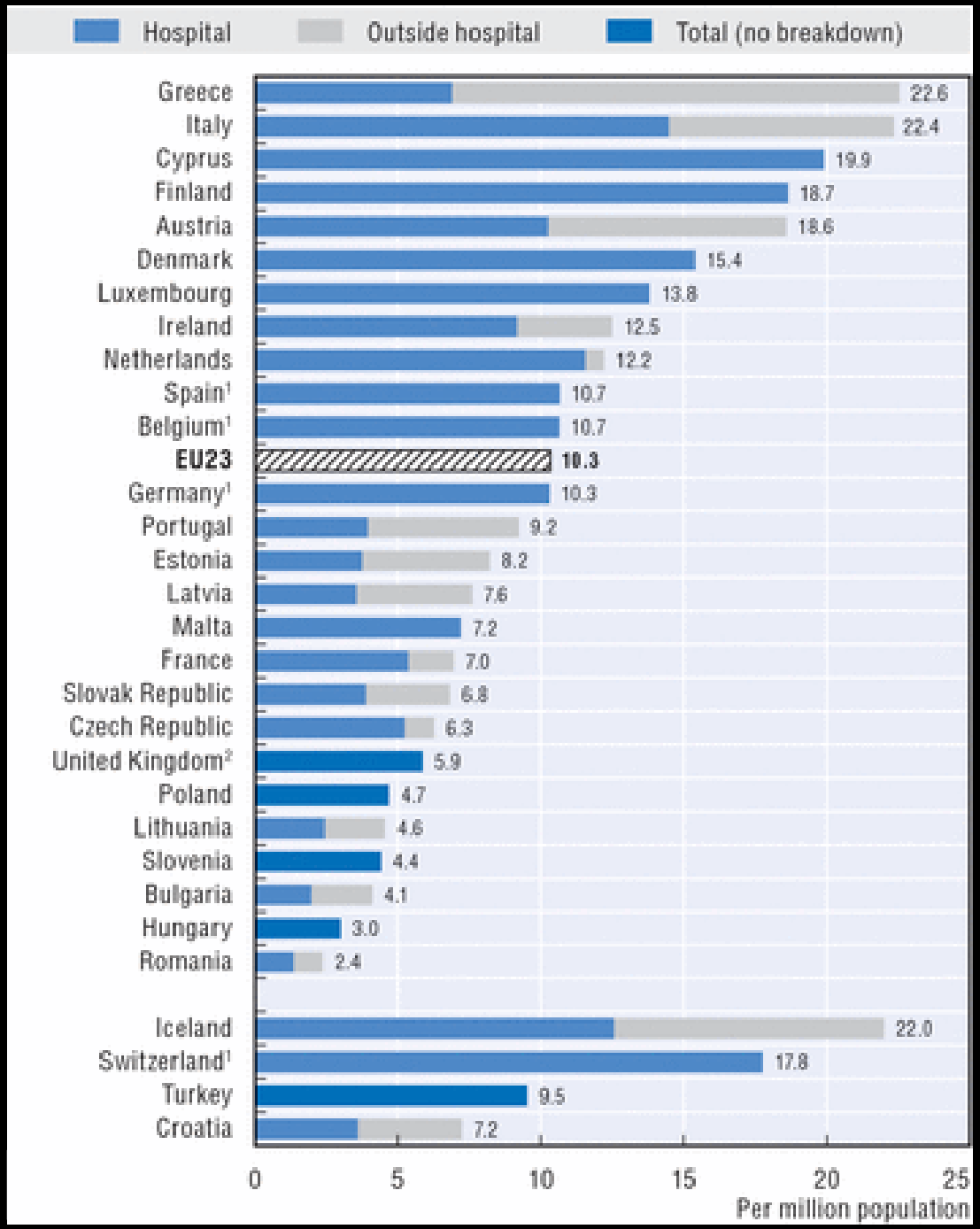


Diffusion MRI
Apparent Diffusion
Coefficient map



T1 dynamic
post gadolinium
contrast agent

Prostate Cancer
Gleason 3+4
T3aN0M0



- Year on year increase in MRI examinations
- Increasing clinical workload worldwide
- USA: 2006-2013
  - Increase from 89.1 to 106.8 MRIs per 1000 population

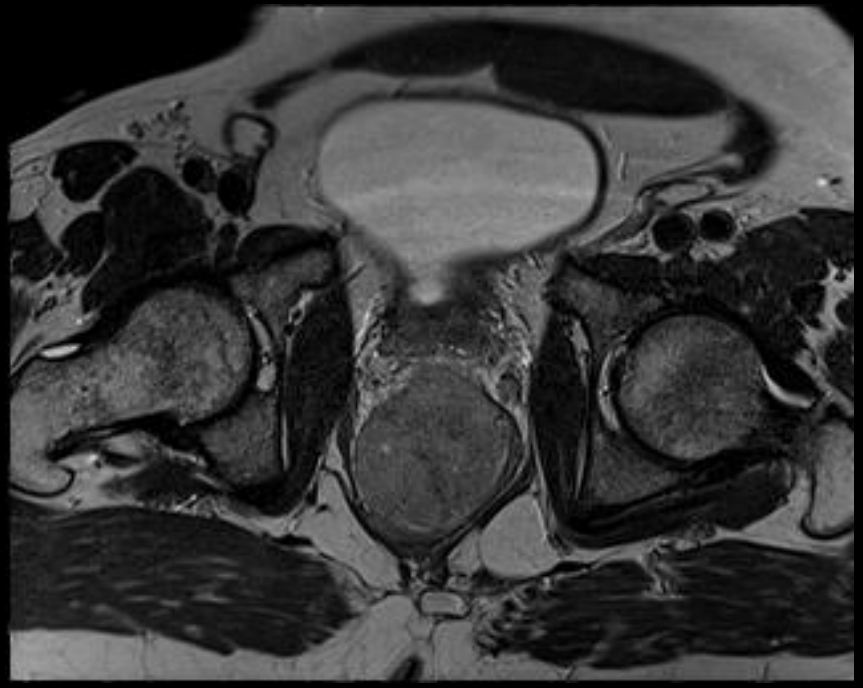
Step change from a problem solving to key diagnostic tool

OECD data:
http://www.oecd-ilibrary.org/

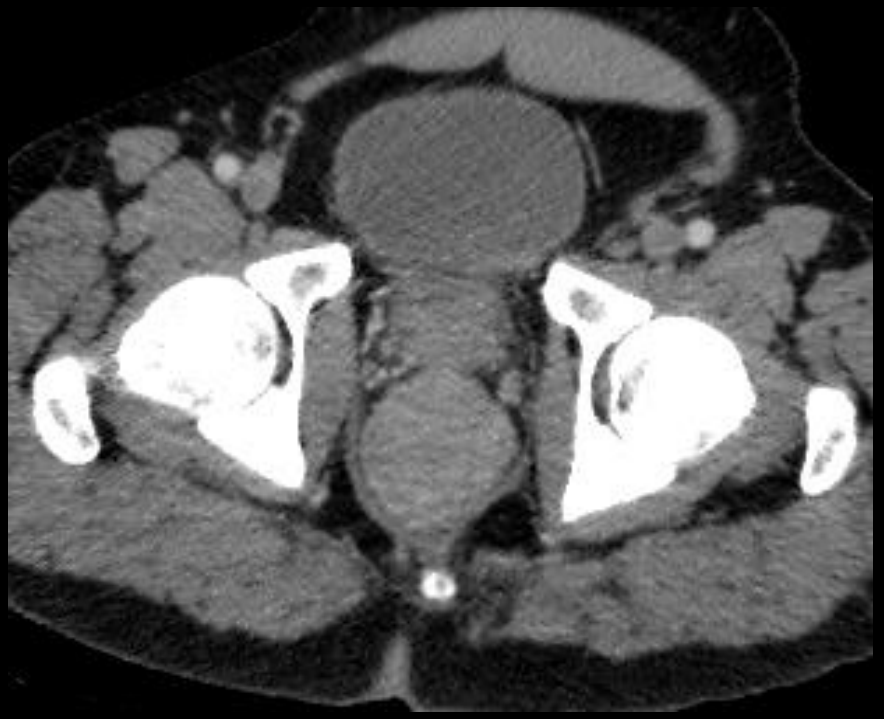
Advantages of MRI

- Good spatial resolution
- High contrast to noise
- Multiple tissue contrast in a single examination e.g. T1, T2, PD, FLAIR, STIR, Diffusion, Post contrast
- Physiological imaging:
  - Dynamic contrast enhanced MRI
  - Diffusion weighted MRI
  - 1H- MR Spectroscopy
  - Blood oxygenation or tissue oxygenation MRI

Advantages of MRI

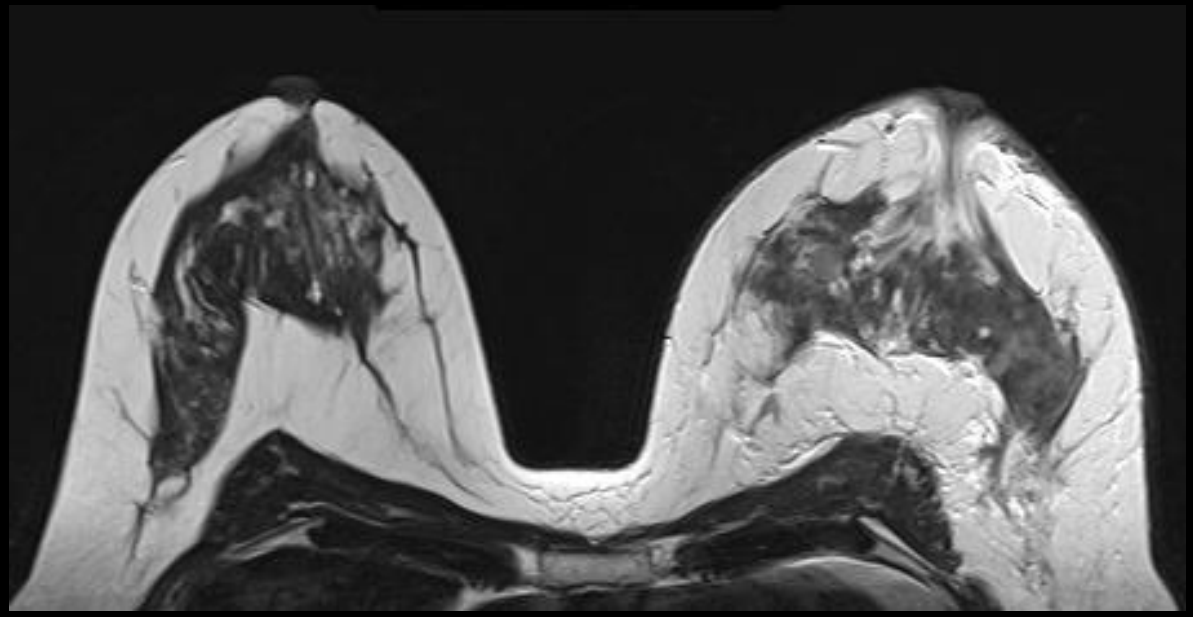


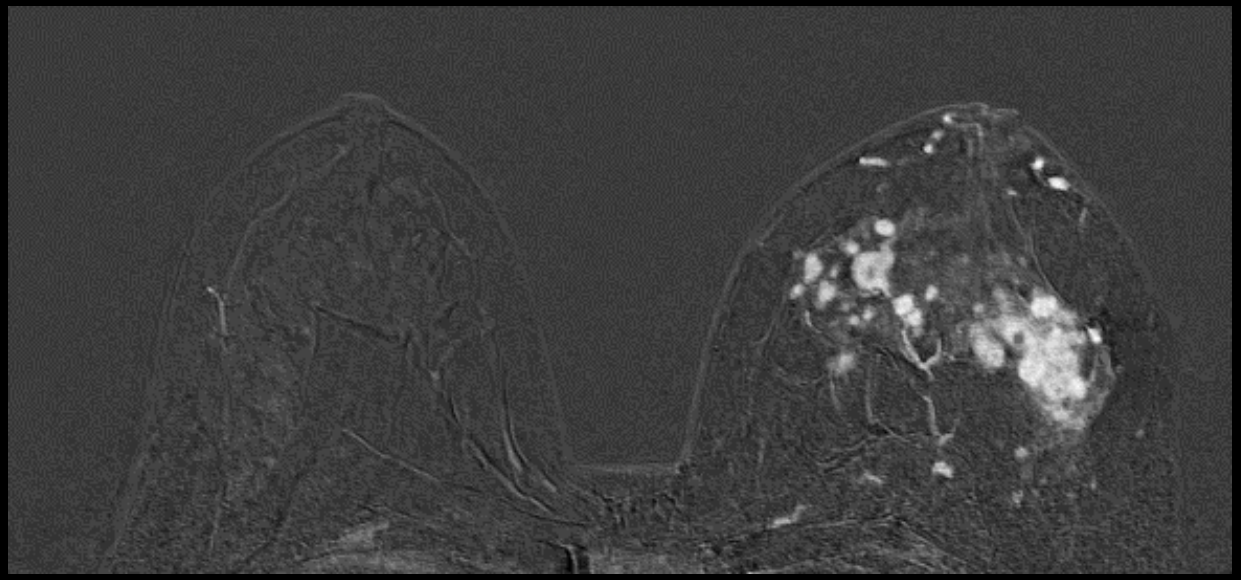
MRI: T2-weighted axial



CT: Contrast enhanced

Higher contrast to noise

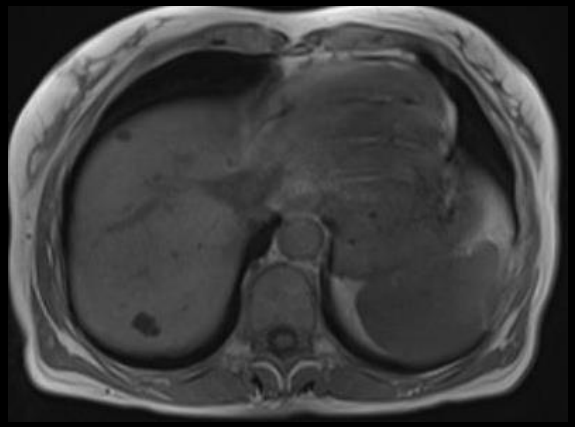


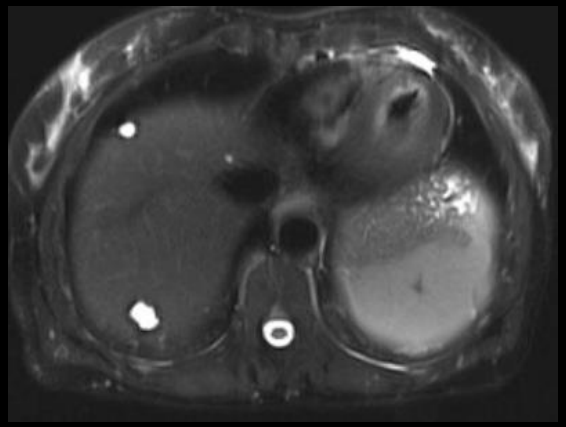


Higher contrast to noise

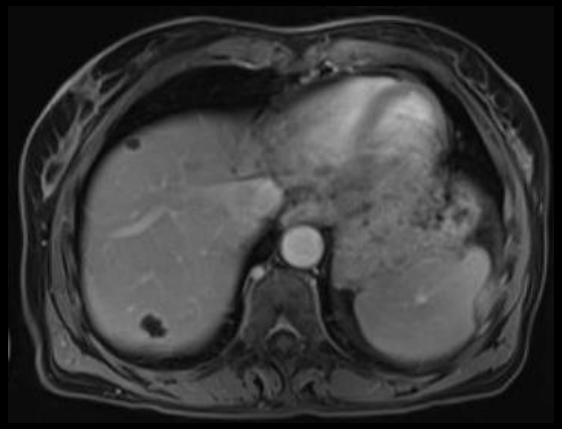
Multiple Tissue Contrast

T1

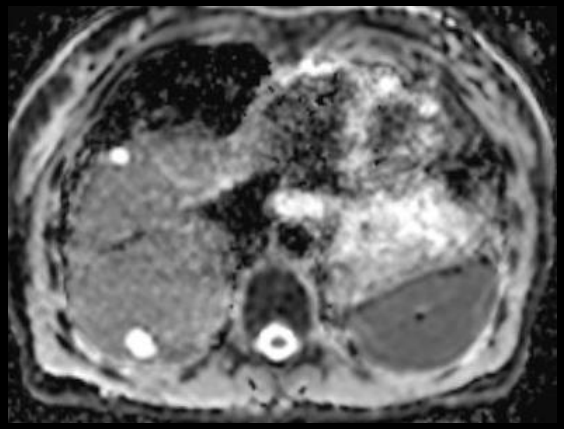




T2
+ fat
suppression



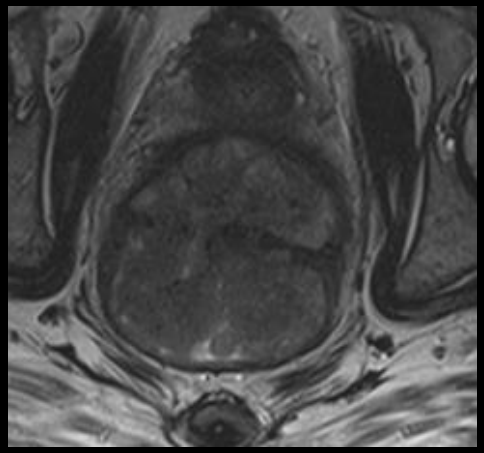
T1
+ gadolinium contrast
+ DIXON fat suppression



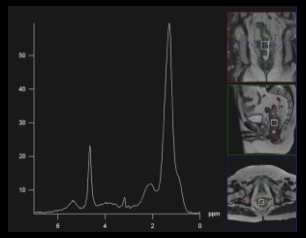
Diffusion
ADC map

Standard Liver MRI Acquisition	
T1 weighted Axial	Gradient echo with Dixon or chemical shift imaging
T2 weighted Axial	HASTE: Half Fourier acquisition single shot TSE with different T2 weighting Propeller/Blade: Periodically rotated overlapping parallel lines with enhanced reconstruction RARE: Rapid acquisition with relaxation enhancement
Diffusion weighted	Echo planar imaging Multiple b-values: b=0-800 s/mm^2
Contrast enhanced T1 weighted Axial ± Coronal/Sagittal	SPGR: Spoiled gradient recalled VIBE: Volumetric interpolated breathhold examination
- Gadolinium chelate	Multiphasic
- Gadoxetic acid (Primovist)	Multiphasic + delayed 15mins

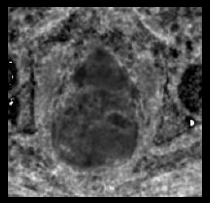
Physiological Imaging



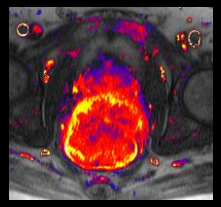
Altered metabolism



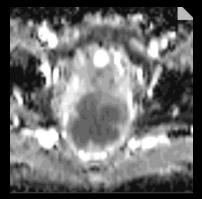
Hypoxic blood volume



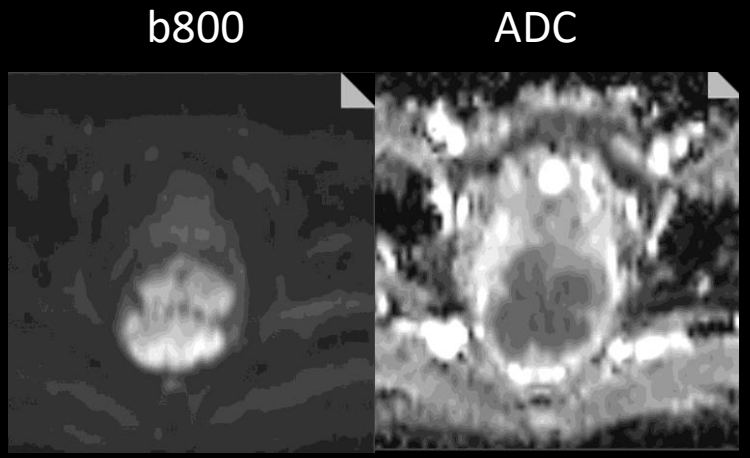
Vascularisation



Water Diffusion



Proliferation
Metabolism



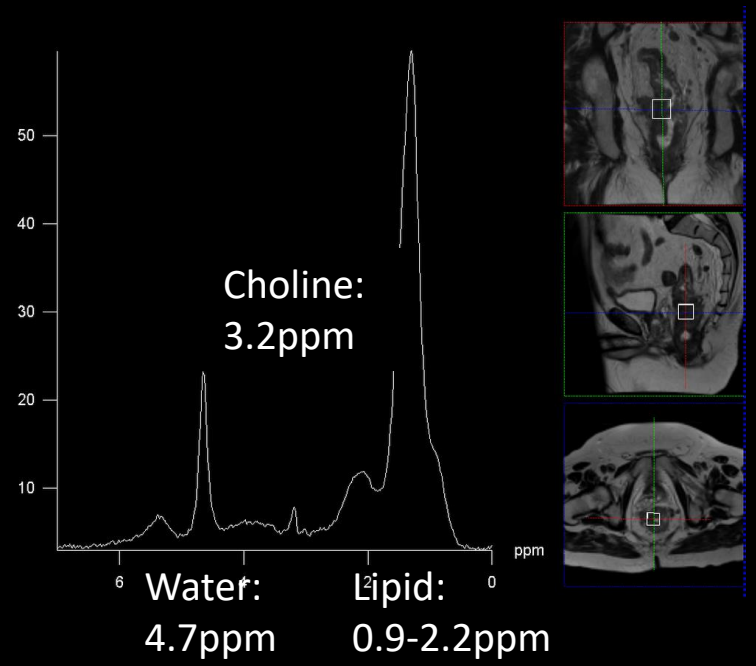
Diffusion weighted MRI

Diffusion weighted MRI
Assessment of water diffusion

Informs on cell density,
extracellular space tortuosity
& integrity of cellular membranes

1H-MRI Spectroscopy
Informs on cellular membrane turnover

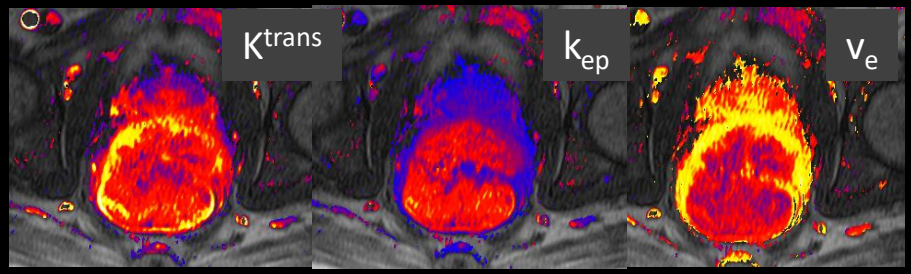
Common metabolites:
Choline: Cell membrane synthesis & degradation
Creatine: Metabolism
Free Lipids: necrosis & apoptosis



MRI Spectroscopy

Perfusion & Angiogenesis
Hypoxia

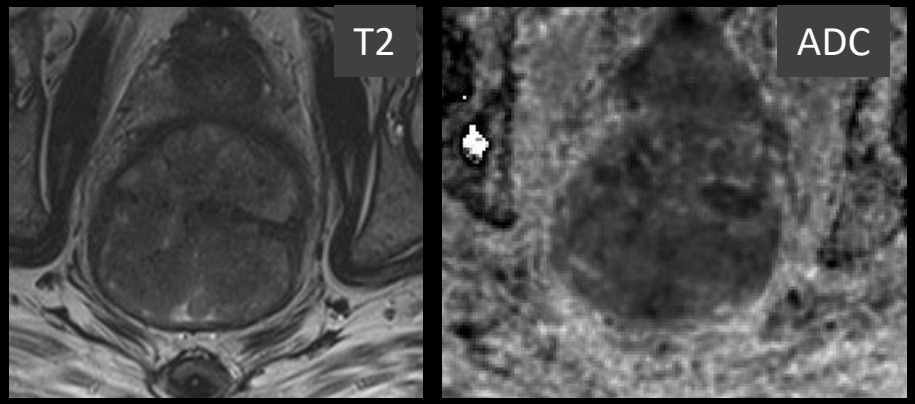
DCE-MRI
Parameters indirectly reflect perfusion, hypoxia & the functioning microvasculature



Dynamic contrast enhanced MRI

Intrinsic susceptibility weighted MRI
Sensitive to paramagnetic deoxyhemoglobin in red blood cells in perfused vessels

Provides information of red cell delivery & level of blood oxygenation

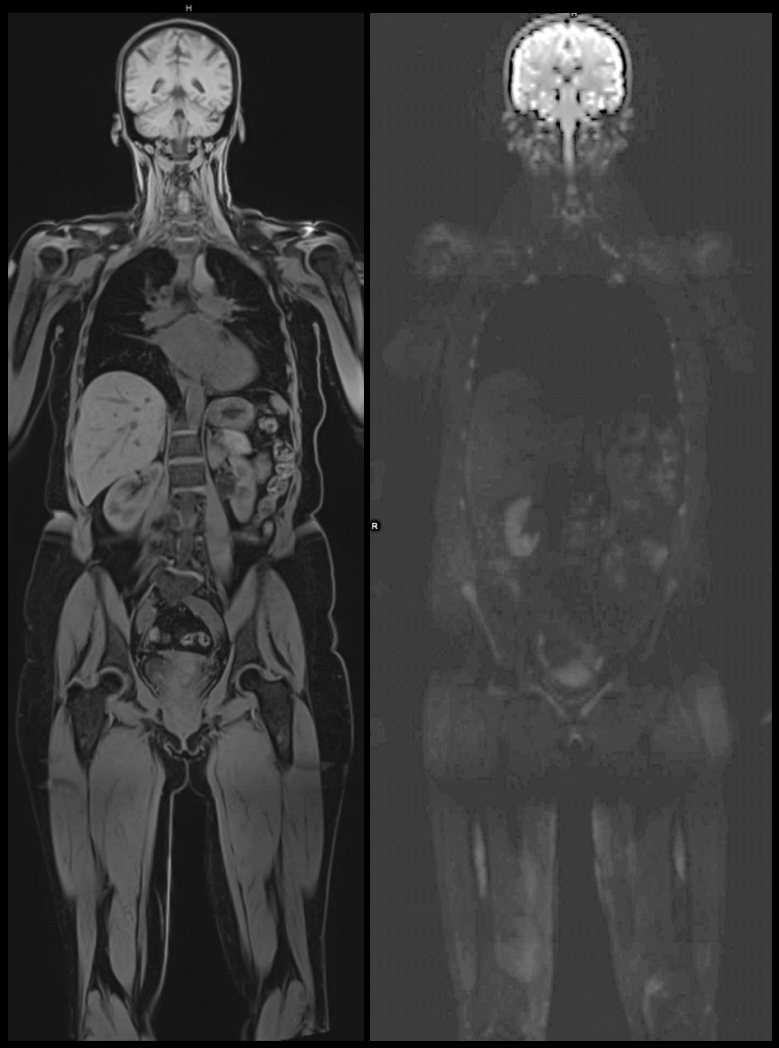


Intrinsic susceptibility weighted MRI

Locoregional to Whole Body MRI

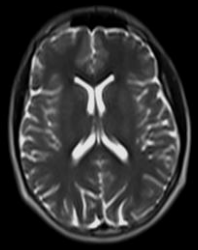
Technical aspects:

- Hardware improvements
- Coil design: multichannel
- Parallel imaging
- High gradient amplitudes
- Methods to improve field inhomogeneity
- Faster sequences
- Integrated PET/MRI:
  MRI attenuation correction



Station

I



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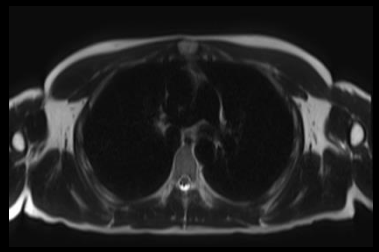

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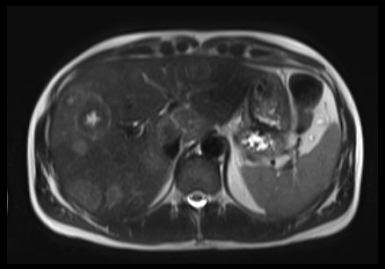

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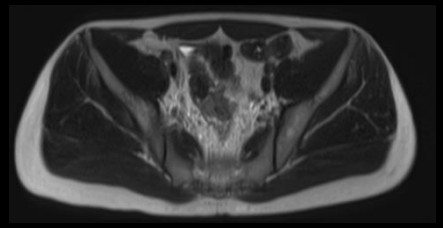

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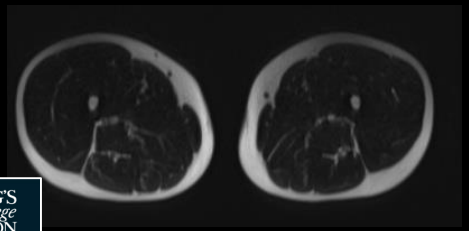

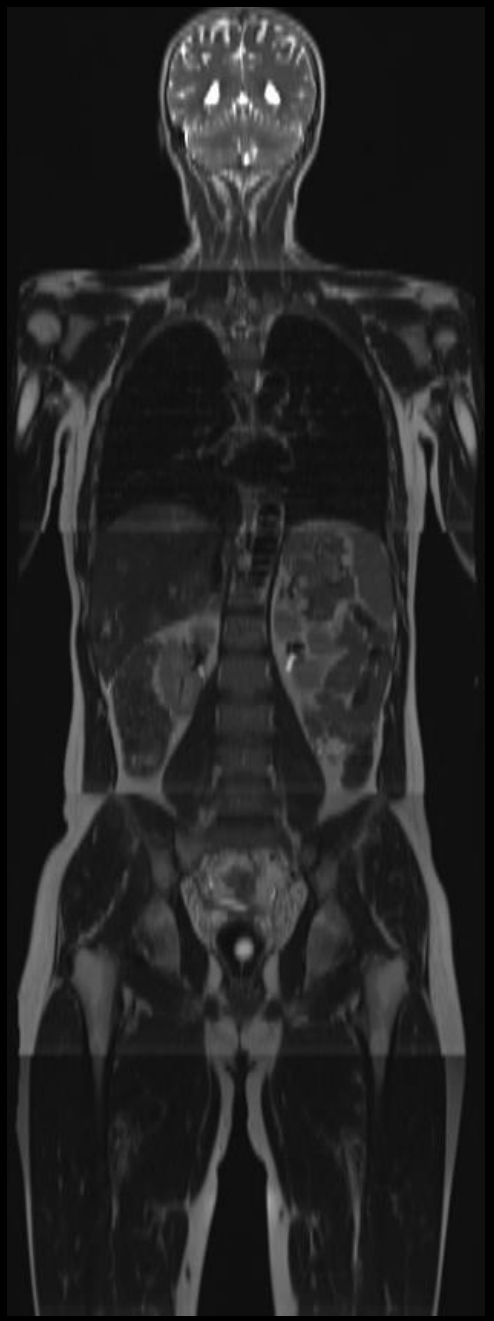

Whole body MRI:

- Coverage: Vertex to mid thigh
- Performed in the axial/coronal plane
- T2 HASTE
- T1 DIXON
- DWI $b_{50,900}$

0mins

30mins

- Additional locoregional sequences

60mins

KING'S College LONDON

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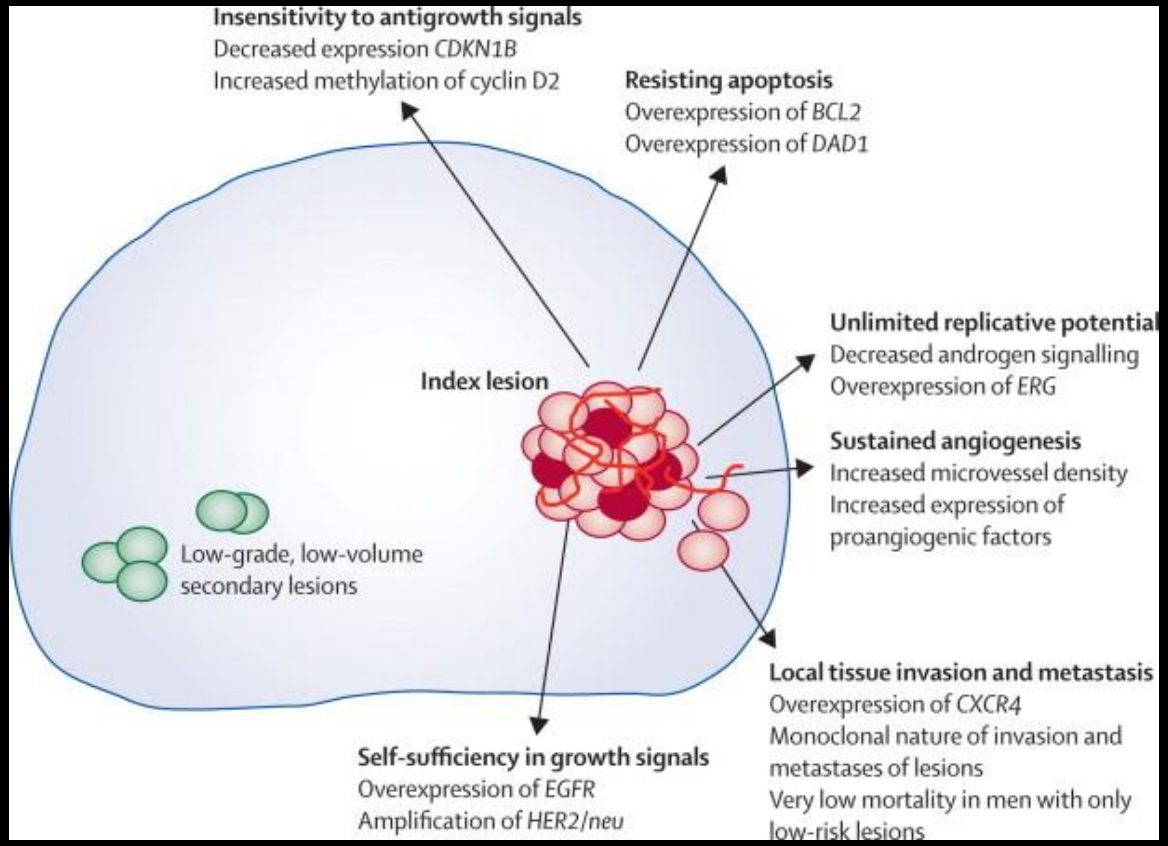
Diagnosis

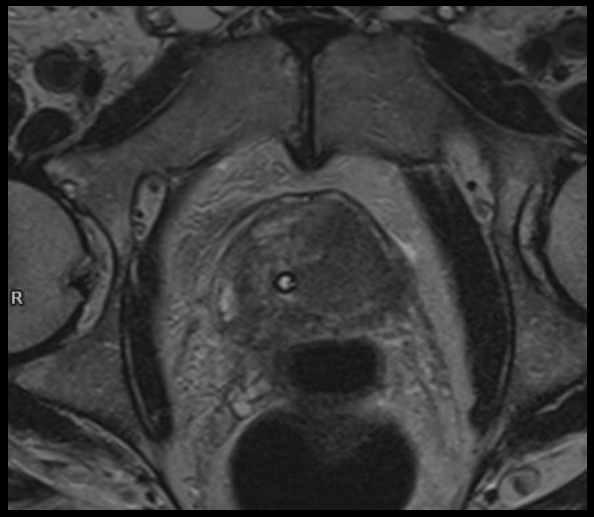
Diagnosis: Prostate Cancer



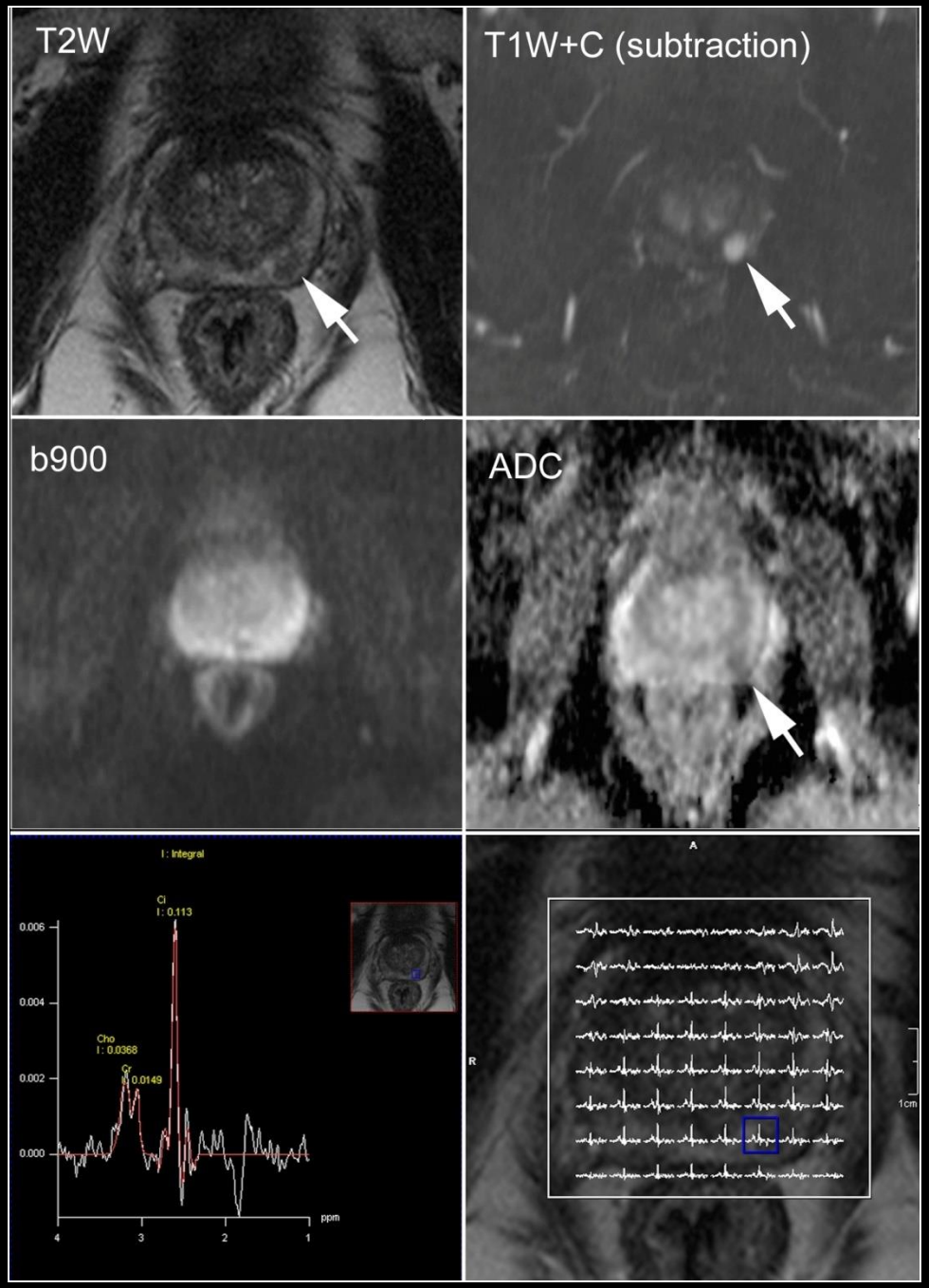
- Not all cancers destined to progress
- Small low Gleason grade lesions do not have same hallmarks as index lesion

Ahmed HU et al . Lancet Oncology 2012; 13: e509–e517

Diagnosis: Prostate Cancer



- MRI first line imaging investigation in patients with elevated PSA
- MRI advocated prior to biopsy for identification of focal lesions & to direct biopsy

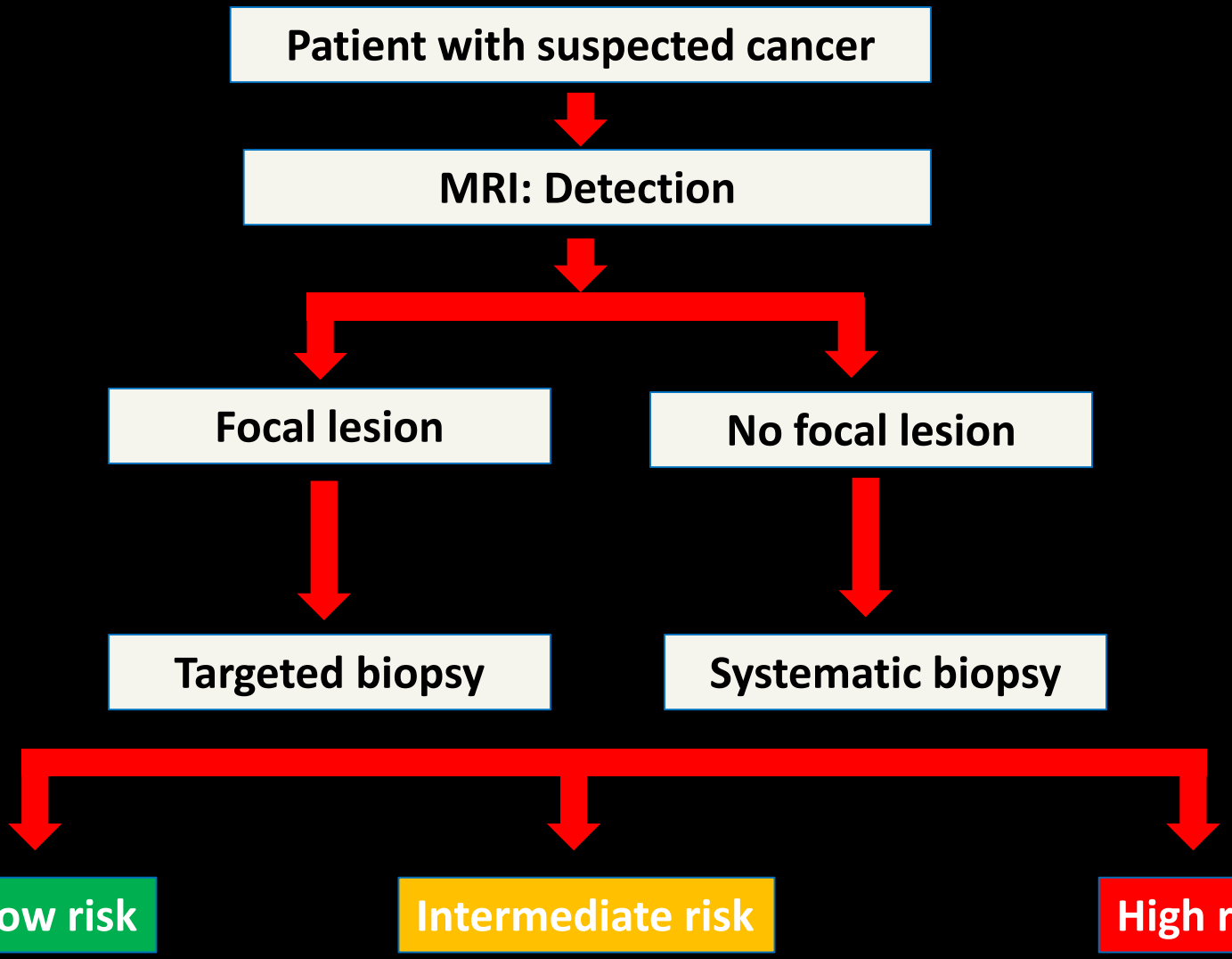


Potential advantages:

- Avoidance of biopsy in patients with normal gland
- Allow targeted versus systematic biopsy

Multi-parametric MRI:

- **T2 MRI**
- **Diffusion MRI**
- **+/-Contrast enhanced MRI**
- **MR Spectroscopy**



cStage	T1-2a
& PSA ng/mL	<10
& Gleason	≤6

cStage	T2b-c
or PSA ng/mL	10-20
or Gleason	7

cStage	≥T3a
or PSA ng/mL	>20
or Gleason	8-10

A Cost-Effective Tool

- Comparison of 10-12 core TRUSGB to mpMRI & mRI guided biopsy
  - Comparable costs but with higher QoL
  - Expected costs per patient: 2423 euros (MRI) vs 2392 (TRUS-GB)
  - **Corresponding QALYs (quality adjusted life years) higher for MRI strategy : incremental cost-effectiveness ratio of 323 euros per QALY**

Rooij et al. Eur Urol 2014; 66 (2014) 430–436

The PROMIS study

- mP-MRI prior to biopsy
- Recruitment: 740 males (target 715)
- TPM (reference standard) & TRUS biopsy (current standard)
- To assess the ability of MP-MRI to identify men who can safely avoid unnecessary biopsy
- To assess the ability of the MP-MRI based pathway to improve the rate of detection of clinically significant cancer as compared to TRUS biopsy
- To estimate the cost-effectiveness of an MP-MRI based diagnostic pathway

El-Shater Bosaily et al. Contemp Clin Trials. 2015 May;42:26-40

The PROMIS study

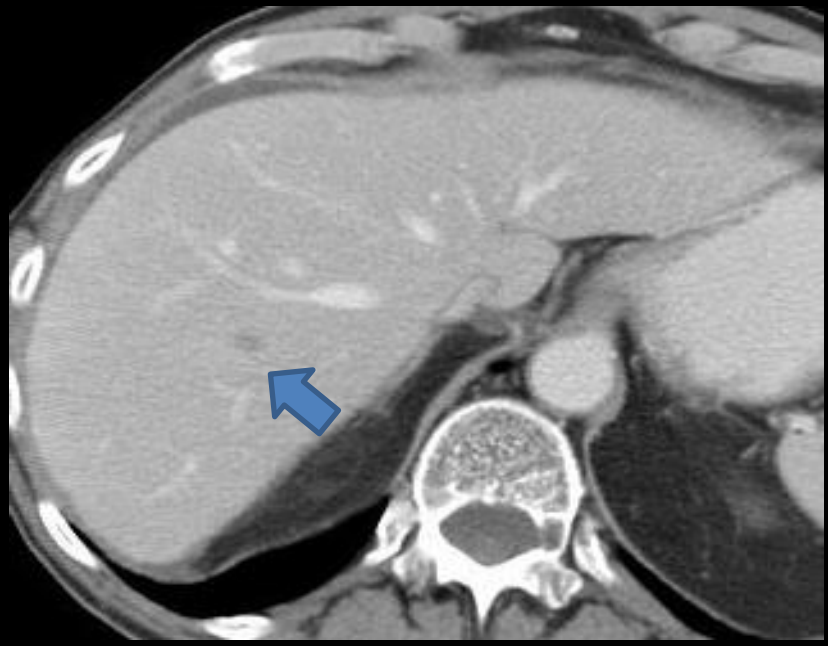
- 576 men: MP-MRI followed by TRUS-& TPM-biopsy
- 408 (71%) had cancer; 230 (40%) clinically significant (G4+3)
- Clinically significant cancer:
  - MP-MRI more SENSITIVE: 93% [95% CI 88-96%] vs TRUS-biopsy, 48% [42-55%]; p<0·0001
  - MP-MRI LESS specific: 41% [36-46%] for MP-MRI vs 96%, [94-98%] for TRUS-biopsy; p<0·0001)
  - 44 (5·9%) of 740 patients reported serious adverse events, including 8 cases of sepsis

Ahmed HU et al. PROMIS study group. Lancet 2017;389(10071):815-822
Kapoor J et al. Eur Urol. 2017 Feb 23. pii: S0302-2838(17)30103-3.

Characterisation

Characterisation

- Indeterminate lesion detected by other imaging
- MRI used as a problem solving tool
- Multi-sequence MRI highlights different properties

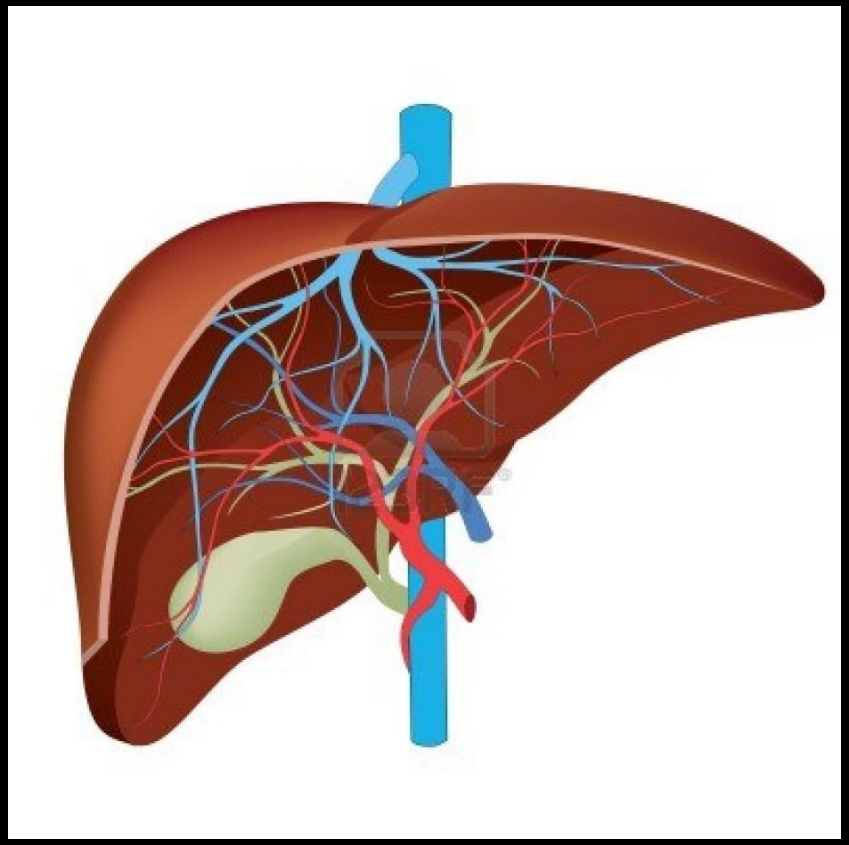


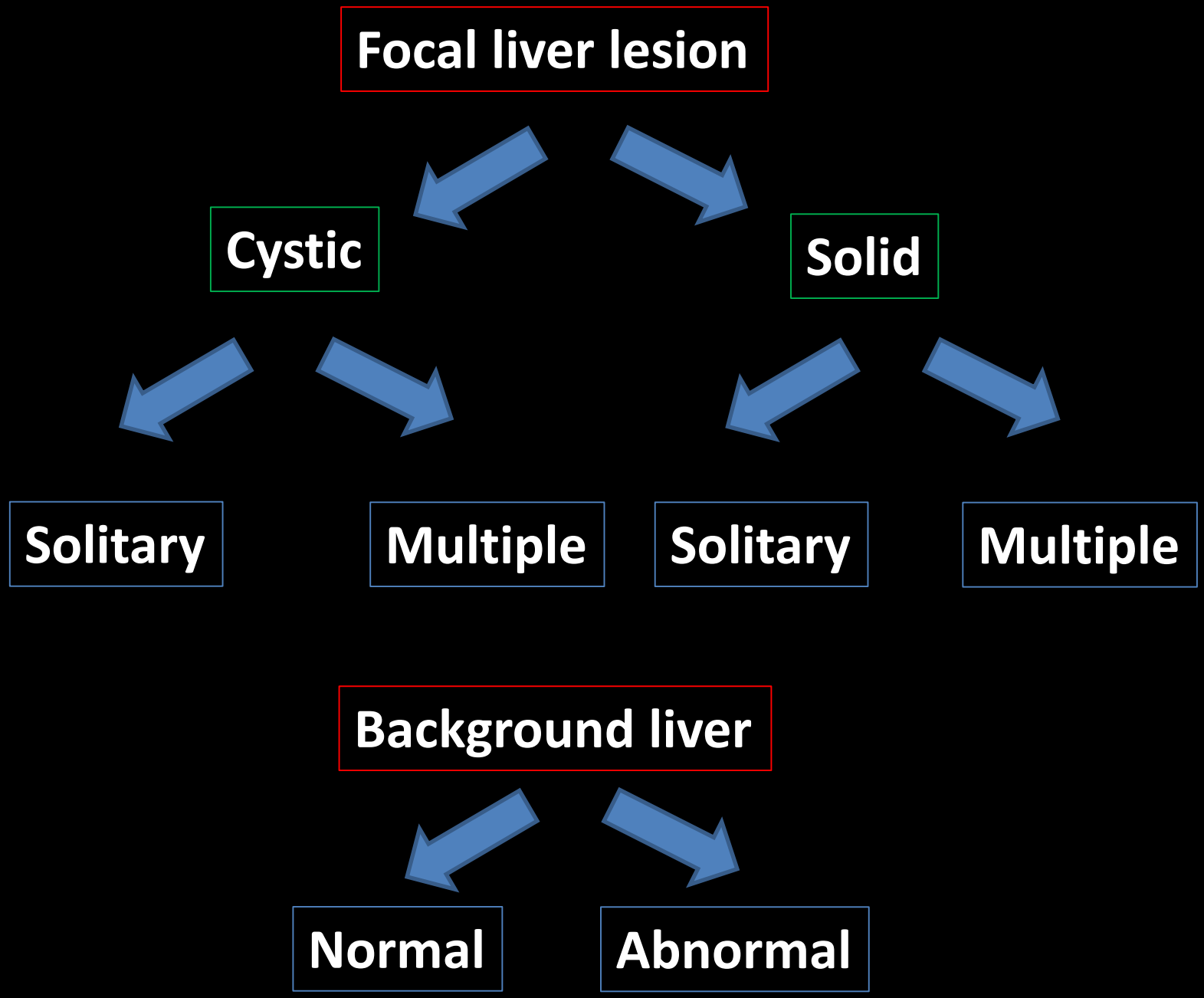
Contrast enhanced CT
Portal venous phase

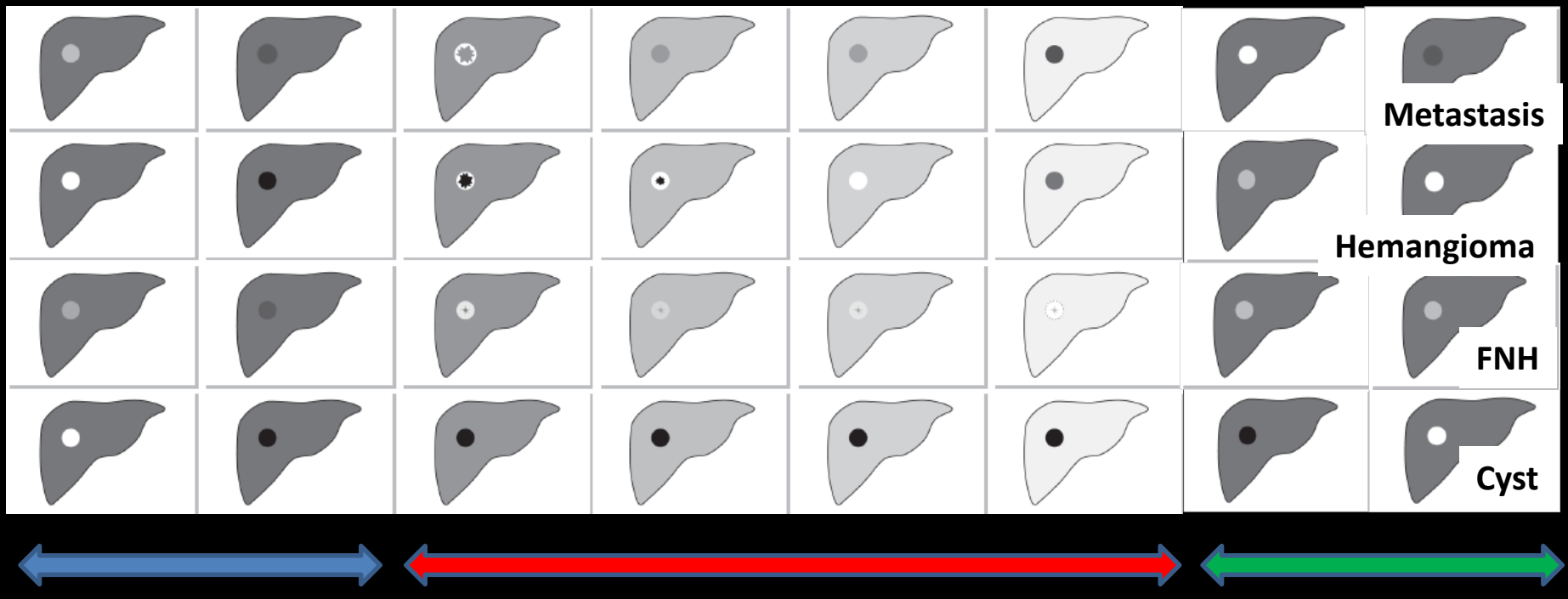
Pitfalls: Dioguardi Burgio et al. Semin Ultrasound CT MR. 2016;37(6):561-572

Liver Physiology

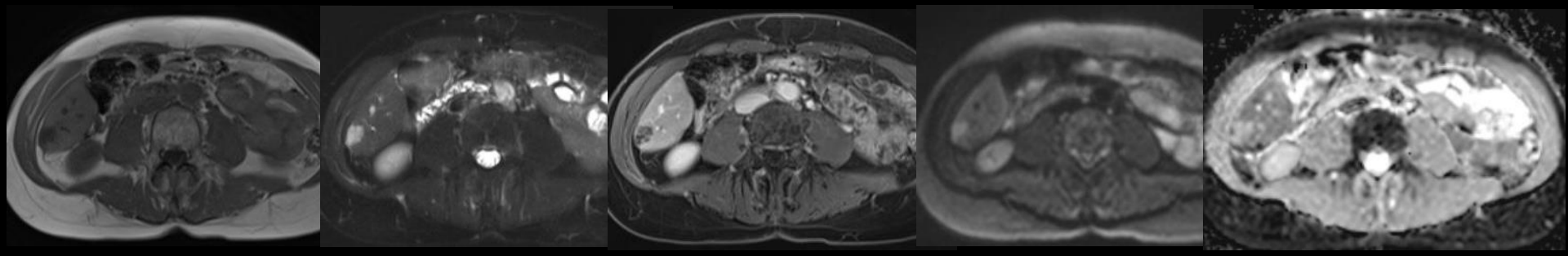
- The liver has a dual blood supply
  - Portal venous input accounts for 60-80%
  - Arterial input from the hepatic artery branch of the coeliac axis accounts for 20-40%
- Implications for timing of intravenous contrast examinations & vascular interventions




Focal liver lesion
Cystic
Solid
Solitary
Multiple
Solitary
Multiple
Background liver
Normal
Abnormal

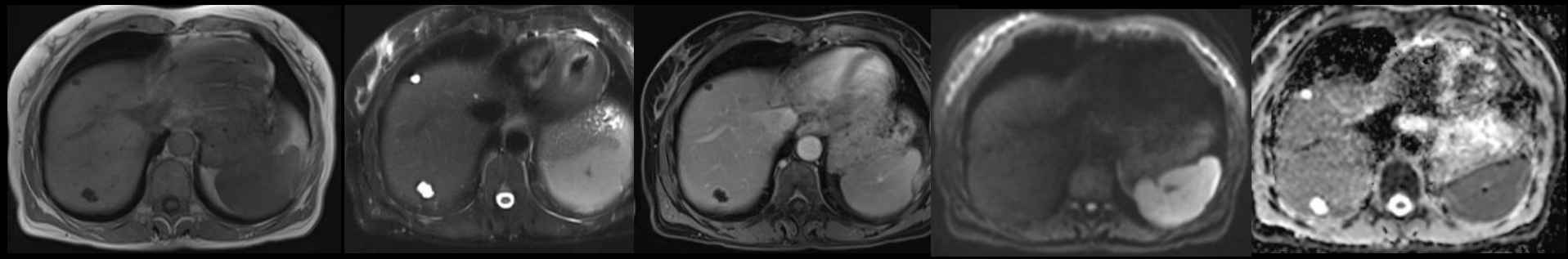

T2
T1
Arterial
Portal
Interstitial
Hepatocyte
High b
ADC
Metastasis
Hemangioma
FNH
Cyst
Morphology
Contrast enhanced
Diffusion

Haemangioma



Morphology IV Contrast Diffusion

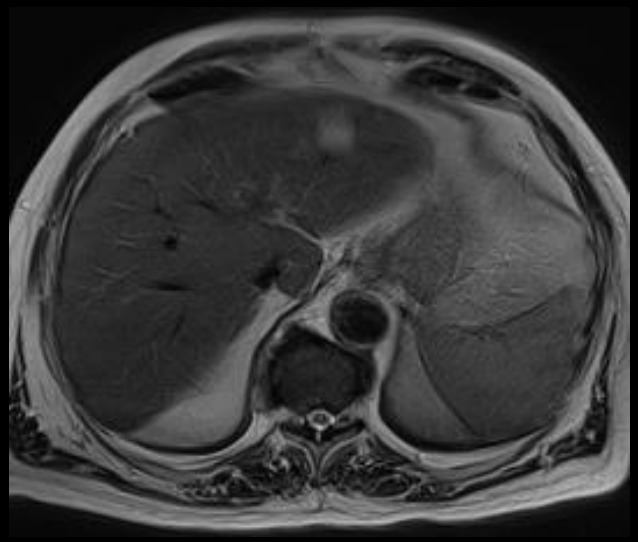
Cyst

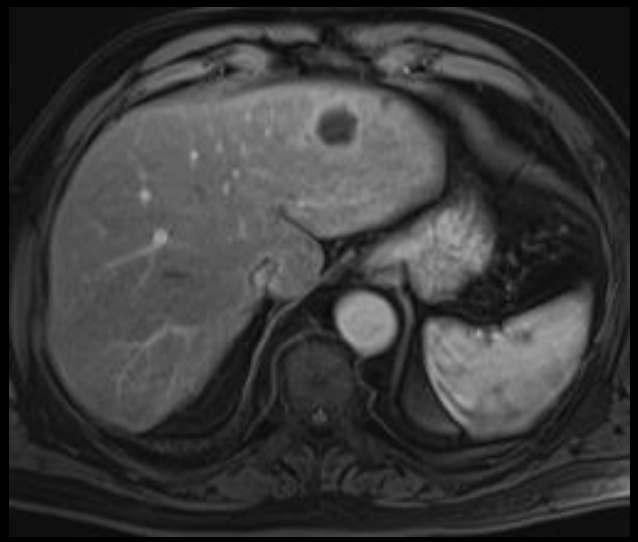


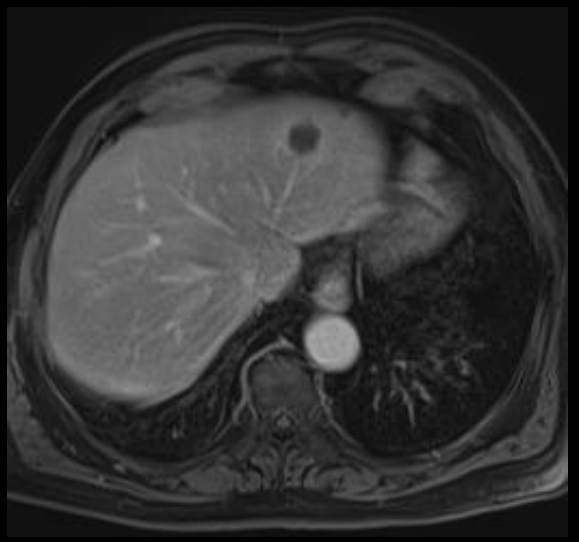
Morphology IV Contrast Diffusion

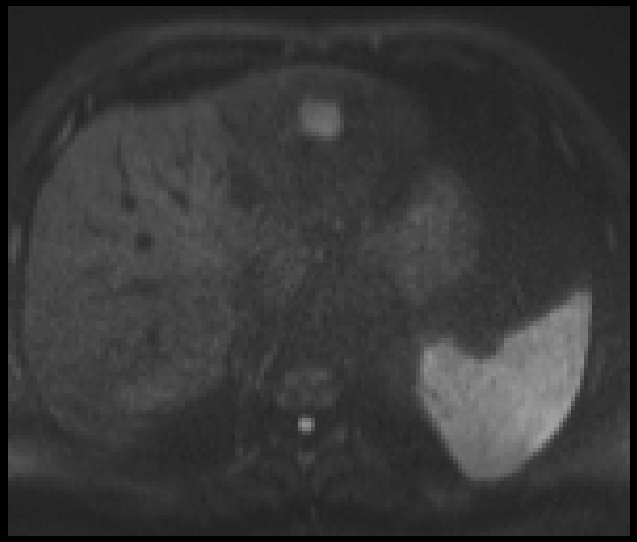
Morphology

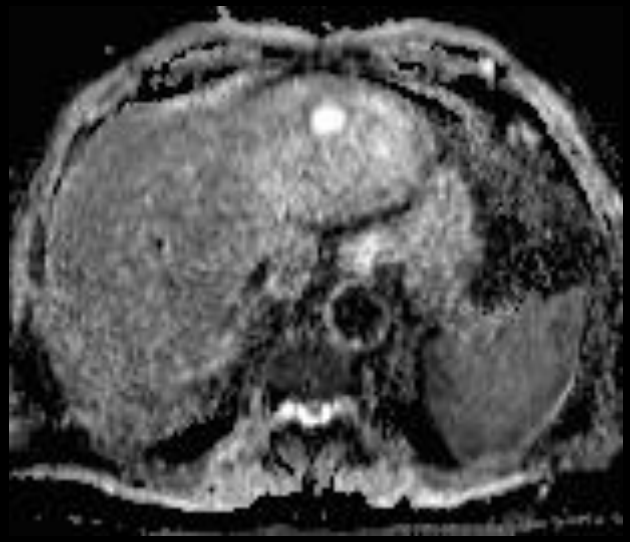
IV Contrast







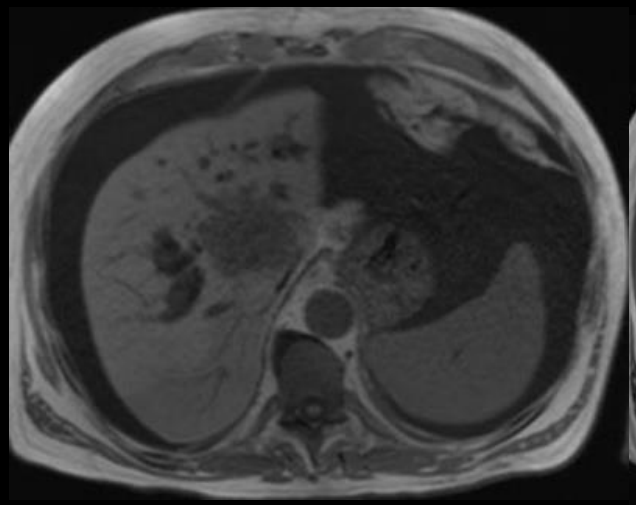


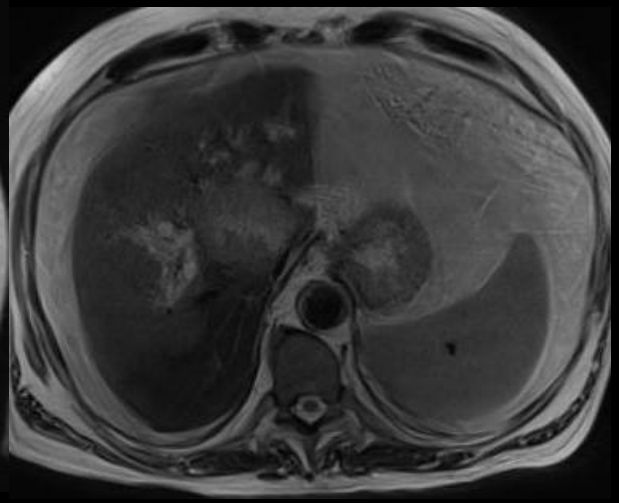


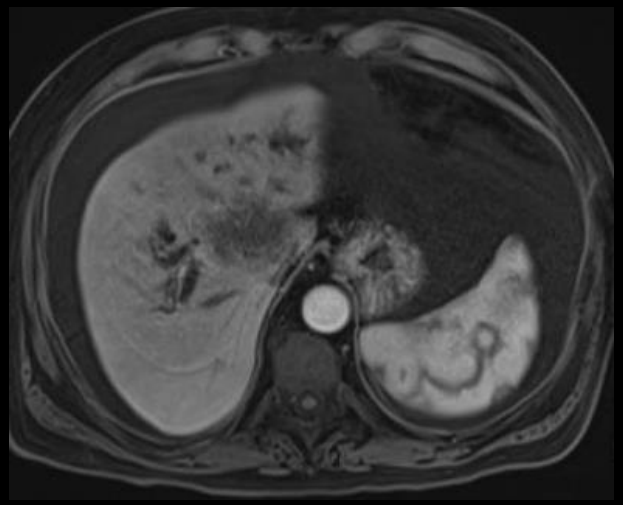
Diffusion

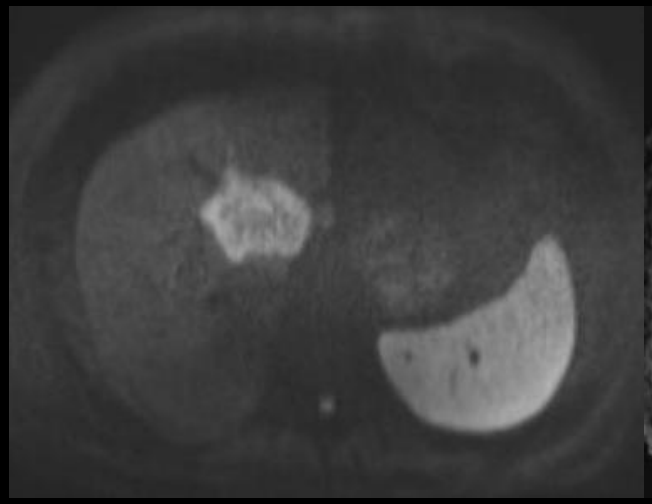
Morphology

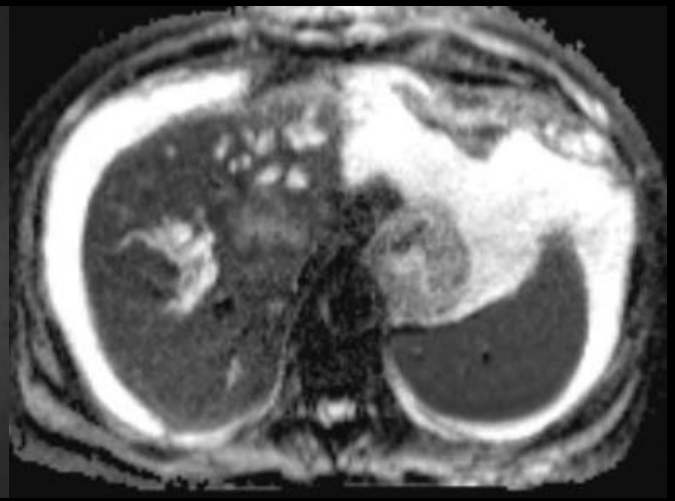
IV Contrast







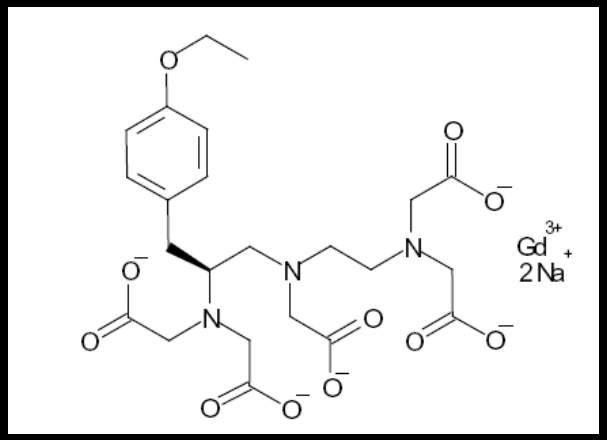




Diffusion

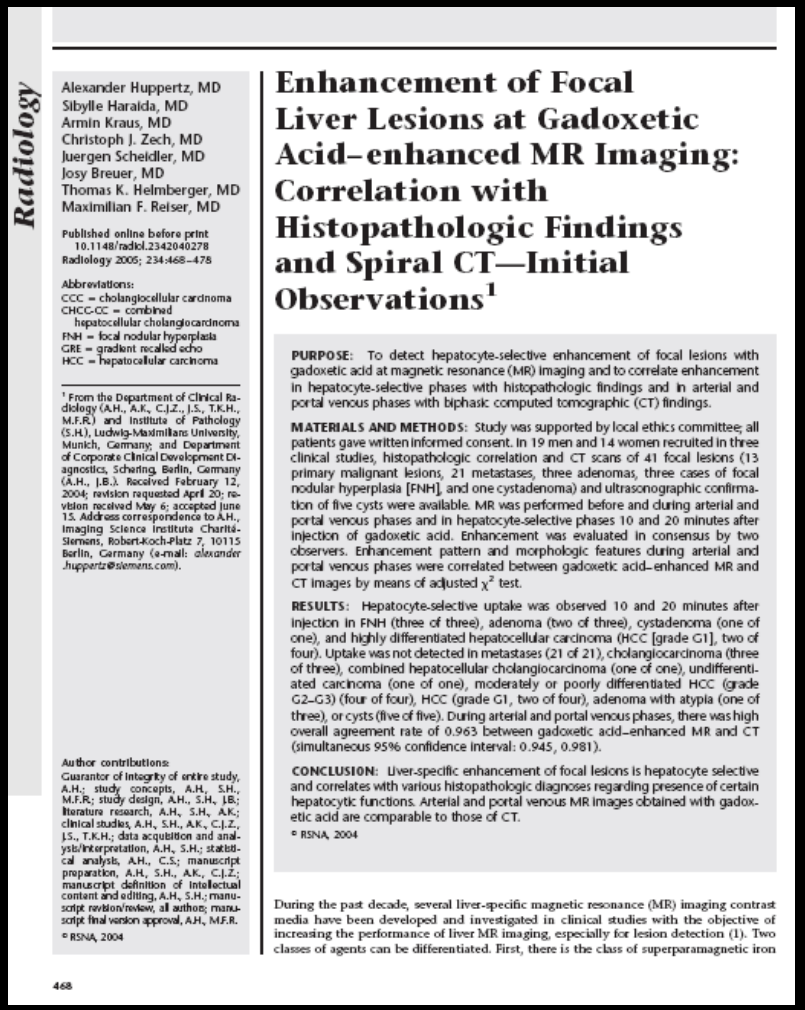
Hepatocyte Specific Contrast Agents

- Characterisation may be improved with hepatocyte specific contrast agents



Gadoxetate disodium

0.025 mmol/kg



Radiology

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Radiology 2005; 234:468–478

Abbreviations:
CCC = cholangiocellular carcinoma
CHCC-CC = combined hepatocellular cholangiocarcinoma
FNH = focal nodular hyperplasia
GRE = gradient recalled echo
HCC = hepatocellular carcinoma

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Author contributions:
Guarantor of integrity of entire study, A.H.; study concepts, A.H., S.H., M.F.R.; study design, A.H., S.H., J.B.; literature research, A.H., S.H., A.K.; clinical studies, A.H., S.H., A.K., C.J.Z., J.S., T.K.H.; data acquisition and analysis/interpretation, A.H., S.H.; statistical analysis, A.H., C.S.; manuscript preparation, A.H., S.H., A.K., C.J.Z.; manuscript definition of intellectual content and editing, A.H., S.H.; manuscript revision/review, all authors; manuscript final version approval, A.H., M.F.R.

Enhancement of Focal Liver Lesions at Gadoxetic Acid–enhanced MR Imaging: Correlation with Histopathologic Findings and Spiral CT—Initial Observations[1]

PURPOSE: To detect hepatocyte-selective enhancement of focal lesions with gadoxetic acid at magnetic resonance (MR) imaging and to correlate enhancement in hepatocyte-selective phases with histopathologic findings and in arterial and portal venous phases with biphasic computed tomographic (CT) findings.

MATERIALS AND METHODS: Study was supported by local ethics committee; all patients gave written informed consent. In 19 men and 14 women recruited in three clinical studies, histopathologic correlation and CT scans of 41 focal lesions (13 primary malignant lesions, 21 metastases, three adenomas, three cases of focal nodular hyperplasia [FNH], and one cystadenoma) and ultrasonographic confirmation of five cysts were available. MR was performed before and during arterial and portal venous phases and in hepatocyte-selective phases 10 and 20 minutes after injection of gadoxetic acid. Enhancement was evaluated in consensus by two observers. Enhancement pattern and morphologic features during arterial and portal venous phases were correlated between gadoxetic acid–enhanced MR and CT images by means of adjusted χ^2 test.

RESULTS: Hepatocyte-selective uptake was observed 10 and 20 minutes after injection in FNH (three of three), adenoma (two of three), cystadenoma (one of one), and highly differentiated hepatocellular carcinoma (HCC [grade G1], two of four). Uptake was not detected in metastases (21 of 21), cholangiocarcinoma (three of three), combined hepatocellular cholangiocarcinoma (one of one), undifferentiated carcinoma (one of one), moderately or poorly differentiated HCC (grade G2–G3) (four of four), HCC (grade G1, two of four), adenoma with atypia (one of three), or cysts (five of five). During arterial and portal venous phases, there was high overall agreement rate of 0.963 between gadoxetic acid–enhanced MR and CT (simultaneous 95% confidence interval: 0.945, 0.981).

CONCLUSION: Liver-specific enhancement of focal lesions is hepatocyte selective and correlates with various histopathologic diagnoses regarding presence of certain hepatocytic functions. Arterial and portal venous MR images obtained with gadoxetic acid are comparable to those of CT.

During the past decade, several liver-specific magnetic resonance (MR) imaging contrast media have been developed and investigated in clinical studies with the objective of increasing the performance of liver MR imaging, especially for lesion detection (1). Two classes of agents can be differentiated. First, there is the class of superparamagnetic iron

Huppertz et al. Radiology 2005;234(2):468-78

Performance: Colorectal Metastases

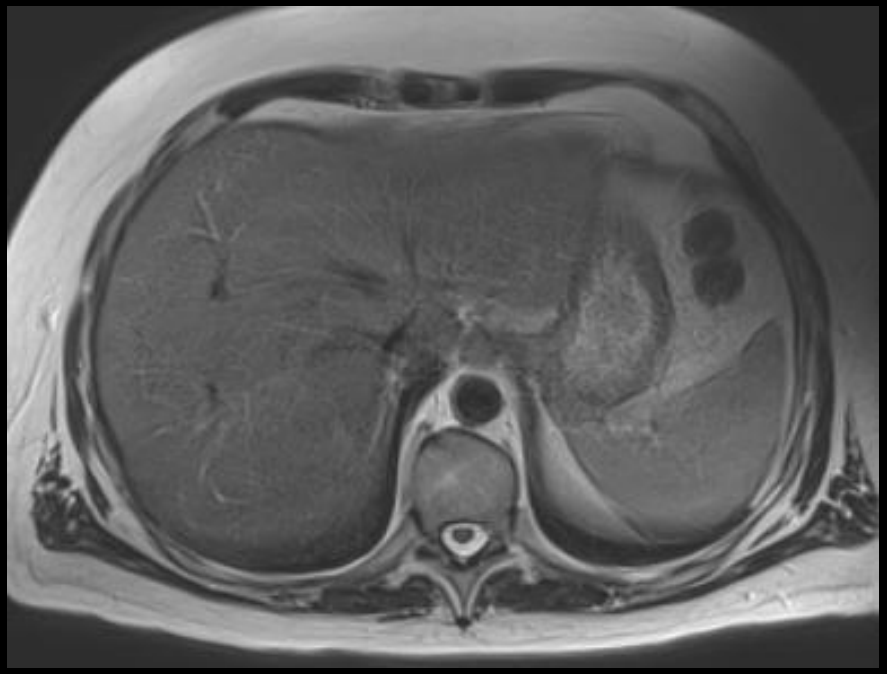
- n=360
- Randomized multicentre trial
- Impact of gadoxetic acid-enhanced MRI
- Comparator: Gd-MRI & CE-CT in patients with suspected colorectal cancer liver metastases

- Gadoxetic acid-enhanced MRI as the initial imaging modality
  - Diagnostic superiority to CE-CT & Gd-MRI

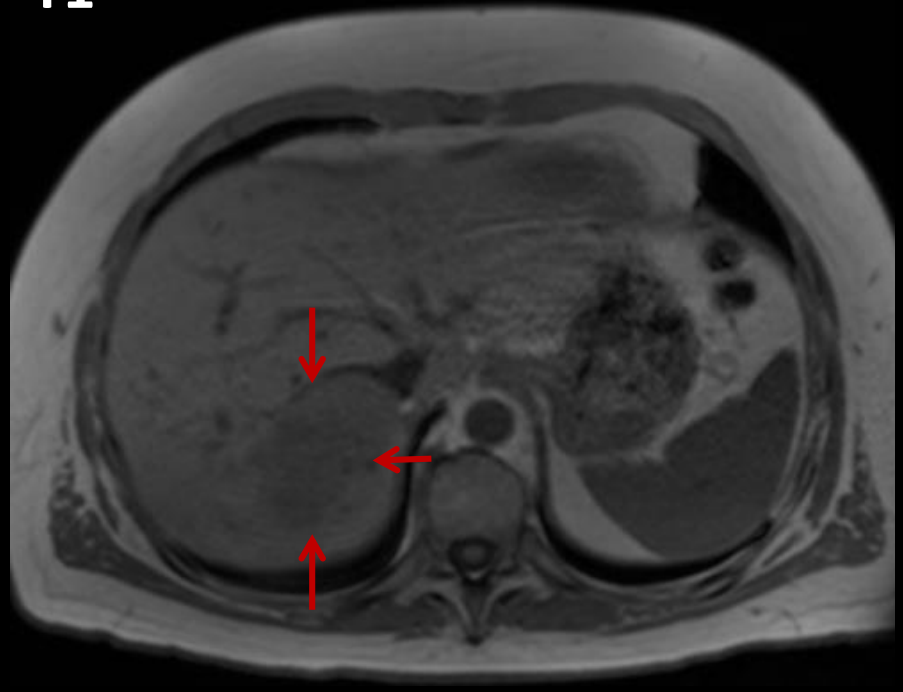
Zech C. Br J Surg 2014;101(6):613-21

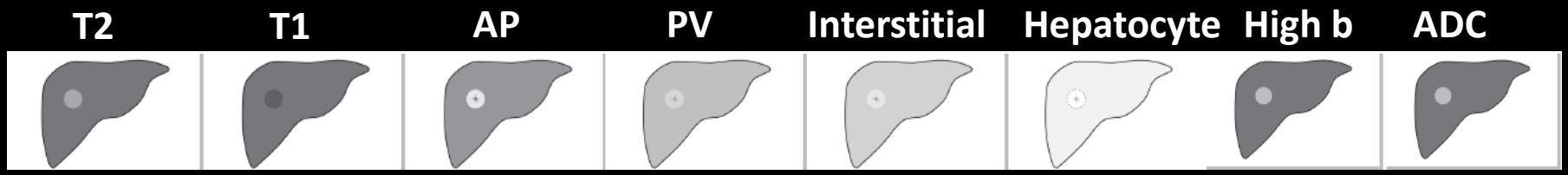
Focal Nodular Hyperplasia

T2

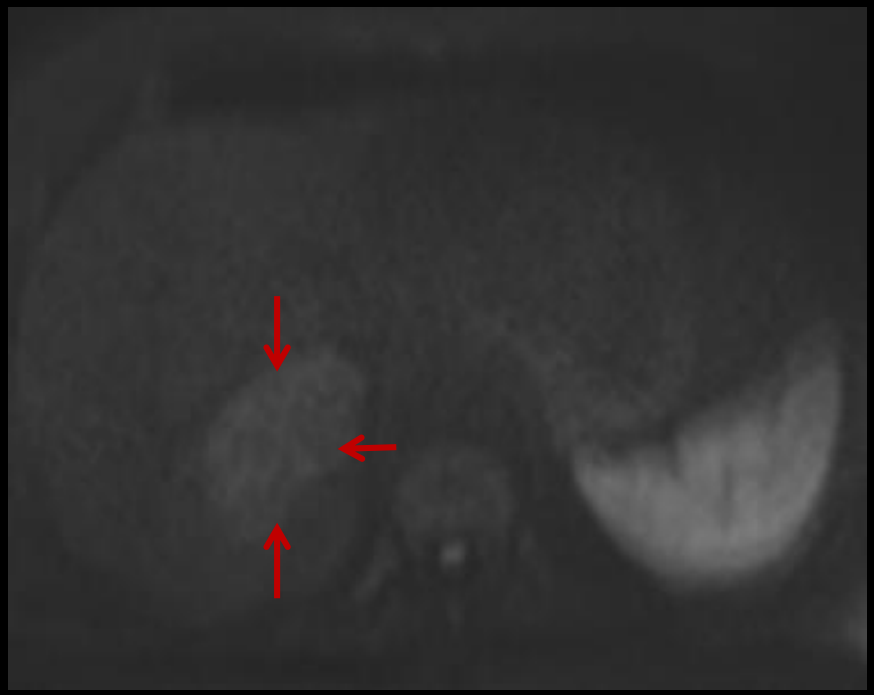


T1

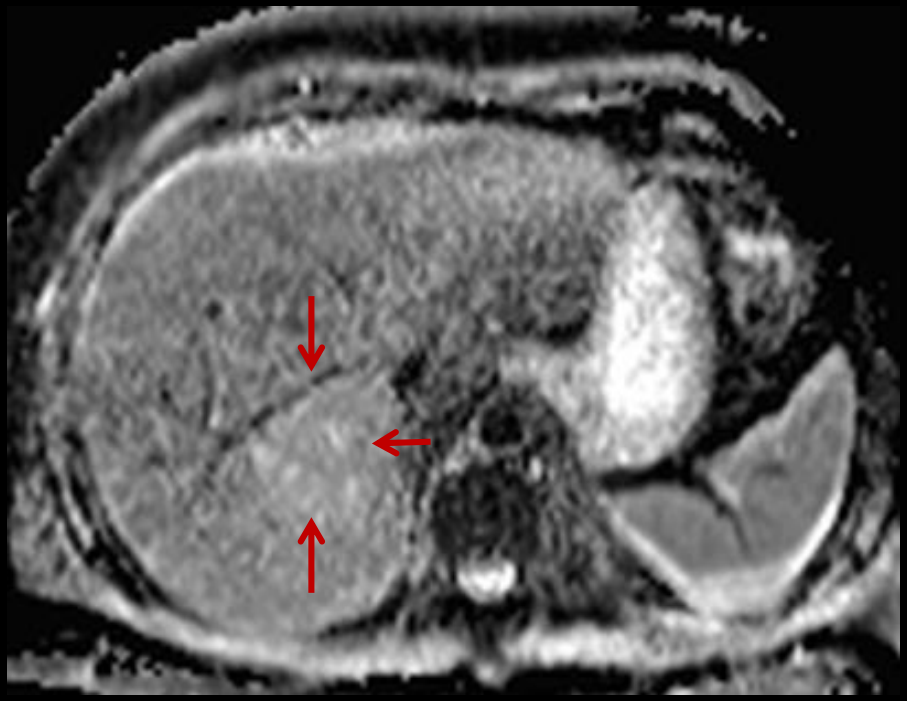


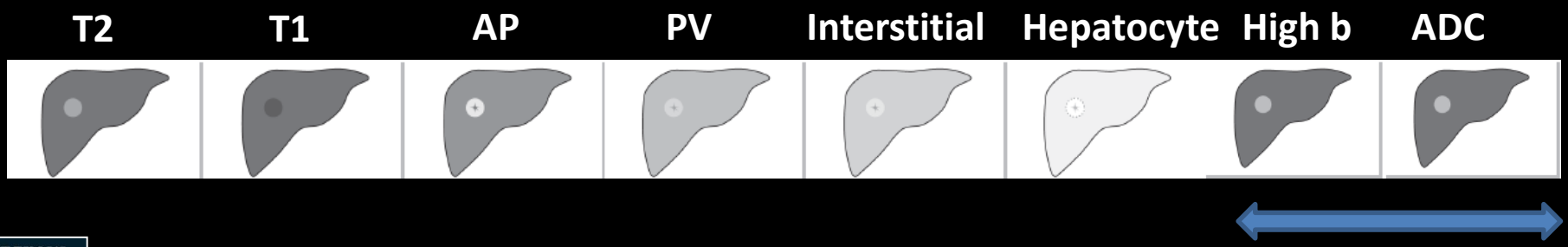


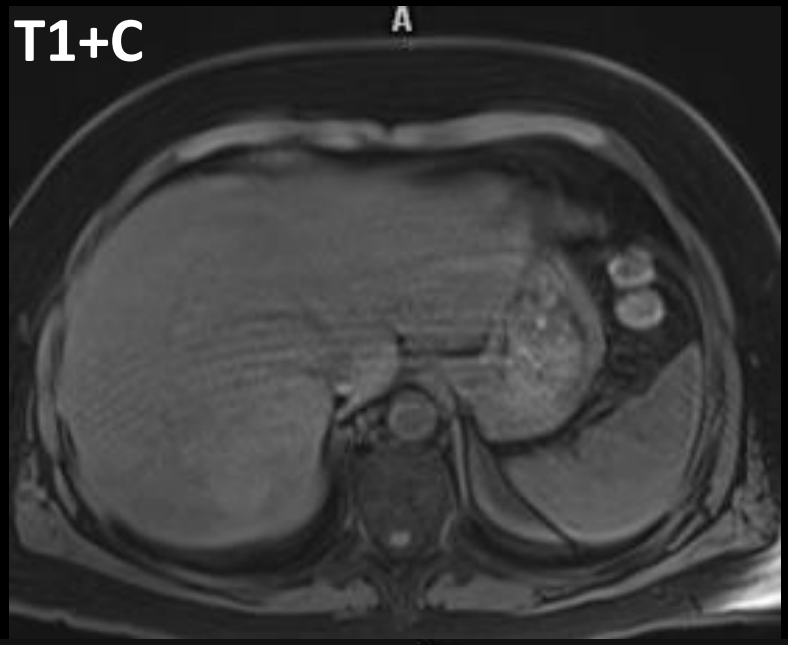
High b value

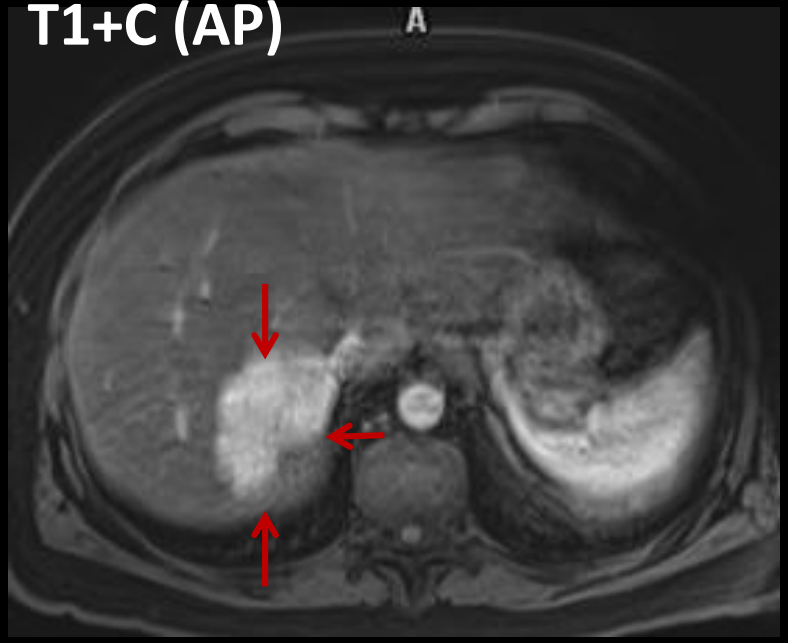


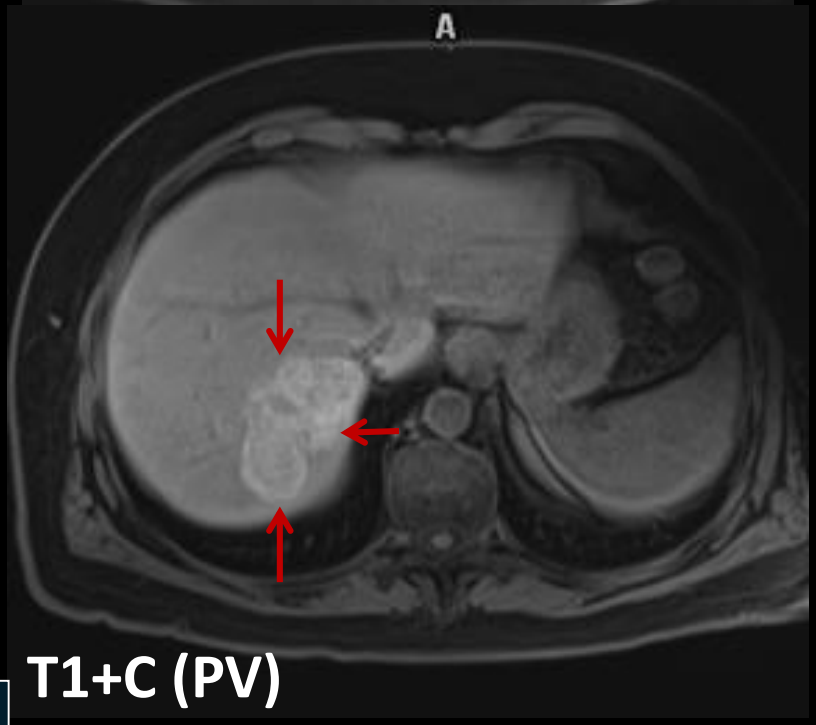
ADC

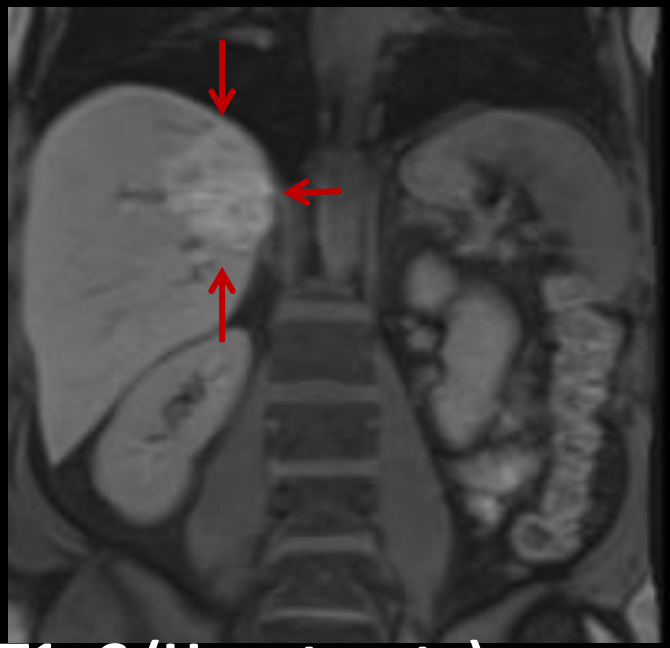






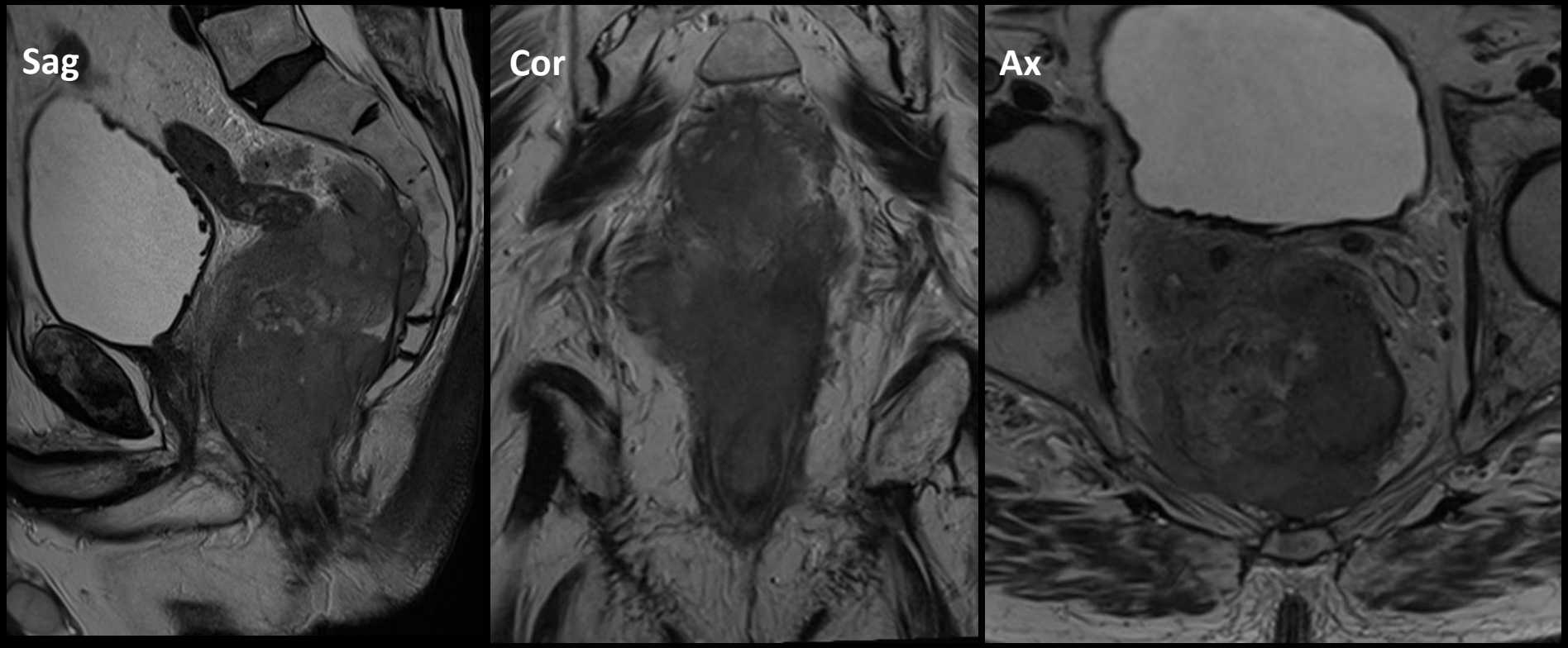




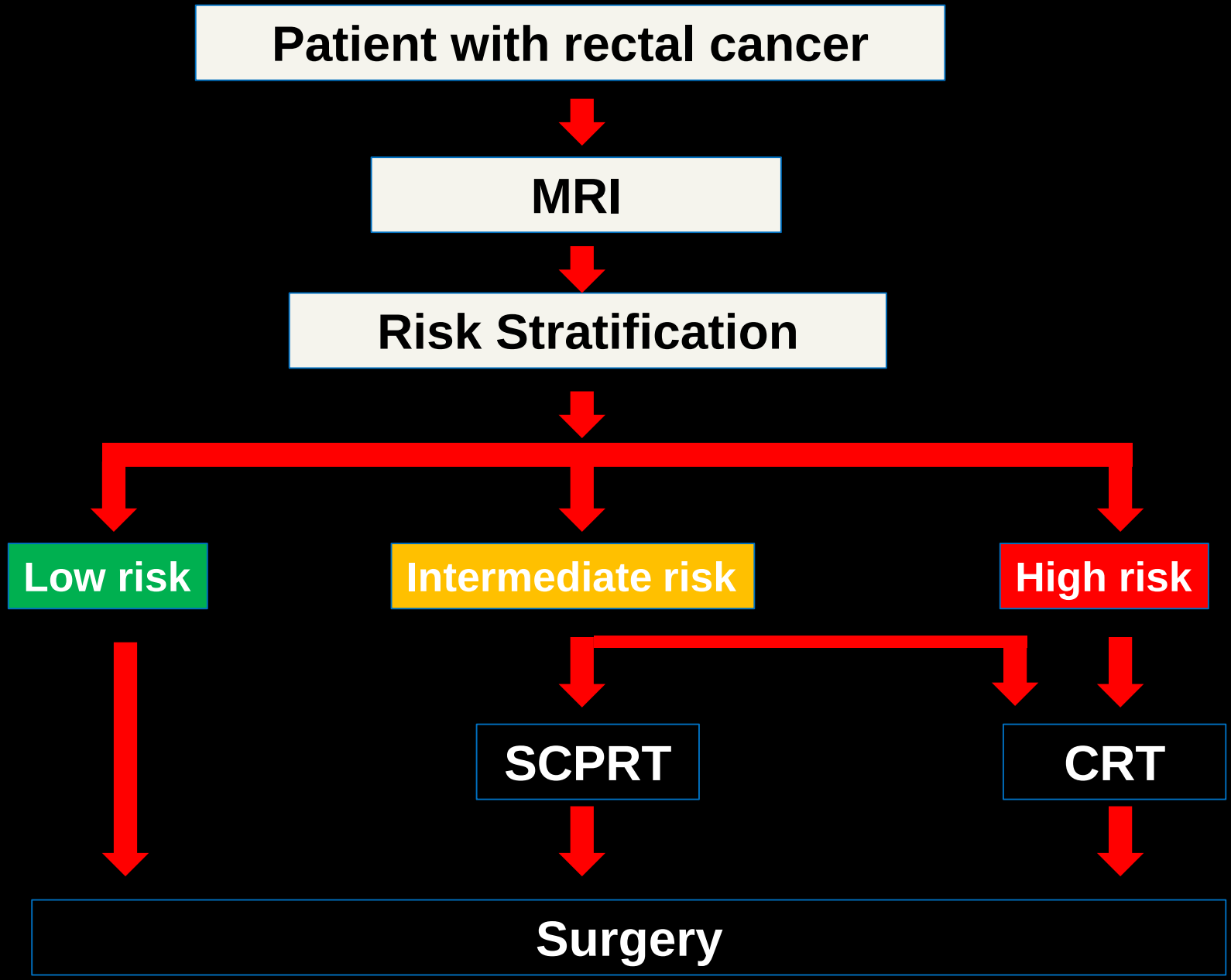


Staging

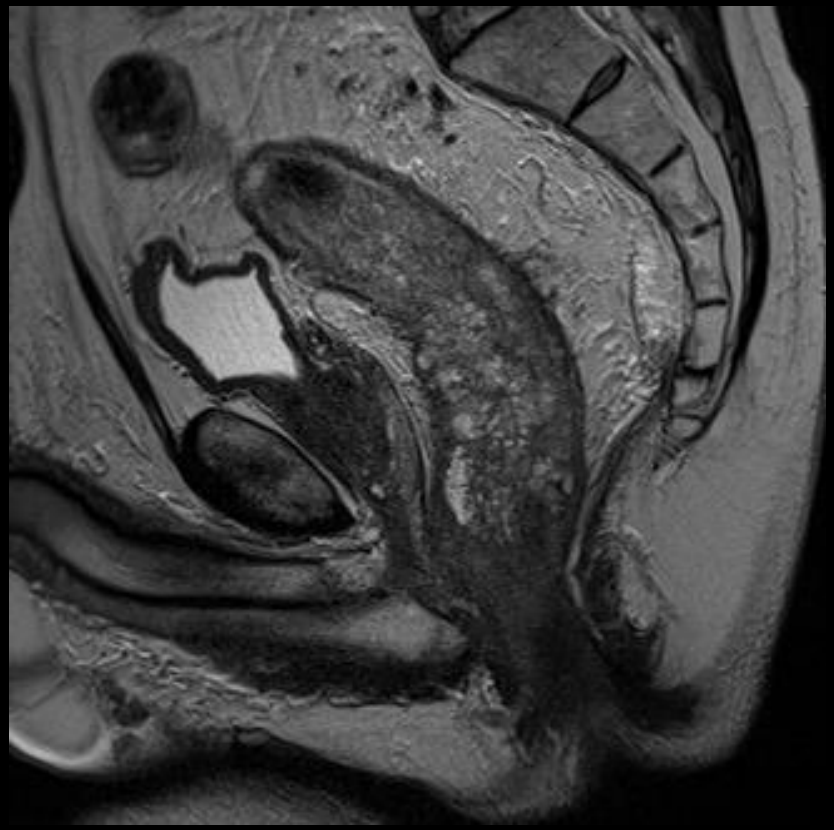
Staging



MRI: Improved Therapeutic Triage in Rectal Cancer


Patient with rectal cancer
MRI
Risk Stratification
Low risk
Intermediate risk
High risk
SCPRT
CRT
Surgery

MRI in Rectal Cancer: Resectability



- Multi-centre: 2002-2003
- n=408: accuracy of MRI in prediction of CRM
- CRM involvement if within 1mm of mesorectal fascia
  - Specificity 92% (95%CI 90-95%)
  - Accuracy 91% (95% 88-94%)

BMJ

Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study

MERCURY Study Group

BMJ 2006;333;779-; originally published online 19 Sep 2006; doi:10.1136/bmj.38937.646400.55

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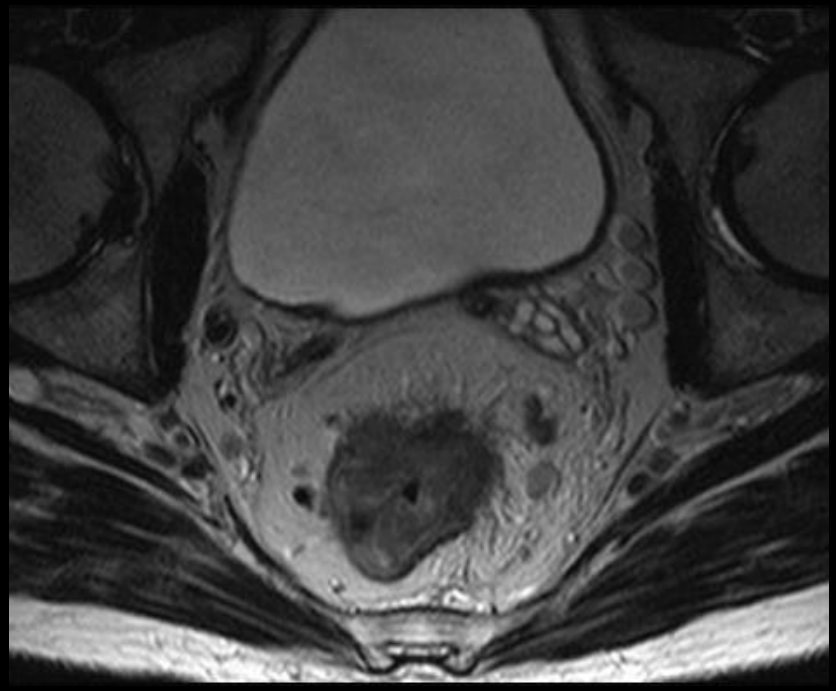
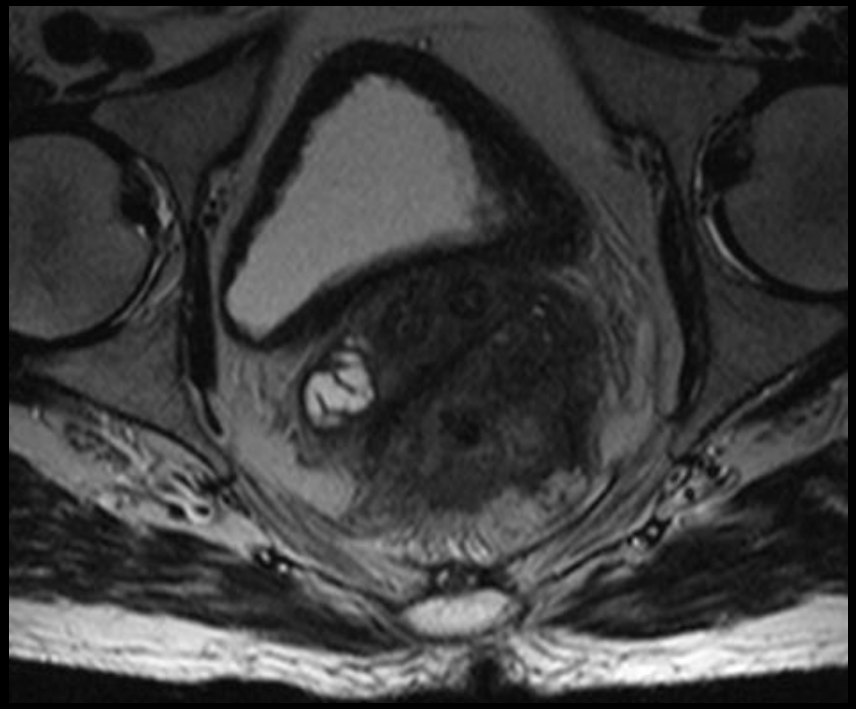
MRI in Rectal Cancer: Resectability



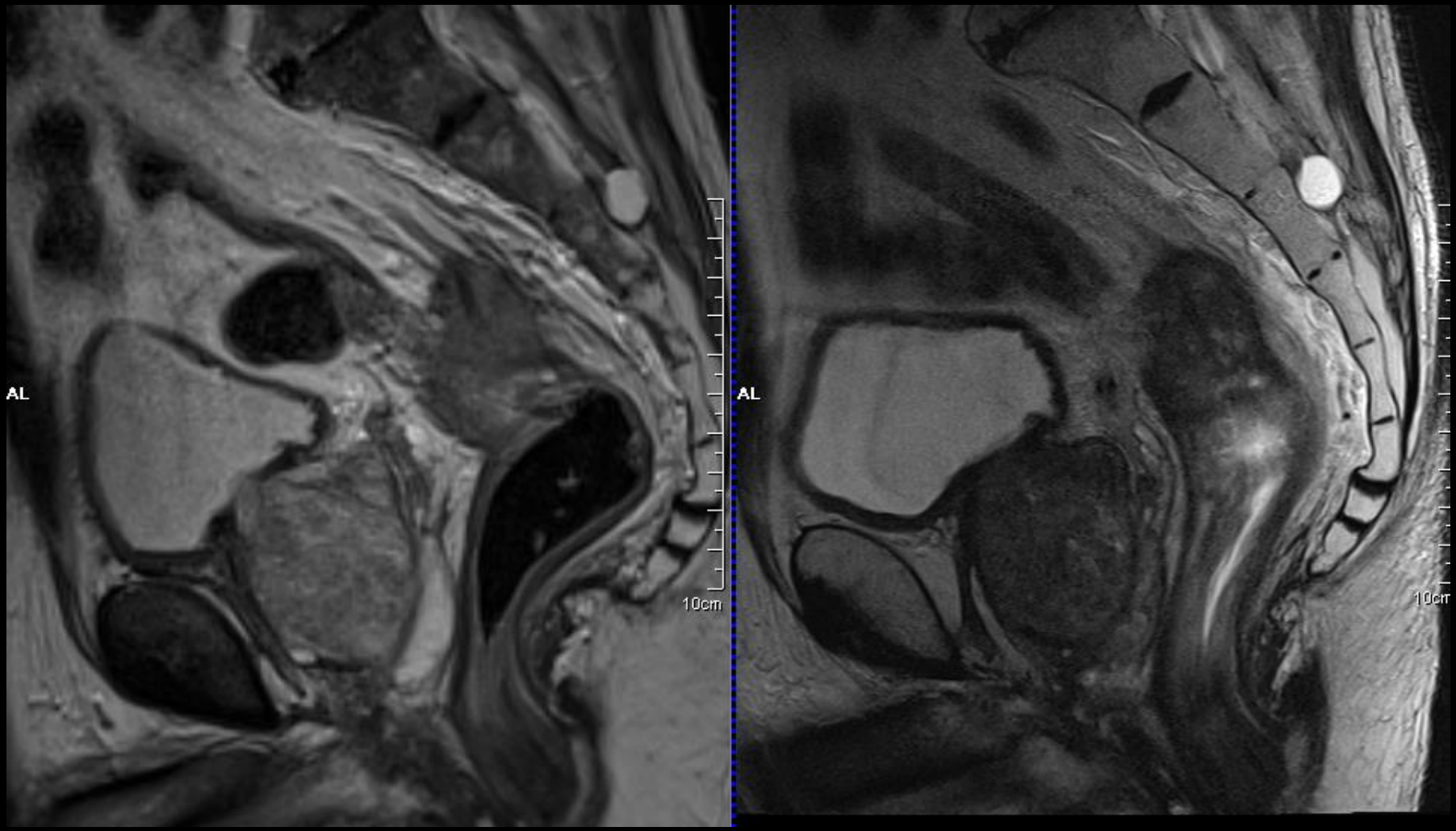
Node positive
EMVI positive



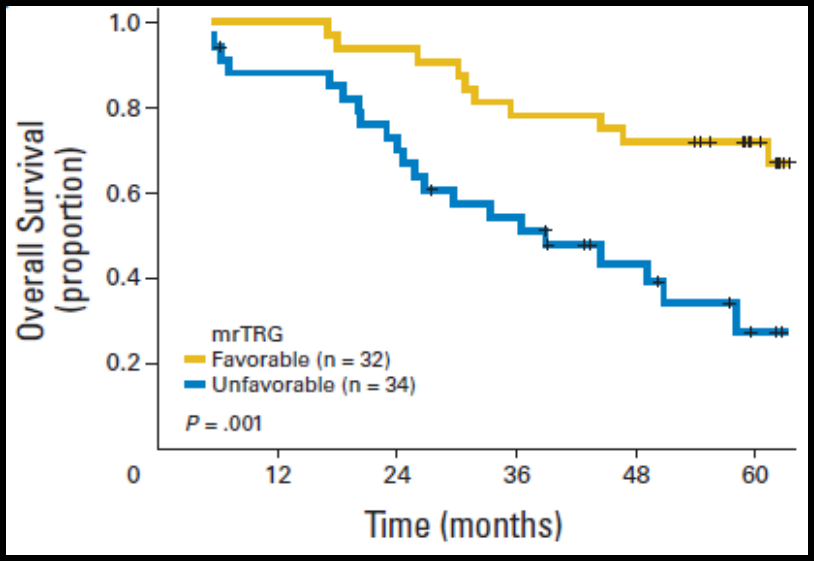
Invasion of adjacent organs

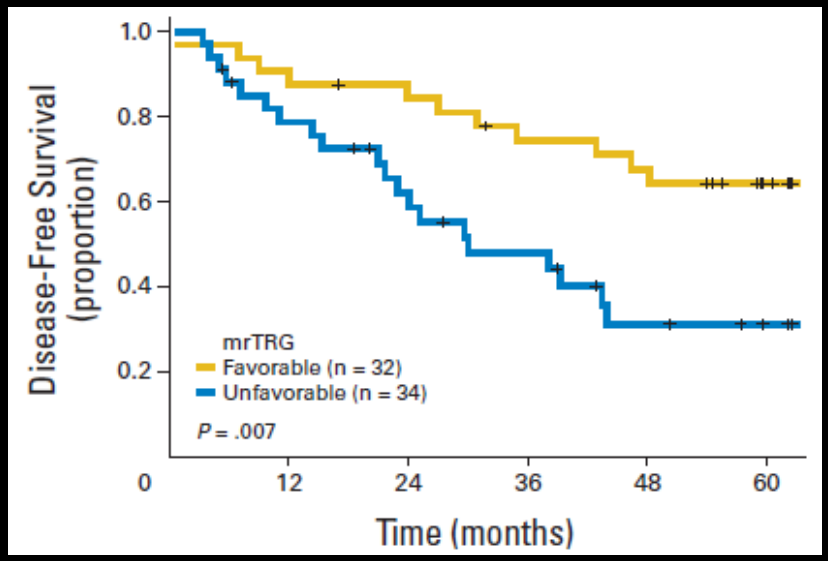
Therapy Response

Therapy Response Assessment



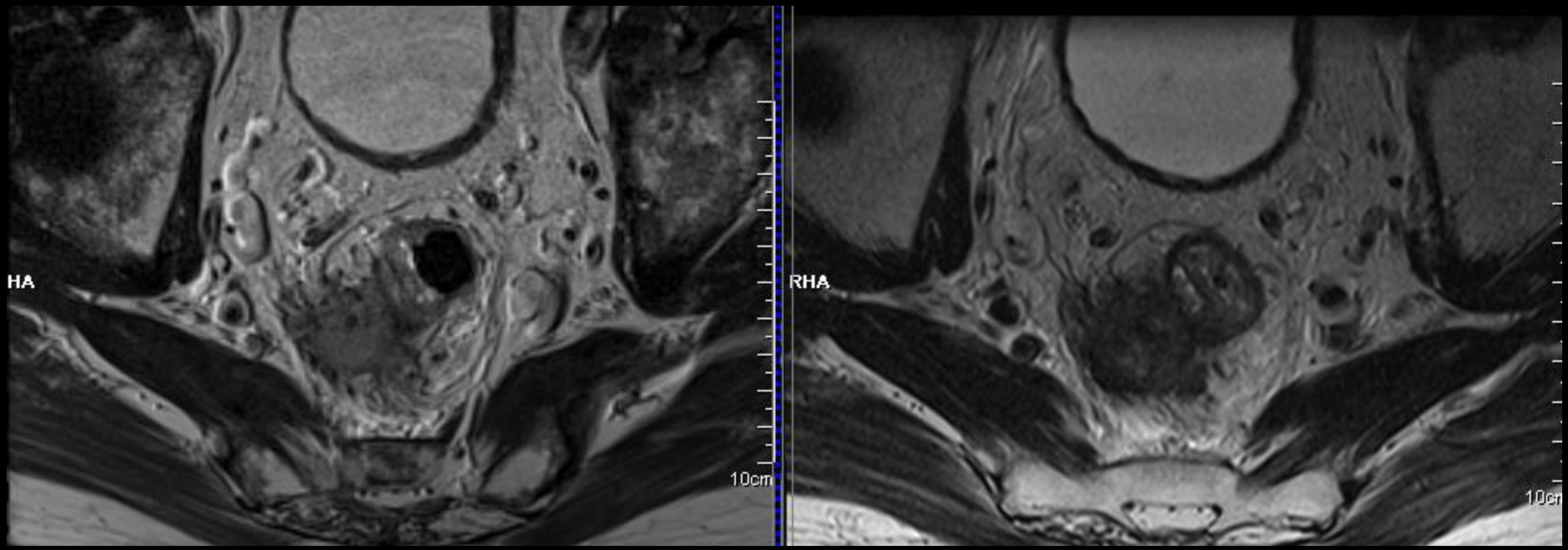
1	Complete response	No visible tumour
2	Excellent response	Predominantly fibrosis, small amount of viable tumour
3	Good response	Mixed areas of fibrosis and tumour
4	Moderate response	More tumour than fibrosis
5	Poor or no response	No fibrosis, only tumour signal visible





Patel et al J Clin Oncol 2011 29:3753-60

Therapy Response Assessment



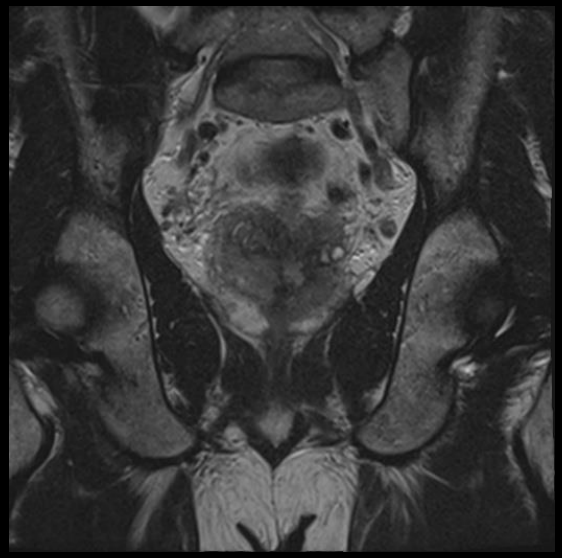
Baseline

Post chemoradiation

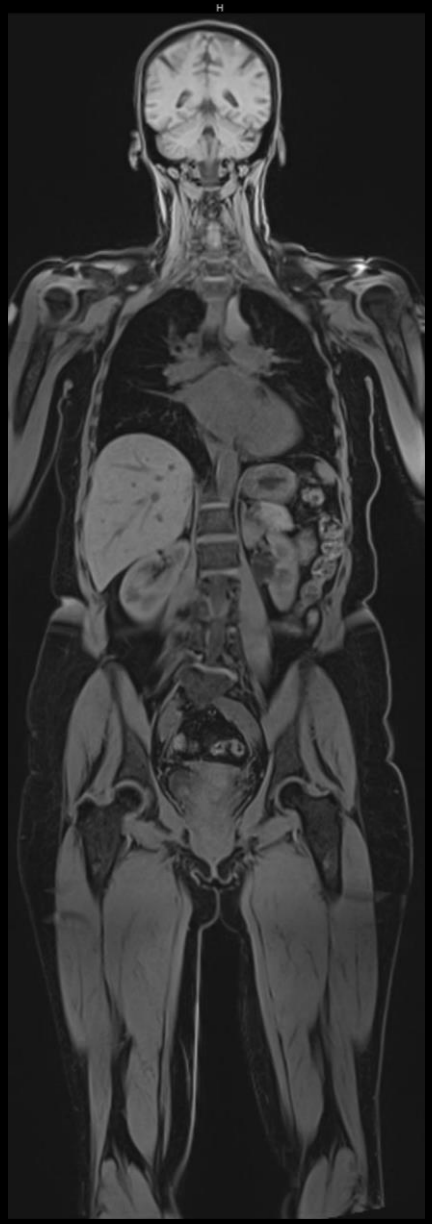
MRI: Mixed areas of tumour & fibrosis

MRI Tumour Regression Grade: 3

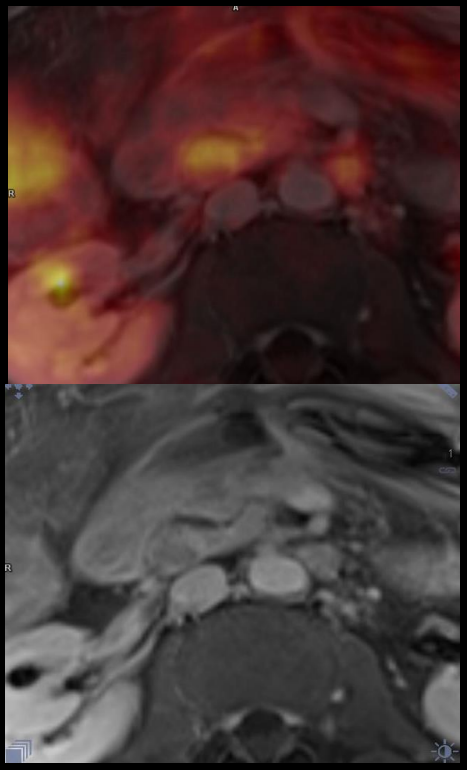
Locoregional MRI



Whole Body MRI



Hybrid PET/ MRI



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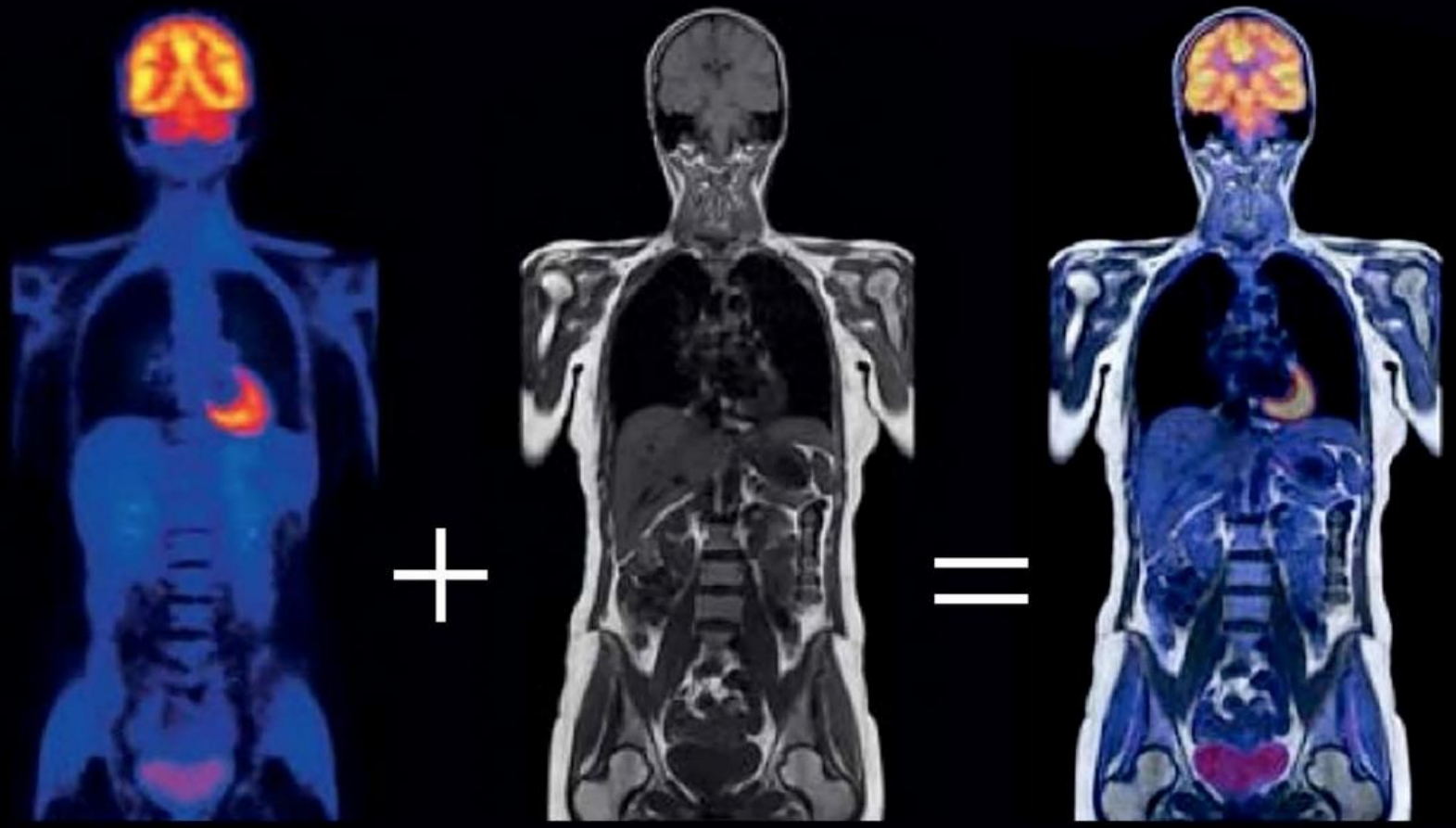
PET/MRI: An Opportunity to Enhance Care



Multi-parametric PET/MRI

PET

- High sensitivity
- Targeted molecular information

- ^{18}F- Fluorodeoxyglucose
- Non FDG tracers

MRI

- High contrast to noise
- High spatial resolution

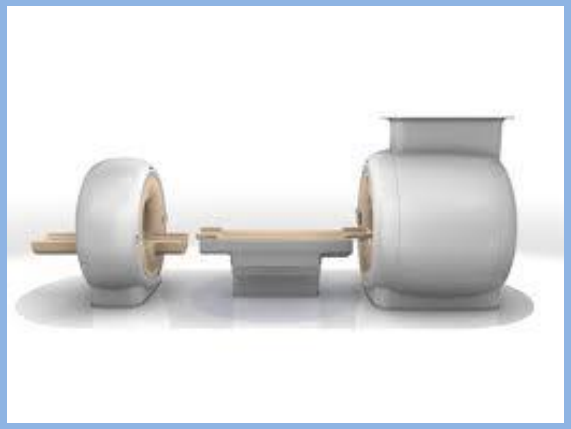
- Diffusion MRI
- Perfusion MRI
- BOLD MRI
- O_2 enhanced MRI
- MR Spectroscopy

120 installed PET/MRI systems worldwide

Bailey et al. Mol Imaging Biol. 2016;18(5):637-50

Simultaneous

Sequential



Siemens

Integrated PET/MRI

Biograph mMR

GE

Integrated PET/MRI

Signa PET/MR

Philips

Sequential PET/MRI

Ingenuity TF PET/MRI

Advantage: Synchronicity

Zaidi H et al. Phys Med Biol 2011;21:3091–3106
Delso G et al. J Nucl Med 2011;52:1914–1922

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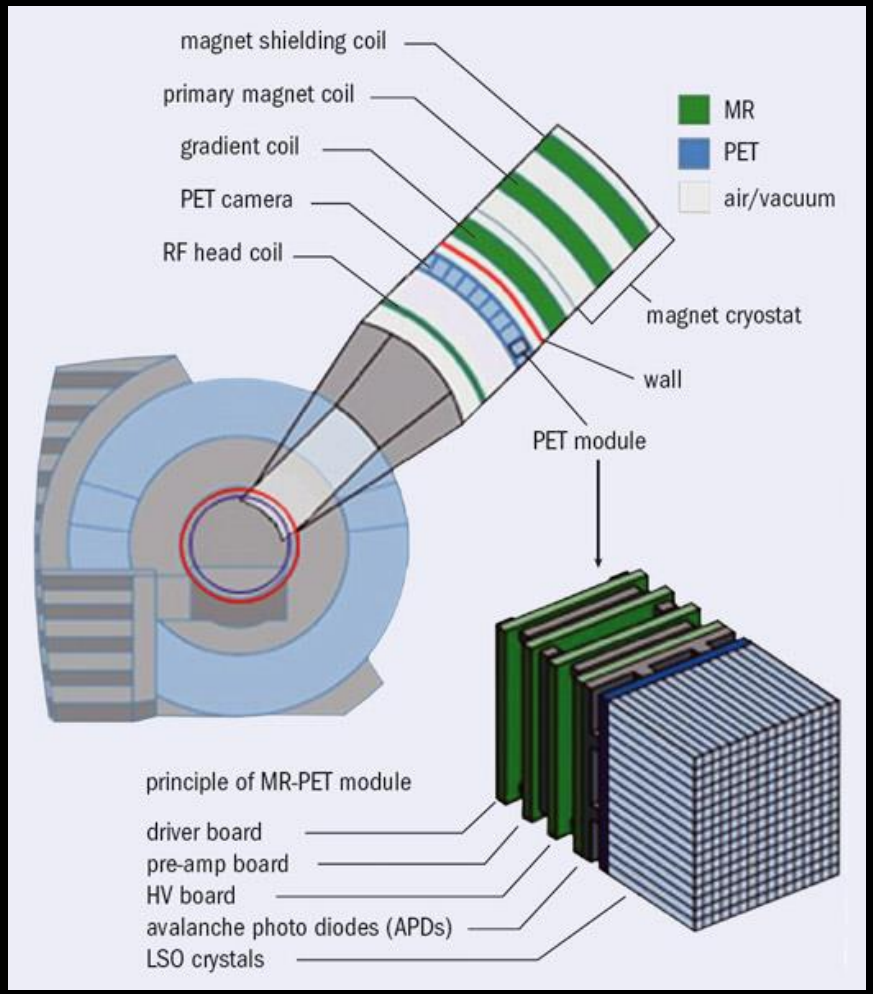
mMR Biograph



Courtesy: Siemens Healthcare

PET camera integrated within MRI scanner

Challenges:

- Changes in path of 511 keV electrons
- Heating & vibration
- Interference with electronics

Redesign:

- New avalanche photodiodes
- Electronics
- Temperature control
- RF shielding around PET

Vandenberghe et al. Phys Med Biol 2015; 60:R115-154

PET/MRI

Siemens Biograph mMR, PET Centre, St Thomas' Hospital , London

Injection

>60 min uptake period

MRAC T1 DIXON	PET DWI	T2 HASTE

Locoregional sequences

Half body: Vertex to Mid thigh
20 minutes

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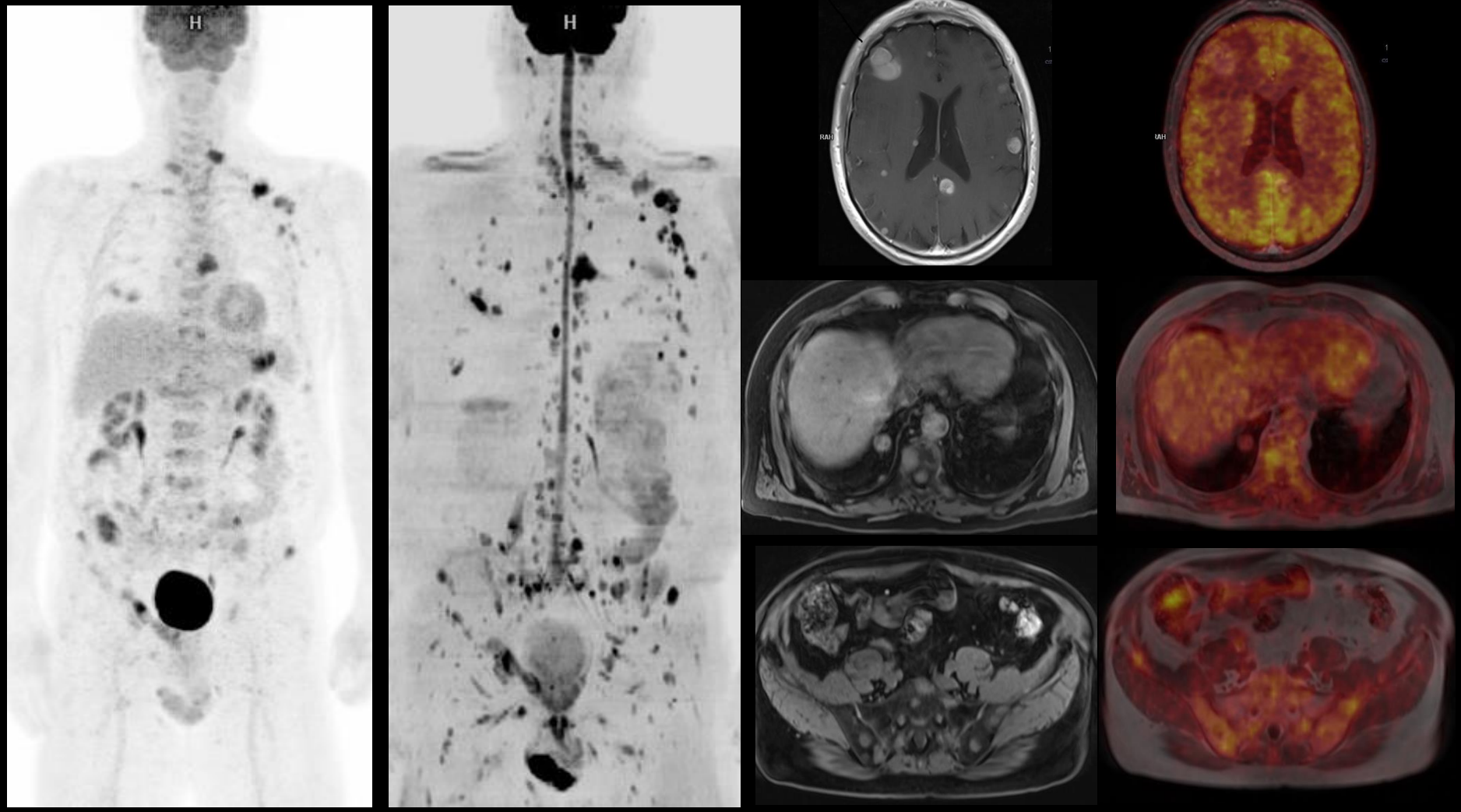
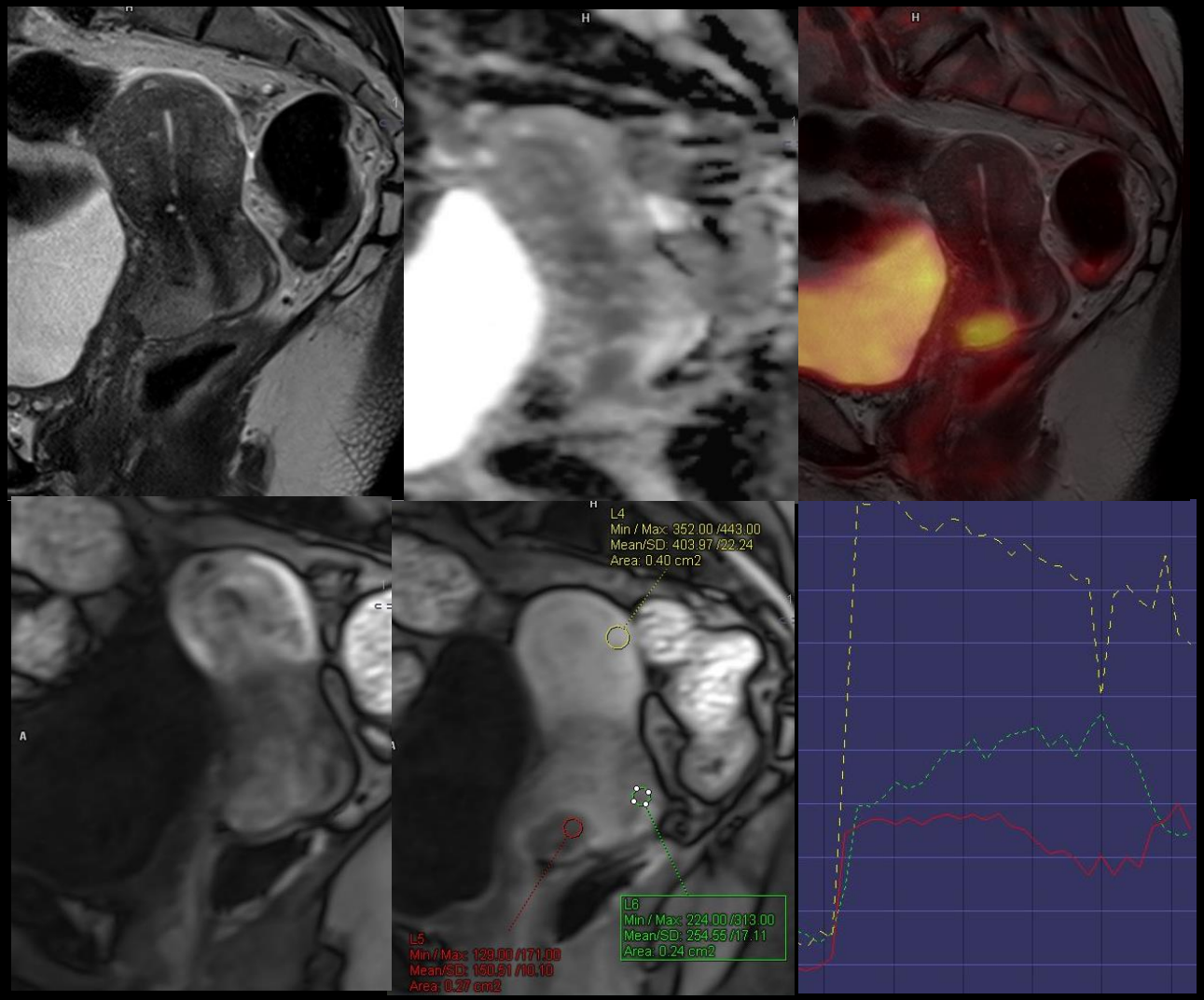
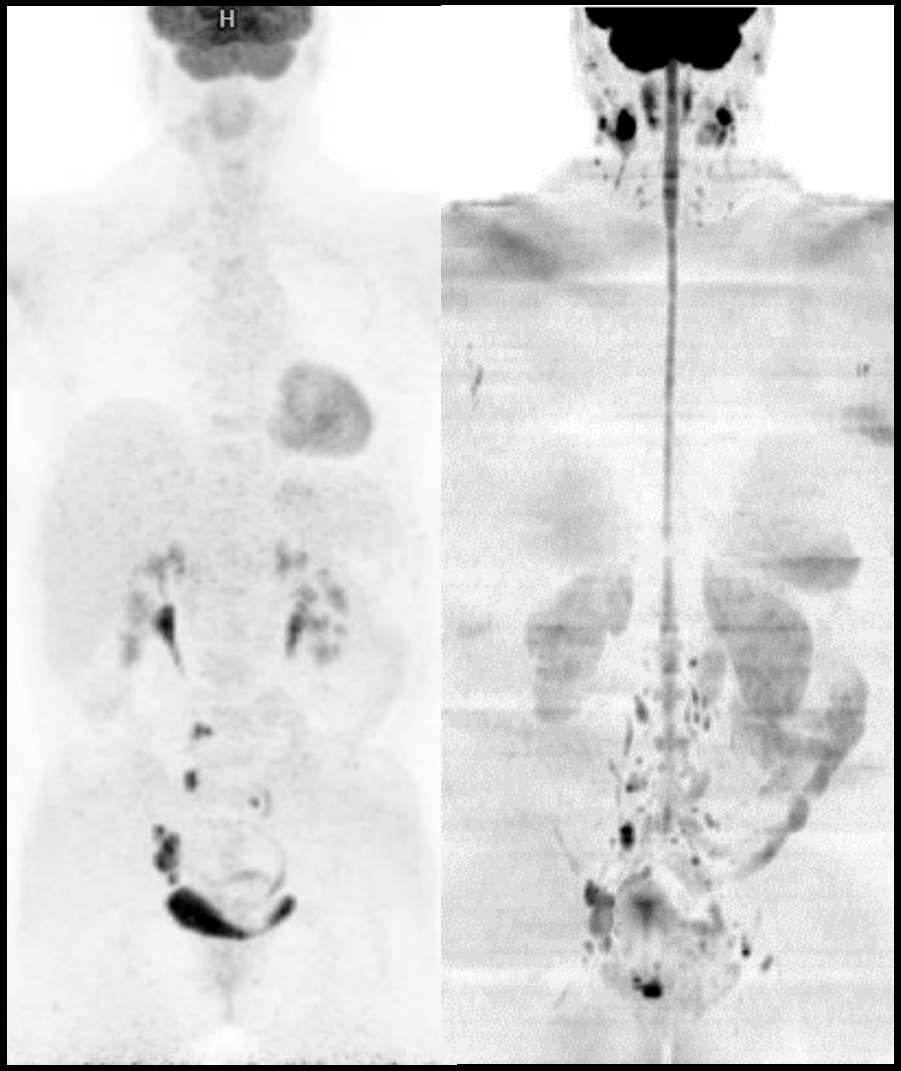
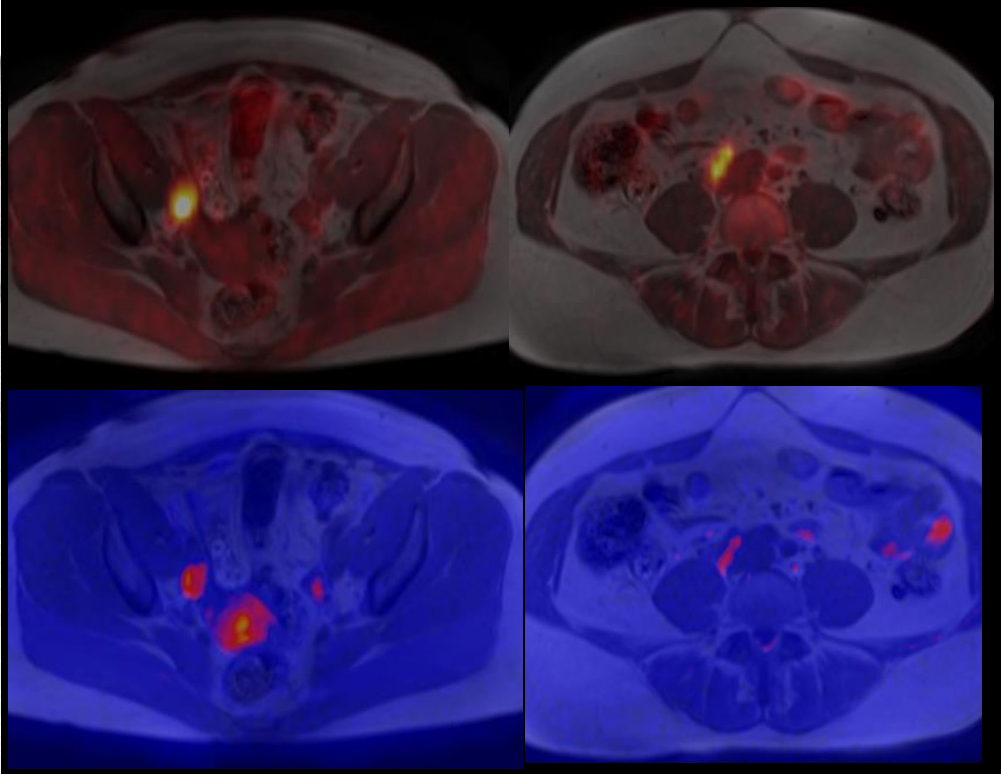


Melanoma: Staging



Cervical Cancer: Staging





Cervical Cancer: Staging

PET/MRI compared to PET/CT

^{18}F-FDG PET/CT and PET/MRI Perform Equally Well in Cancer: Evidence from Studies on More Than 2,300 Patients

Claudio Spick[1], Ken Herrmann[1,2], and Johannes Czernin[1]

[1]Ahmanson Translational Imaging Division, Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, California; and [2]Department of Nuclear Medicine, University Hospital Würzburg, Würzburg, Germany

Learning Objectives: On successful completion of this activity, participants should be able to (1) describe the different PET/MRI designs available for cancer assessment, (2) understand how photon attenuation correction for PET/MRI is done, and (3) evaluate whether PET/MRI provides diagnostic advantages over PET/CT in cancer.

Financial Disclosure: Dr. Czernin has ownership (unrelated to the paper) in Sofie Biosciences, Momentum Biosciences, and Trethera Corporation. Dr. Herrmann has ownership (unrelated to the paper) in SurgicEye and Sofie Biosciences and is a member of the advisory board of Octreo Pharm Sciences GmbH. The authors of this article have indicated no other relevant relationships that could be perceived as a real or apparent conflict of interest.

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^{18}F-FDG PET/CT has become the reference standard in oncologic imaging against which the performance of other imaging modalities is measured. The promise of PET/MRI includes multiparametric imaging to further improve diagnosis and phenotyping of cancer. Rather than focusing on these capabilities, many investigators have examined whether ^{18}F-FDG PET combined with mostly anatomic MRI improves cancer staging and restaging. After a description of PET/MRI scanner designs and a discussion of technical and operational issues, we review the available literature to determine whether cancer assessments are improved with PET/MRI. The available data show that PET/MRI is feasible and performs as well as PET/CT in most types of cancer. Diagnostic advantages may be achievable in prostate cancer and in bone metastases, whereas disadvantages exist in lung nodule assessments. We conclude that ^{18}F-FDG PET/MRI and PET/CT provide comparable diagnostic information when MRI is used simply to provide the anatomic framework. Thus, PET/MRI could be used in lieu of PET/CT if this approach becomes economically viable and if reasonable workflows can be established. Future studies should explore the multiparametric potential of MRI.

Key Words: PET/CT; PET/MRI; oncology; cancer diagnosis; staging; therapy monitoring

J Nucl Med 2016; 57:1–11
DOI: 10.2967/jnumed.115.158808

PET, which was invented by Phelps and Hoffman in the 1970s, was deployed clinically in the late 1980s and early 1990s (*1,2*). However, clinical acceptance remained limited until integrated PET/CT scanners, developed by Townsend, became commercially available in 2000 (*3*). The success of PET/CT was swift and spectacular. The number of oncologic PET/CT studies increased from 25,000 in 1996 to more than 2 million in 2014. This success had several reasons. The most important was that the accuracy of ^{18}F-FDG PET/CT for staging cancer was higher than that of PET or CT alone (*4*). Another was creation of the landmark National Oncology PET Registry, which resulted in broadening of PET reimbursement by the Centers for Medicare and Medicaid Services (*5*). In addition, oncologists were better able to visualize and appreciate the molecular information provided by PET when the images were viewed within the anatomic framework provided by CT, and the use of ^{18}F-FDG served as a useful "contrast agent" for radiologists by highlighting anatomically underappreciated yet suggestive lesions. Finally, the cost of PET/CT equipment and imaging was acceptable and only marginally affected cancer care costs, and studies were sufficiently short to maintain high patient throughput (*6–8*).

The adoption of PET/MRI has been much slower than that of PET/CT. Since its introduction in 2010, approximately 70 systems have been placed worldwide, mostly in academic centers. Equipment pricing, operational costs, and logistics likely account for the slow adoption. In addition, it is difficult to prove a diagnostic advantage when other modalities have already achieved remarkable accuracy. Potential advantages of PET/MRI include high soft-tissue contrast and functional MRI capability. Thus, the promise of PET/MRI includes multiparametric imaging to further improve the diagnosis and phenotyping of cancer. However, rather than focusing on potential synergy between the capabilities of functional MRI and molecular PET, most research has used MRI almost exclusively to provide the anatomic framework for the PET signal. Thus, most studies have compared the diagnostic accuracy of predominantly anatomic PET/MRI with that of ^{18}F-FDG PET/CT in cancer.

The current review serves two main purposes. First, it briefly describes PET/MRI scanner design concepts and discusses technical and operational issues. It then determines whether published data on cancer suggest any significant diagnostic advantages of PET/MRI over PET/CT or vice versa. Such an analysis is justified and informative

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E-mail: jczernin@mednet.ucla.edu
Published online ••••••••••••.

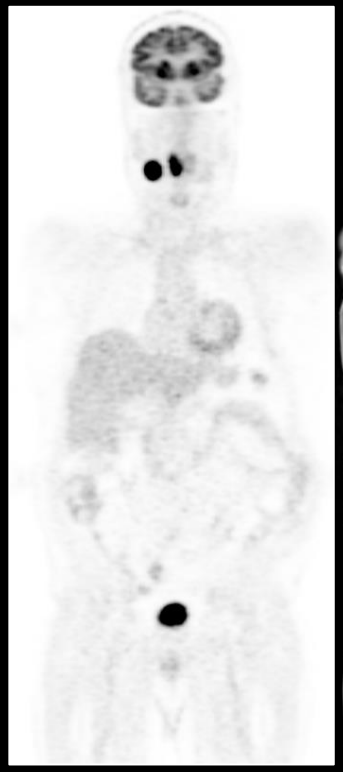
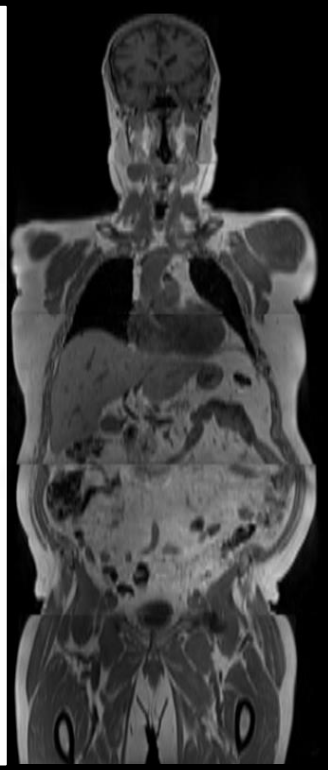
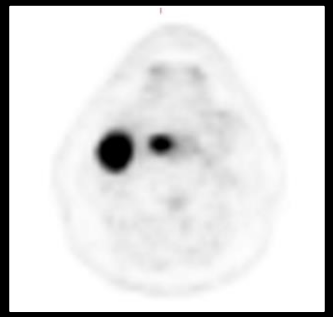
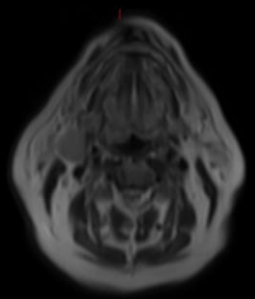
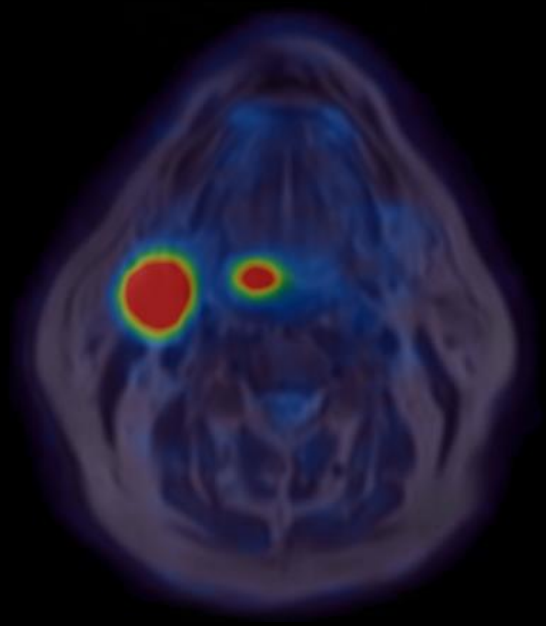
Studies to date:

- Test performance
  - Comparison of PET performance
  - MRI versus CT as anatomical localiser
  - Limitations:
    Study design, heterogeneity, lack of independent reference standard

Spick et al. J Nucl Med 2016;57:1-11

KING'S College LONDON

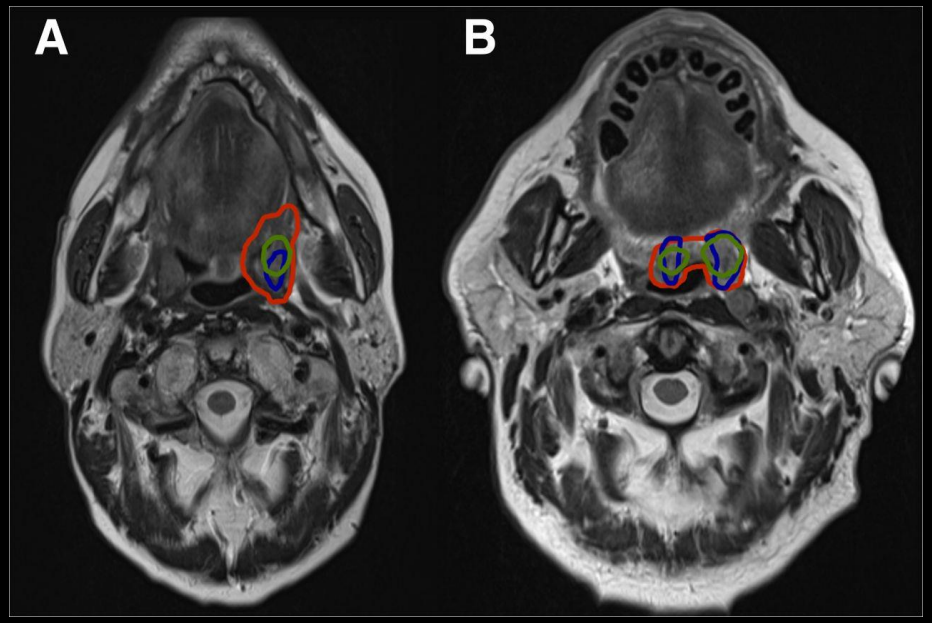
KING'S HEALTH PARTNERS

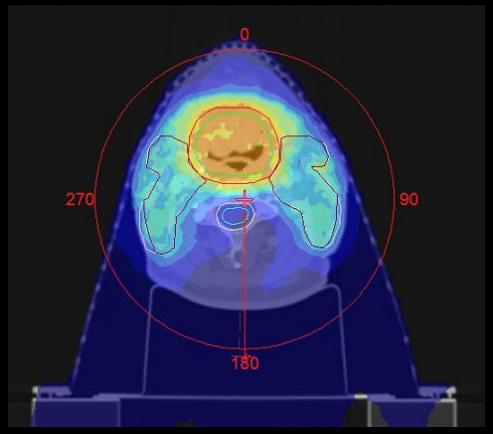
Primary Sites	Studies	Patients	Comparator	Findings	Author
Lymphoma n=281	6	28 61 25 18 48 101	PET/CT PET/CT PET/CT PET/CT PET/CT N/A	• Comparable performance between PET/MRI & PET/CT	Heacock Hermann Sher Atkinson Grueneisen Kirchner

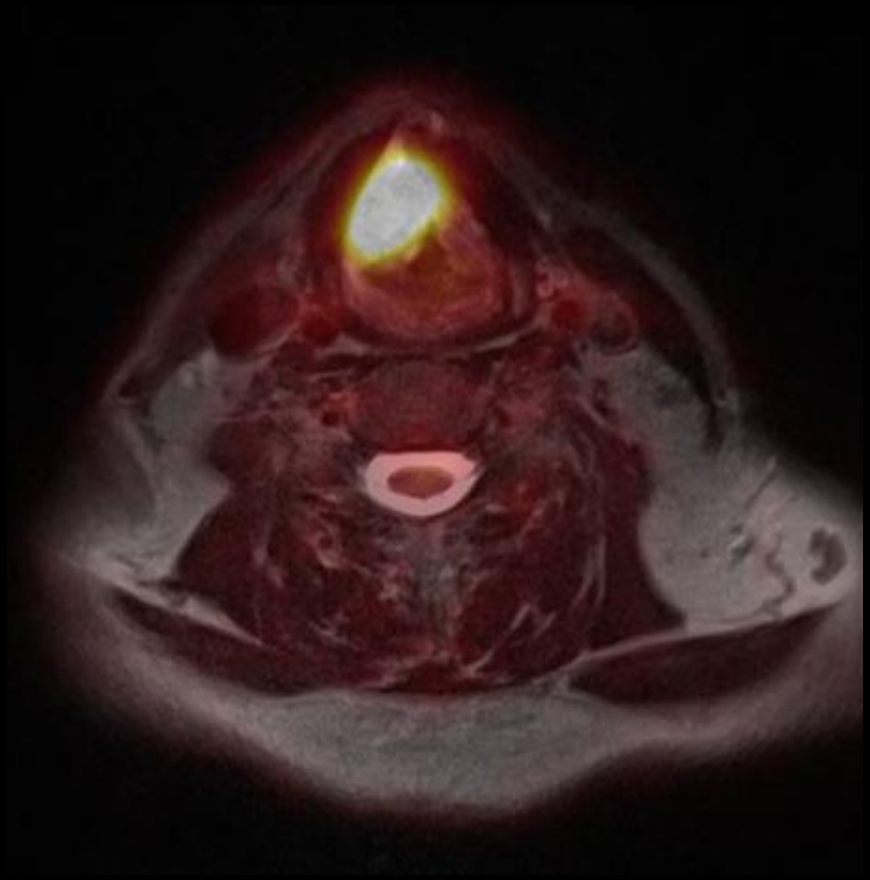
Feasibility Studies

- Head & Neck cancer
- n-12
- Repeated PET/MRI on 2 occasions
- MRI T2, MRI DWI & PET SUV volumes assessed
- Voxel per voxel comparison & cluster analysis feasible



Rasmussen et al. J Nucl Med 2017;58(1):69-74





An exploratory study to assess the feasibility of incorporating PET/MR in the radiotherapy pathway of patients with head & neck cancer & guide adaptive dose escalation. Funding: Guy's & St Thomas' Charity Hospitals Cancer Fund

Courtesy: Guerrero Urbano, Barrington, Michelidou

Summary

- MRI is used widely in clinical practice
- Increasing MRI numbers per annum reflects step change from a problem solving tool to a first line diagnostic tool
- MRI allows high resolution anatomical imaging to be combined with physiological (DWI, DCE-MRI) and molecular imaging (MRS)

Summary

- Technological advances: whole body MRI possible in patient acceptable scanning times
- Hybrid scanners (PET/MRI) open new avenues for research in cancer imaging & opportunities to improve patient experience

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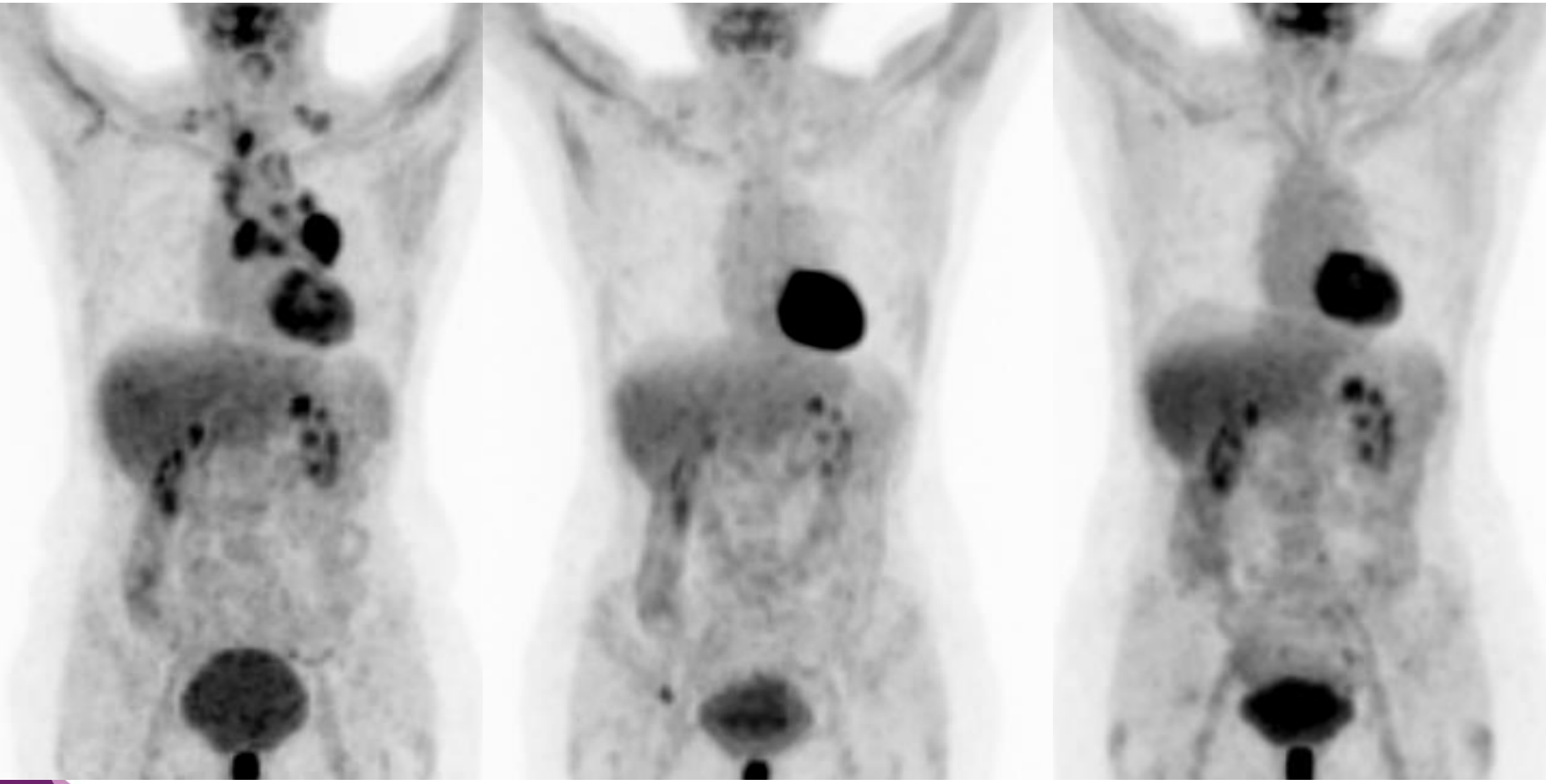
Lung Cancer: FDG-PET/CT in NSCLC

Ursula Nestle

supplemented by slides from: Bart Reymen, A.v. Baardwijk, M. Öllers

Lung cancer: cure with the help of PET/CT



9.3.2010

20.12.2010

7.3.2012

FDG-PET in NSCLC

- Evidence from the literature on PET for RTP:

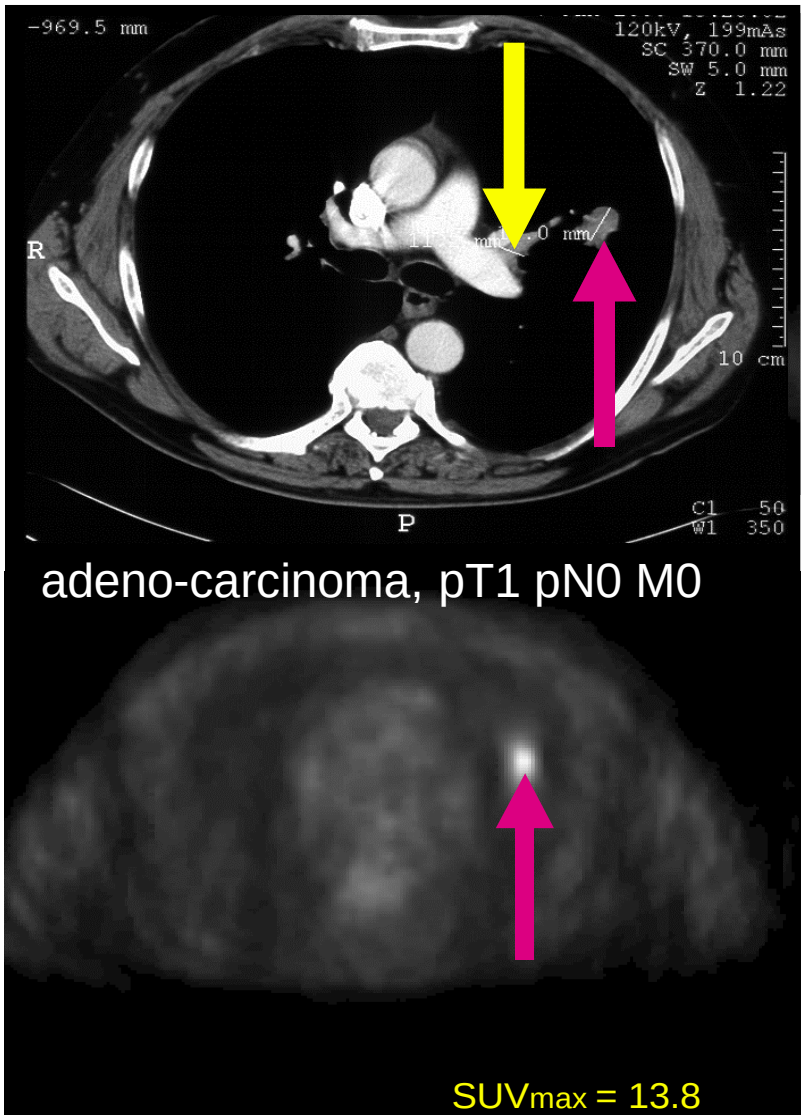
Diagnostic data

- PET as a surrogate end point for treatment efficacy

- The timing of PET for follow-up of radiation treatment

- Evolutions

Solitary pulmonary nodules (SPN)



FDG-PET for detection of malignancy in SPN:

- Accuracy: 91%
- PPV 91%
- NPV 90%

false negative findings due to:

- very small lesions (<1,2 cm)
- special histologic subtypes
  (z.B. Carcinoids, G I -adeno-carcinomas)
- diabetes
- first weeks after chemotherapy

Hellwig, Pneumologie 2001; 55; 367-377

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SPN: probability of malignancy

Prior Probability of Malignancy: 50 Enter a number from 1 to 100 %

Clinical Characteristics

Likelihood Ratios

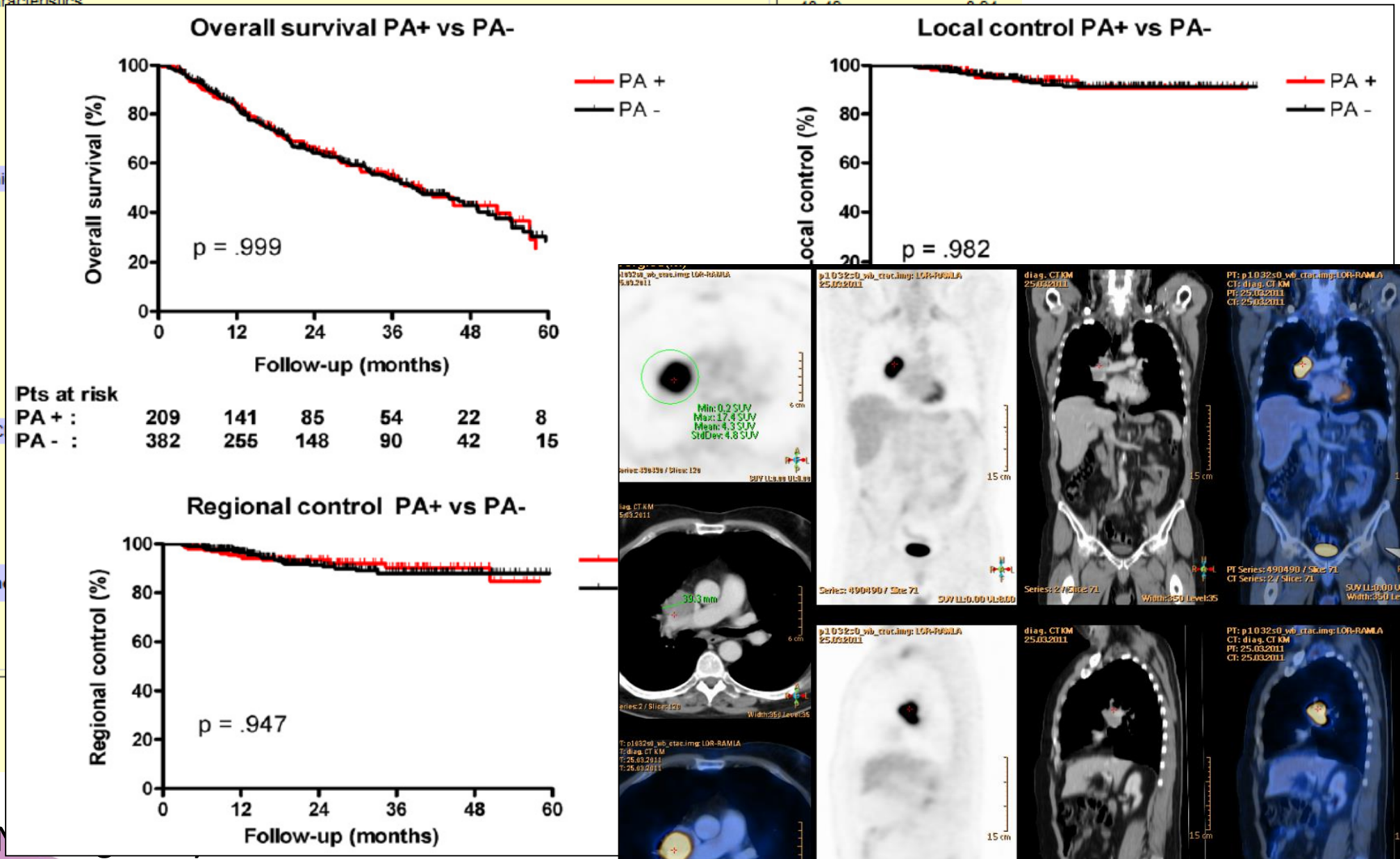
20-29	0.05
30-39	0.24

Radiographi

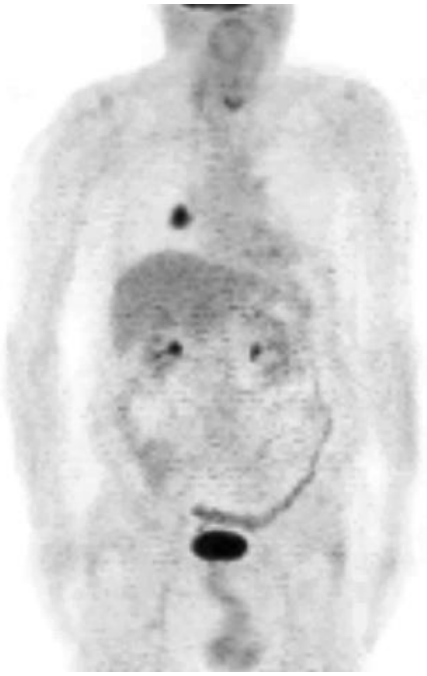
Additional C

Th

SPN



N-Staging of NSCLC by FDG-PET



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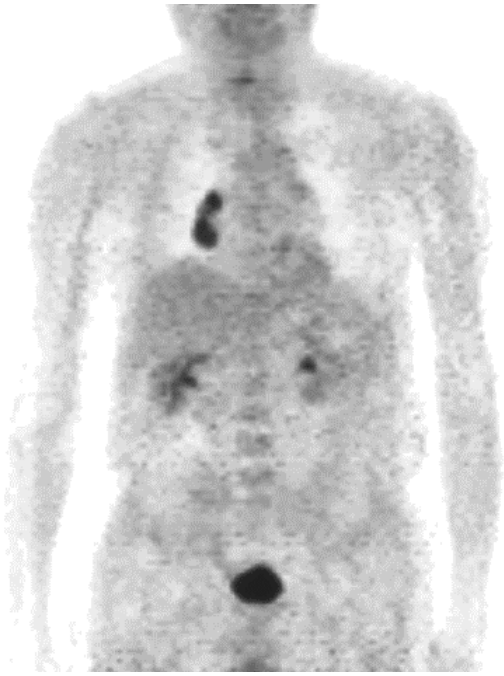
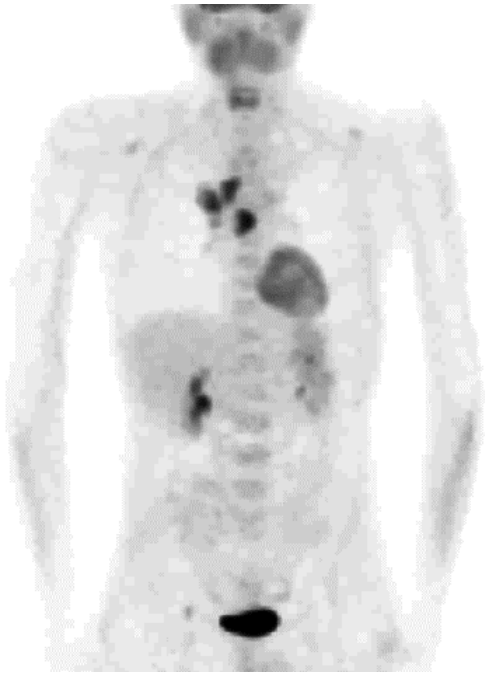
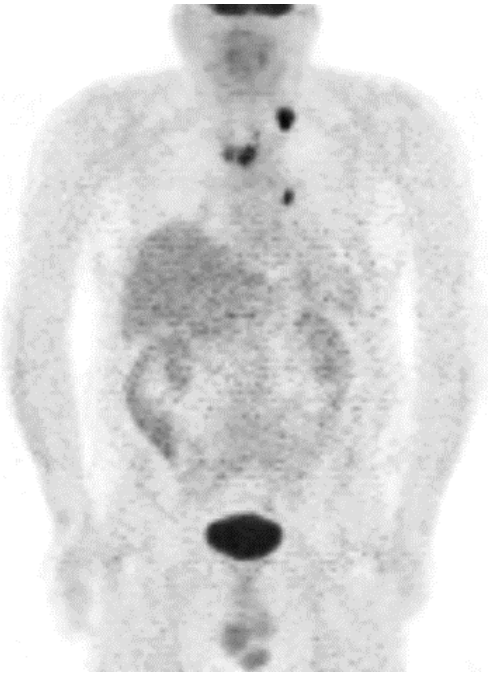


N1



N2



N3

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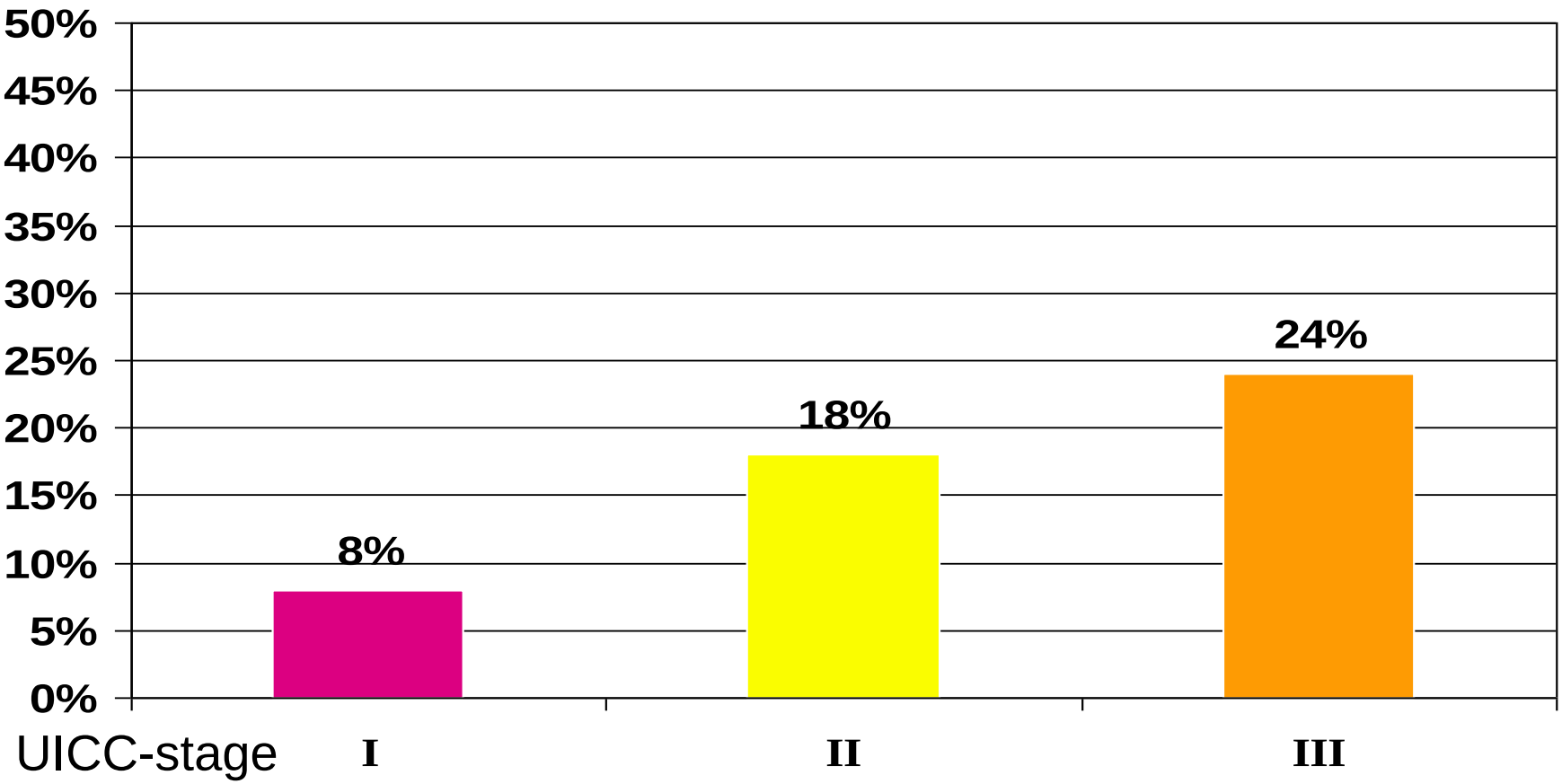
FDG-PET: M-staging

Unexpected distant metastases after conventional staging



MacManus, M., Int J Radiat Oncol Biol Phys 2001

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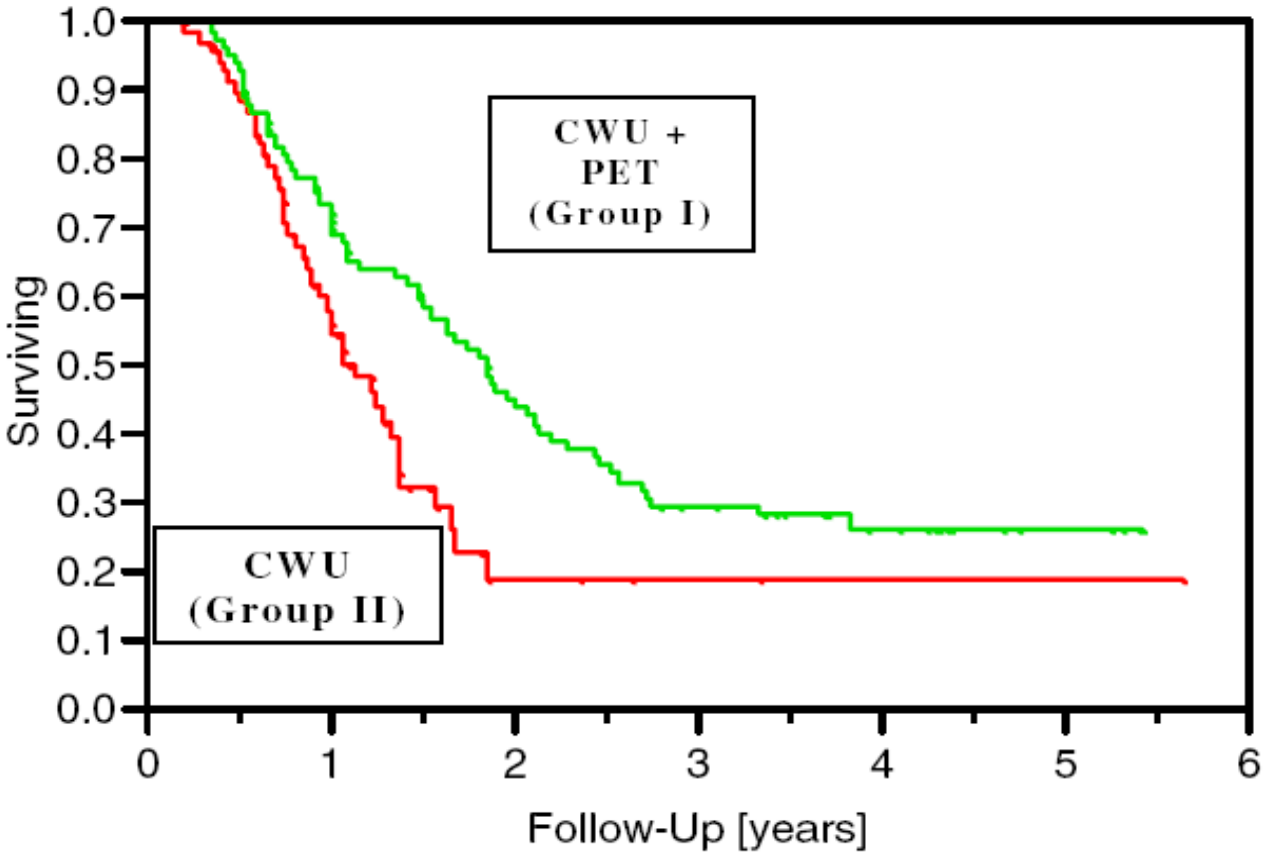
Impact of FDG-PET staging before radio-/chemotherapy on prognosis



n=188; NSCLC
Neoadjuvant radio-chemotherapy

FDG-PET	115
no FDG-PET	73

Prognostic factors in final evaluation:

PET performed	p<0,01
Complete resection	p=0,02

Eschmann, EJNMMI 2007 34; 54-59

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FDG-PET in NSCLC

- Evidence from the literature on PET for RTP:

FDG-PET in RT-planning

- PET as a surrogate end point for treatment efficacy

- The timing of PET for follow-up of radiation treatment

- Evolutions

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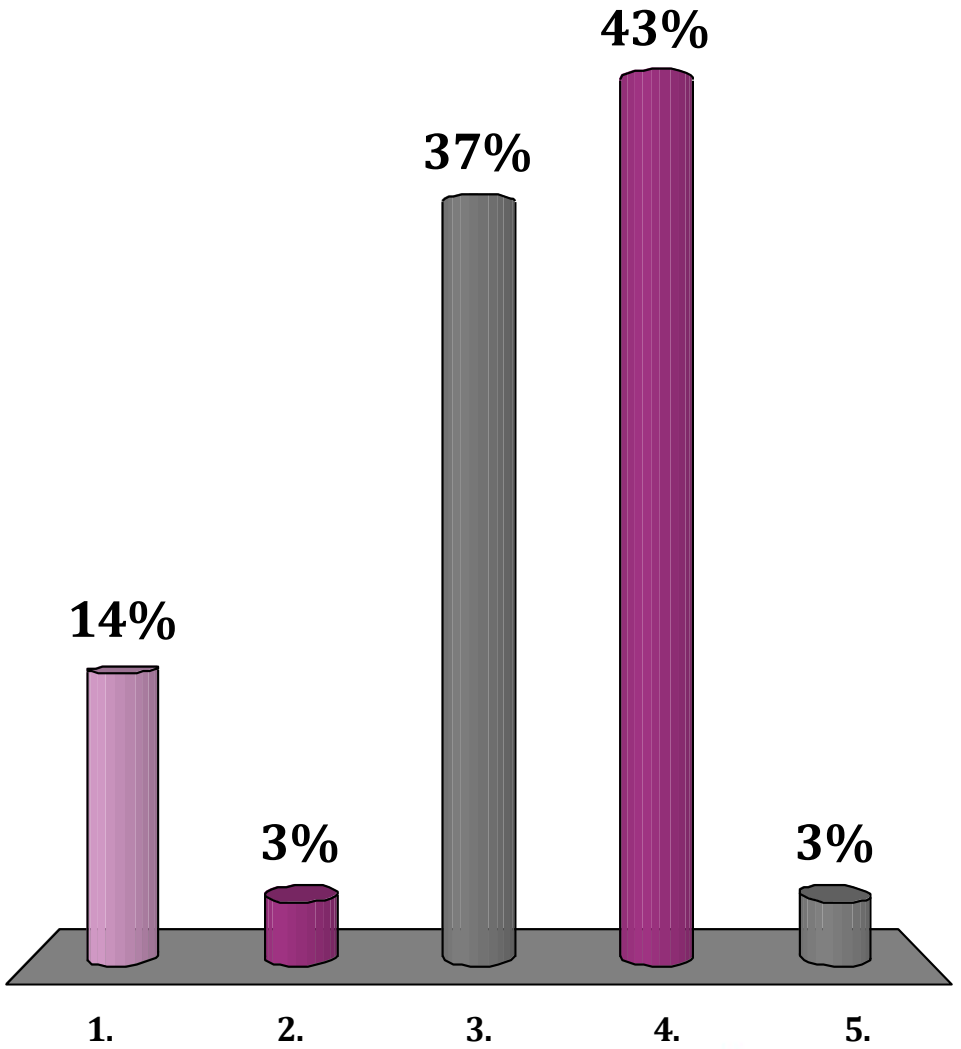
In your center, do you use functional imaging for radiotherapy planning?

1. never
2. FDG-PET for lung cancer
3. FDG-PET for lung and other types of cancer
4. FDG and other tracers in many types of cancer
5. PET and other molecular imaging spectroscopy



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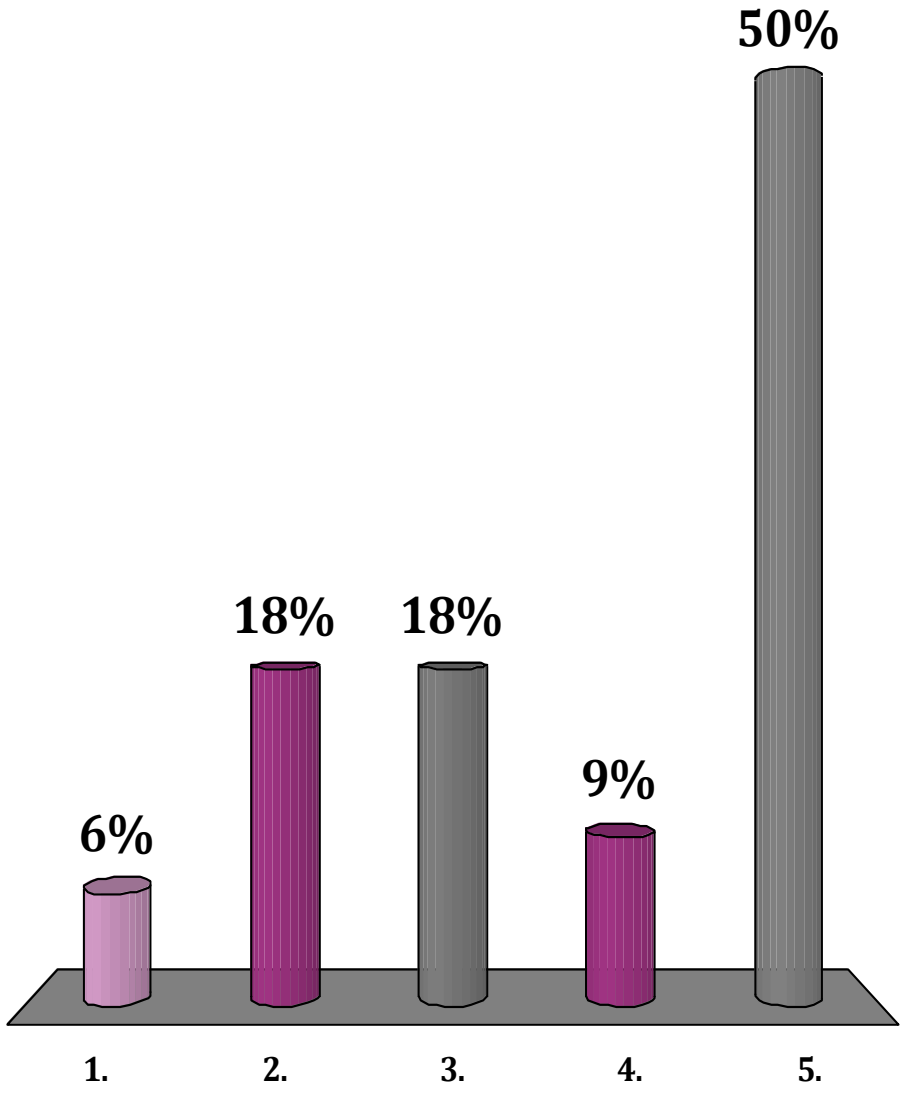
How do you / would you use functional imaging for radiotherapy planning?

1. never
2. side by side viewing
3. coregistered in TPS
4. coregistered in treatment position @diagnostic acquisition (no RTT involved)
5. coregistered in treatment position @planning acquisition (RTT involved)



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Potential impact of FDG-PET in RT-planning of NSCLC

Table 1
Literature reports on the impact of FDG-PET on radiotherapy planning in lung cancer

Author	Study	Patients	PET/CT image fusion	Method of GTV contouring (PET)	Change of GTV, PTV using PET	Increase of GTV, PTV using PET		mment
Hebert et al. [46]	Prospective	20	Comparison X-ray, CT, PET	Visual evaluation of FDG-PET	GTV 7/20 P (35%)			may be useful for eation of lung cancer
Kiffer et al. [54]	Retrospective	15	Graphical co-registration of coronal PET with AP simul	Visual evaluation of FDG-PET	GTV: 7/			etects positive lymph not useful in tumor tion
Munley et al. [63]	Retrospective	35						lements CT ation
Nestle et							ease of field size 3 P (9%)	Change of field size in patients with dys- or atelectasis
Vanuytse						GTV: 16/73P (22%) 11P = pathology 1P-unnecessary 4P-insufficient	GTV: 29/73P (40%) 25P = pathology 1P-inappropriate 3P-insufficient	PET data vs. pathology: 36 P(49%) = pathology 2 P(3%) inappropriate 7 P(10%) insufficient
MacManus et			sults used for treatment planning, no image fusion	Visual evaluation of FDG-PET	GTV: 22/102 P(21%)	GTV: 22/102 P(21%) Inclusion of structures previously considered uninvolved by tumor	GTV: 16/102 P(15%) Exclusion of atelectasis and lymph nodes	Post-PET stage but not pre-PET stage was significant associated with survival
Kalff et al. [53]	Prospective	34	No image fusion	Visual evaluation	22/34 altered treatment delivery	n.e.	11/34 reduction of treatment volume	Part of a study on impact of FDG- PET on various endpoints (n = 105)
Giraud et al. [40]	Prospective	12	CT/PET image fusion	Visual evaluation of FDG-PET	GTV, PTV 5/12 P(42%)	n.e.	n.e.	4/12 P lymph nodes 1/12 atelectasis and distant meta.
Mah et al. [62]	Prospective	30	Image coregistration CT-PET using external fiducial markers	50% intensity level of max. FDG uptake	GTV: 5/23 P (22%) FDG-avide lymphnodes	PTV: 30—76% of cases (varied between the 3 physicians)	PTV: 24—70% of cases (varied between the 3 physicians)	(a) Addition of PET does lower physician variation in PTV delineation

All studies: significant changes in planning parameters
Relevant aspects:
- Atelectasis
- Lymph node staging

Summarized in: Nestle, Radiotherapy and Oncology 2006 81, 209-225

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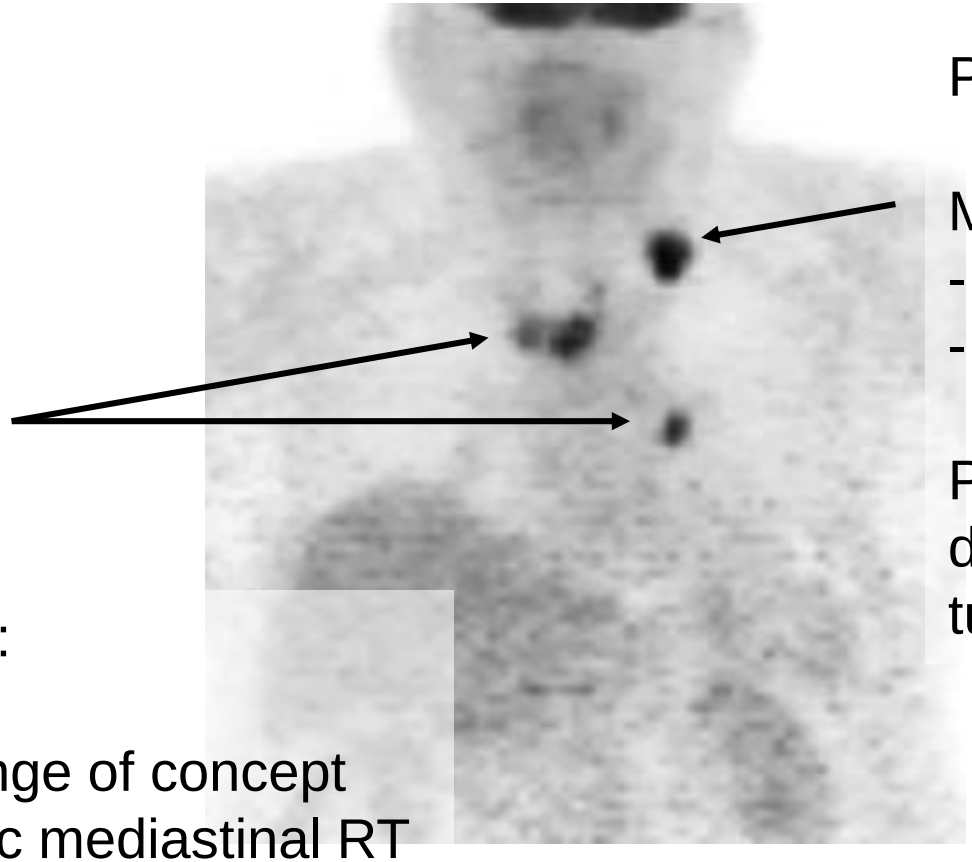
Areas of potential impact of FDG-PET in RT-planning of NSCLC



Primary tumor:

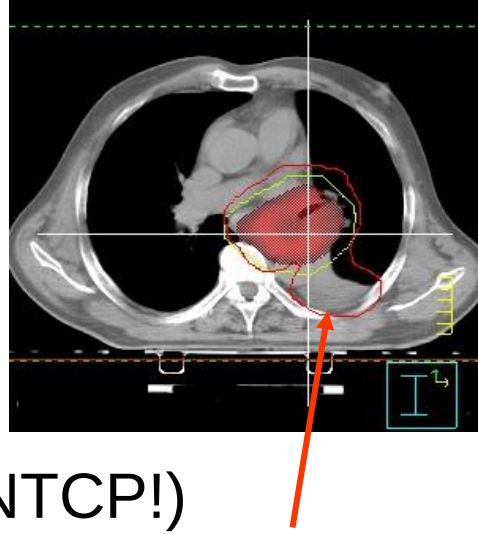
More exact GTV delineation:
- atelectasis
- (mediastinal border)

Possible benefit in PTV due to depiction of tumor movement

Lymph nodes:

Possible change of concept of prophylactic mediastinal RT due to improved N- staging

Atelectasis



Significant potential benefit by FDG-PET in RT planning (NTCP!)

CT: problem in differentiation tumor vs. atelectasis (similar density)
PET: depicts atelectasis with slightly higher uptake than normal lung but much lower than tumor (Gerbaudo EJR 2007 64; 401-405)
cave: false positive uptake in post-obstructive inflammation

Histologic correlation of PET-findings with pathology are lacking (atelectasis no problem concerning thoracic surgeons)

Pathophysiologic considerations support use of PET for RT-planning (why should FDG fail to accumulate in tumour infiltrating atelectatic lung?)

Pitfalls

- Broncho-alveolar carcinoma: limited/no uptake of FDG
- Border tumor and atelectasis: not validated with pathology
- Post-obstruction pneumonia: increased uptake of FDG
- Inflammatory diseases: increased uptake of FDG
- Heart: or mediastinal involvement?
- Movement of tumor: blurring of PET signal
  → 4D PET-CT

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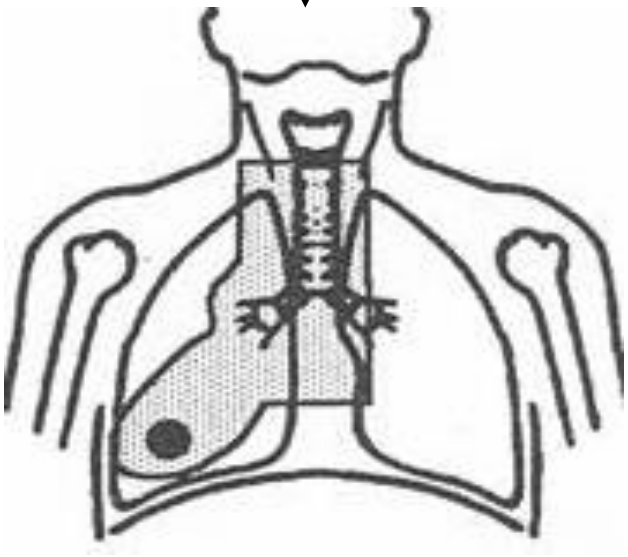
Lymph nodes:
Changing CTV-concept in mediastinum

Non systematic nodal spread
Diagnostig uncertainty
of CT based N-staging



Perez, Brady 1992

„Elective nodal irradiation“ (ENI)
= Prophylactic inclusion of large parts of mediastinum in CTV

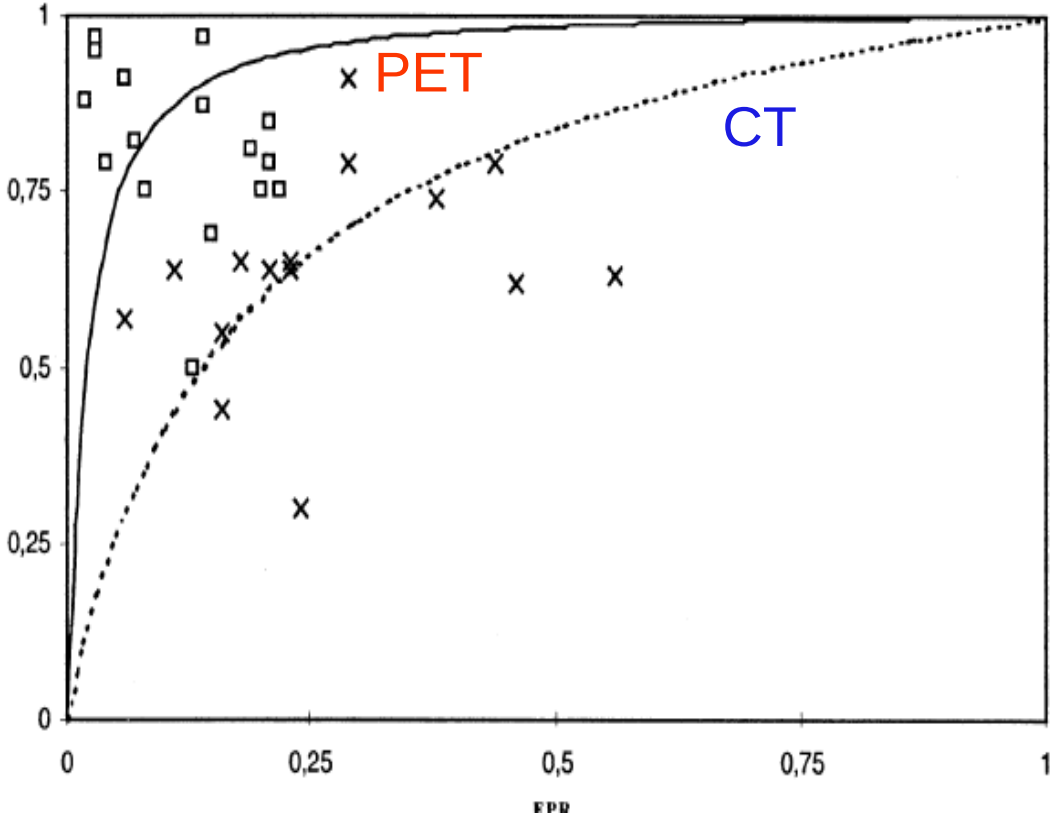
→ high doses to large volumes of normal tissue
→ limited possibility for dose escalation

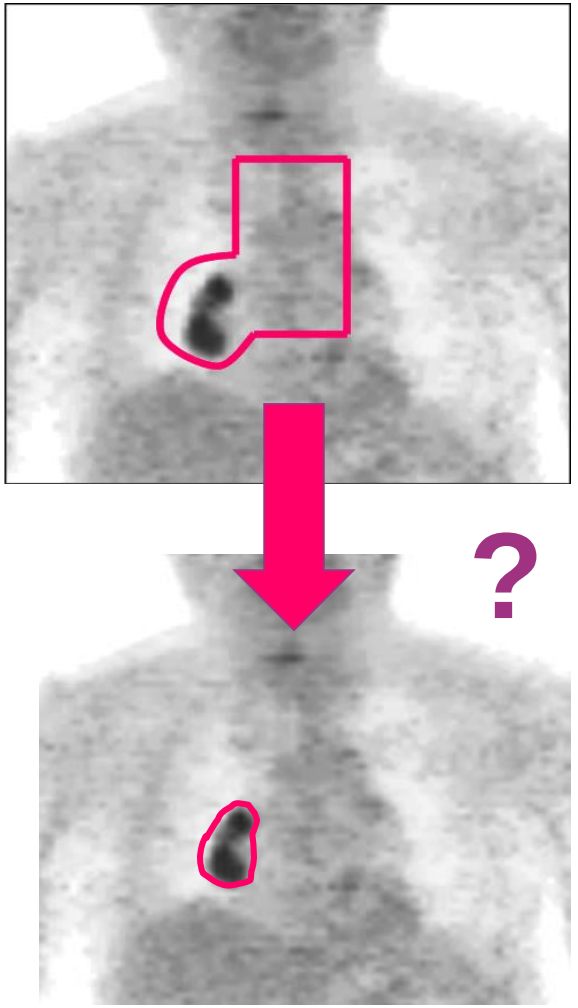
No randomised prospective data supporting ENI

→ Concept of ENI presently being left

FDG-based CTV vs. ENI

Residual risk of undetected LN-metastases in FDG-PET much lower than in CT





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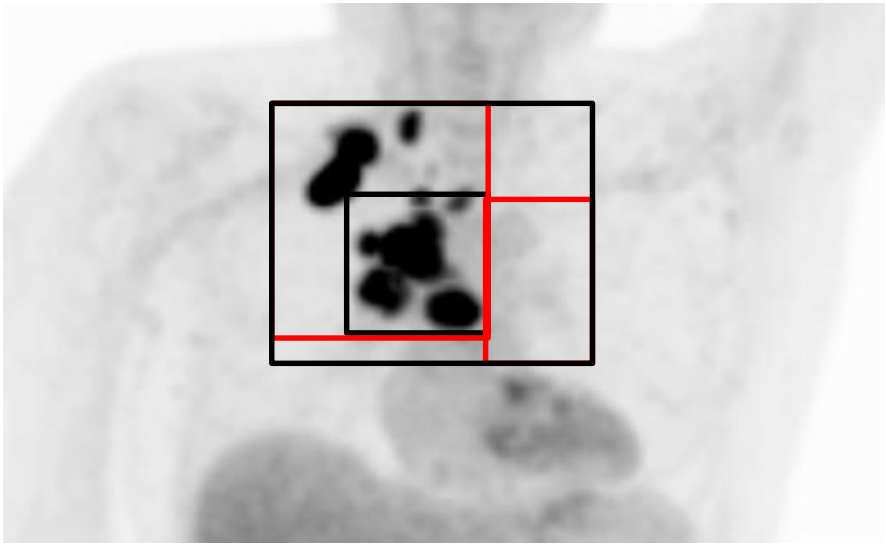
CTV: where are the nodes?



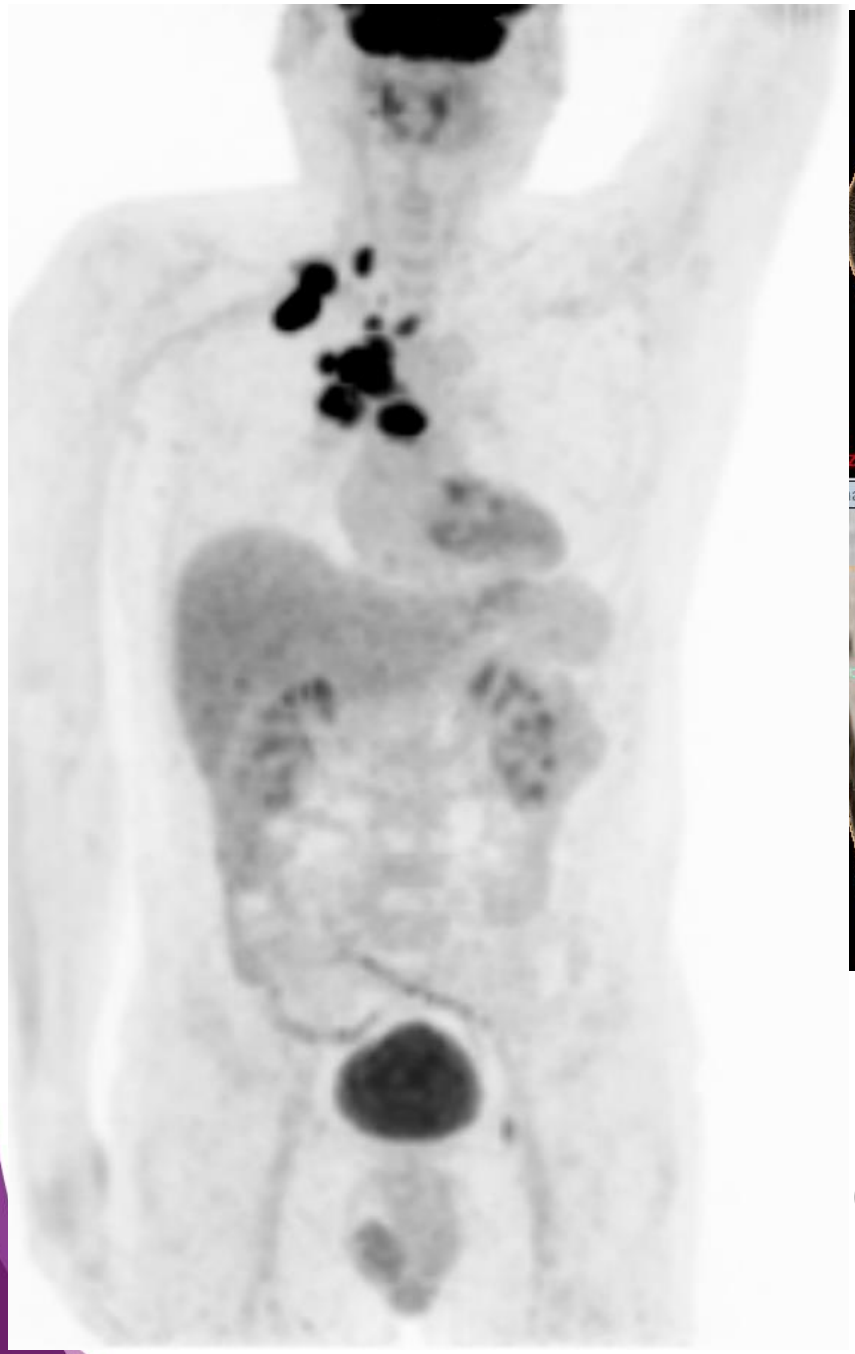
diagnostic imaging:

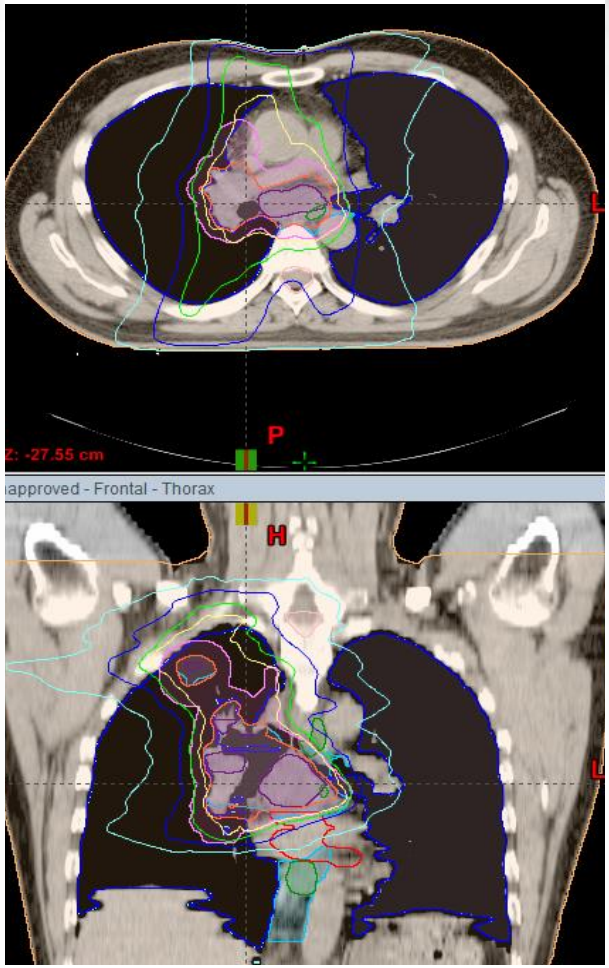
RT treatment planning:

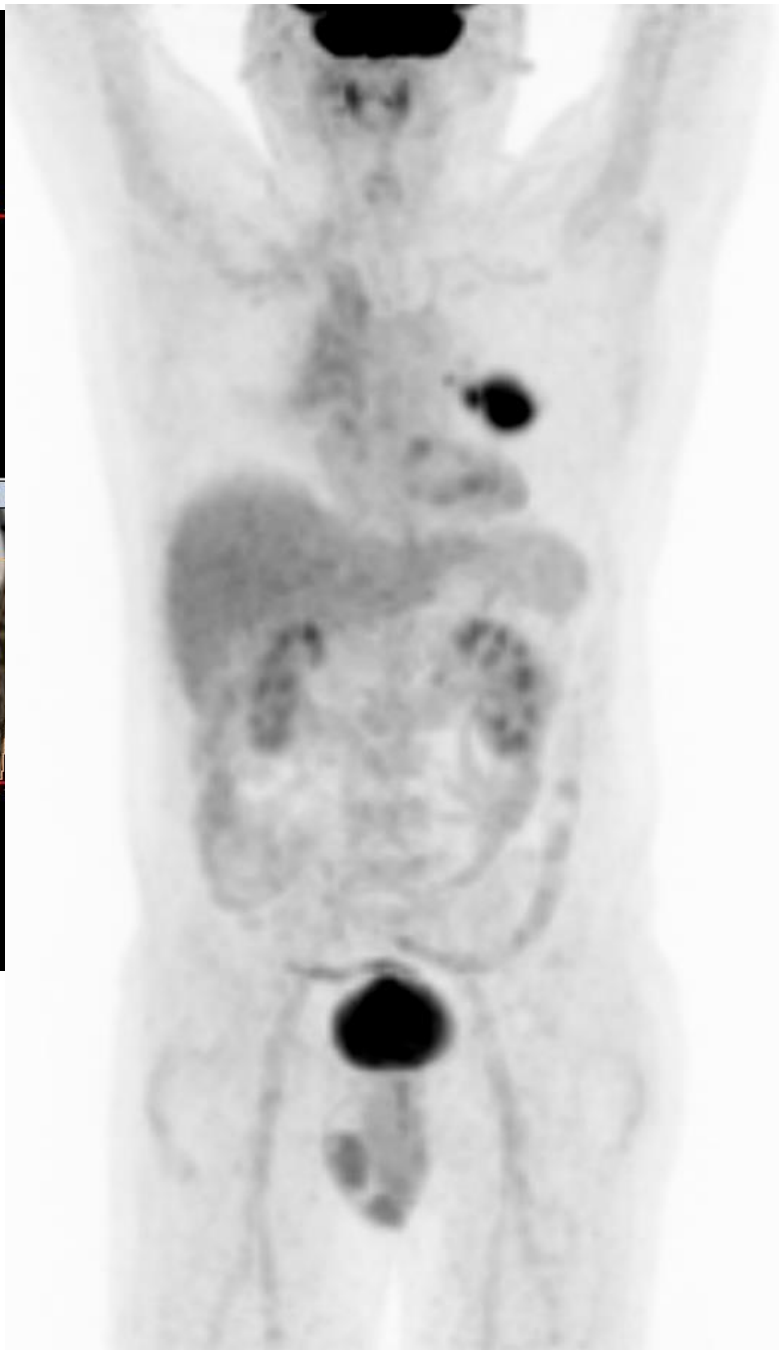
Treat what?

19.4.2012

14.12.2012







NSCLC (SCC) IIIb;
RCT 07/2012; Platin,
66 Gy/2 Gy

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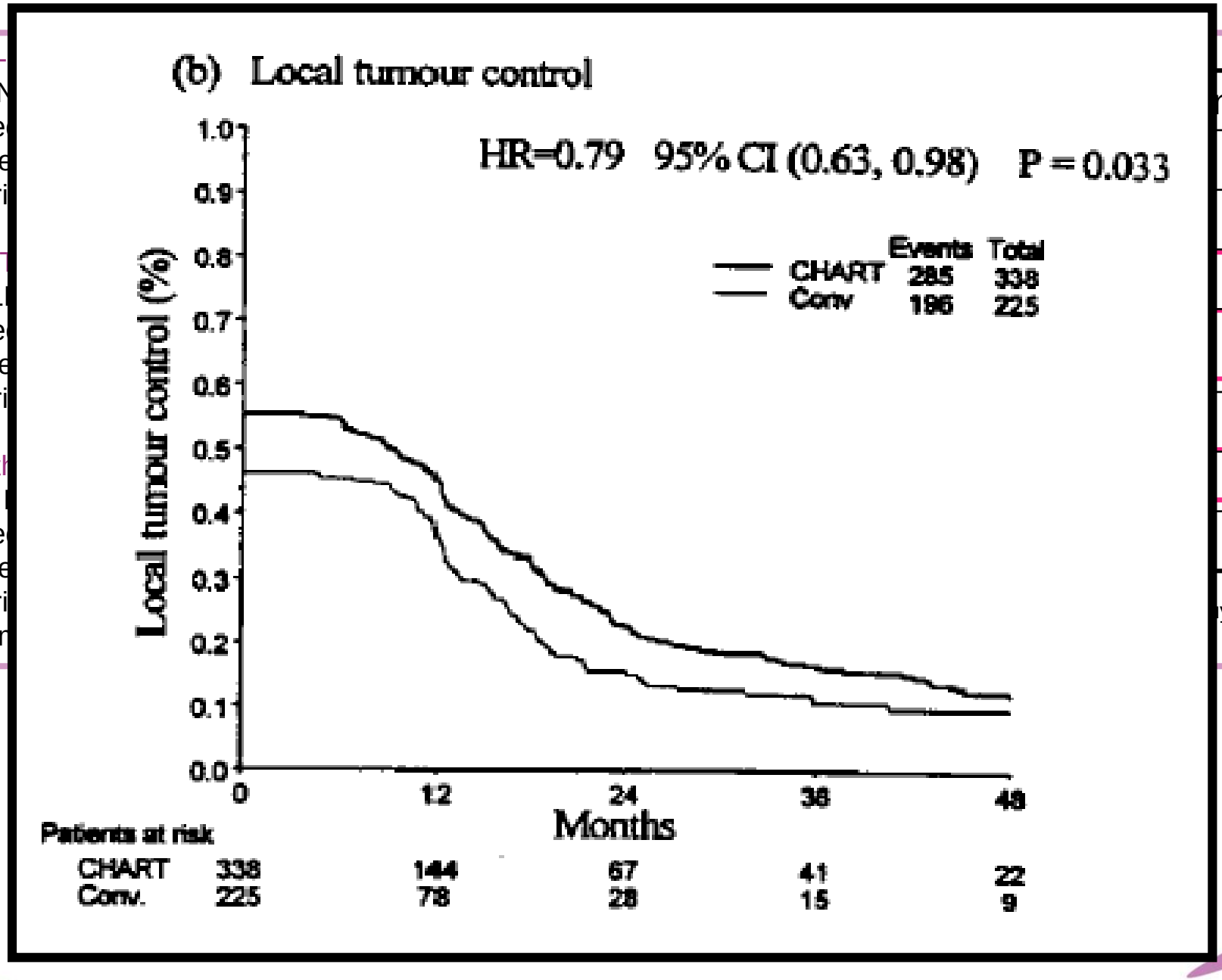
Out field recurrences: Residual risk

RT of CT-
96/988 LN
not treate
overtreate
residual ri

RT of PET
84/ 988 LI
not treate
overtreate
residual ri

RT of both
129/ 988
not treate
overtreate
residual ri
overtreatr



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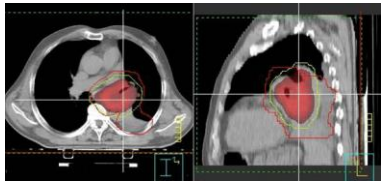
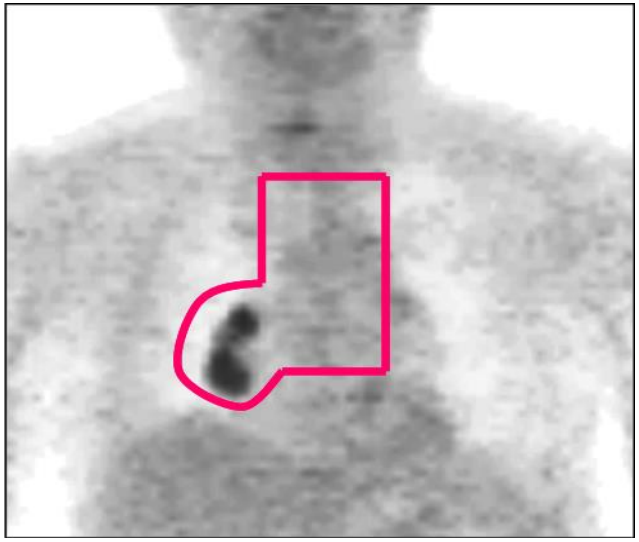
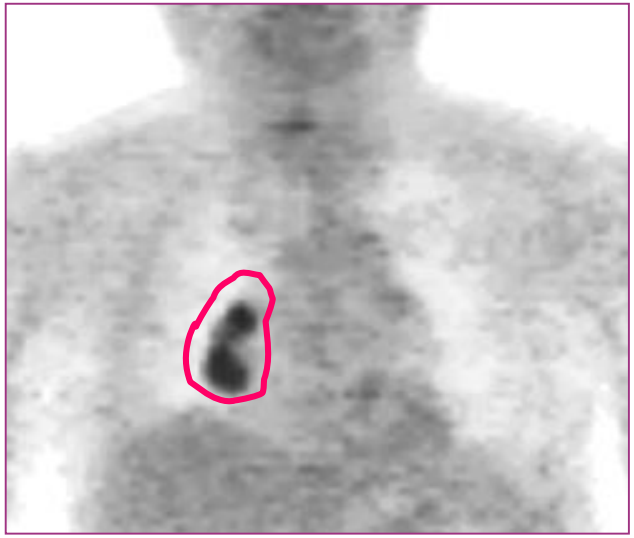
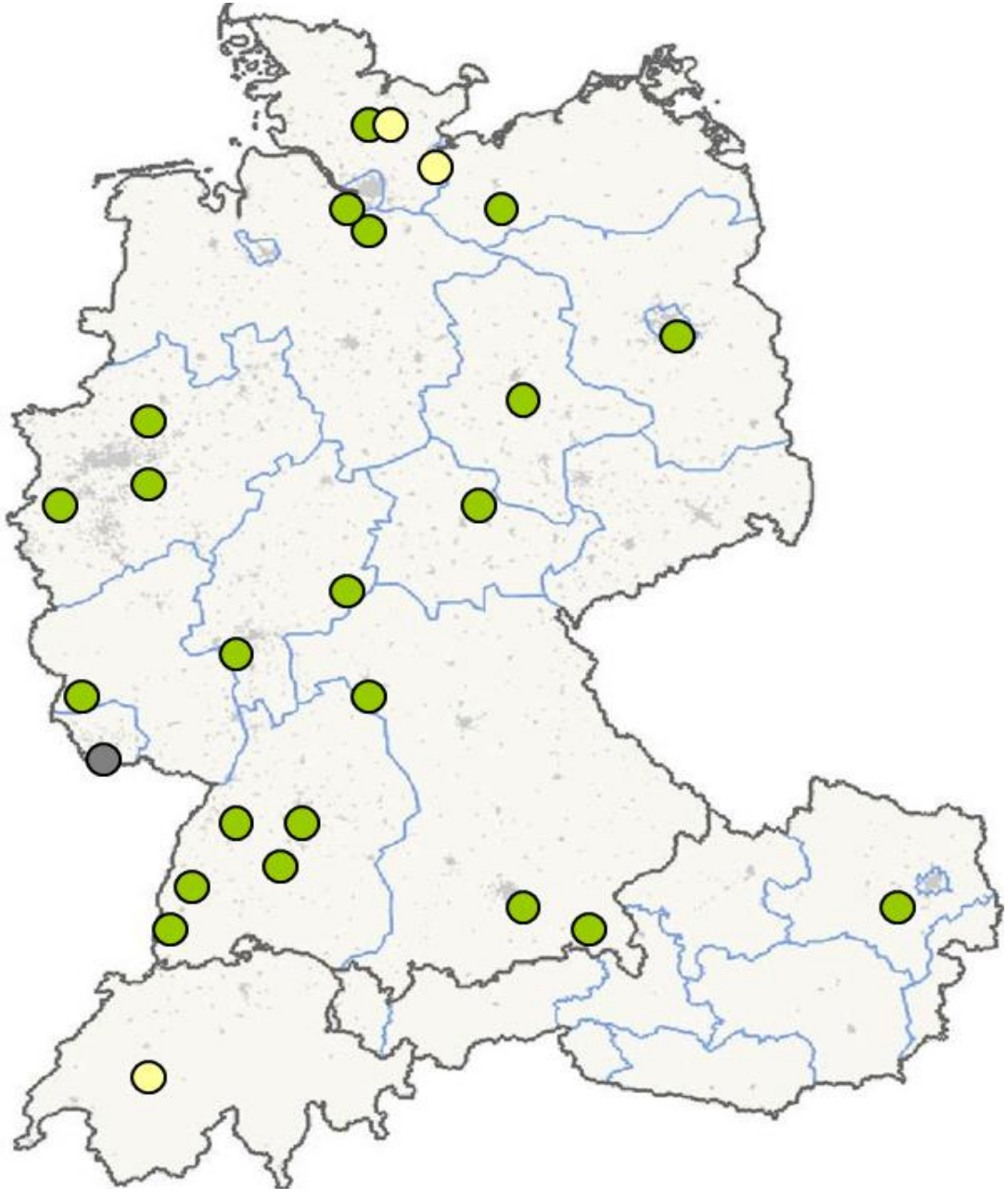
PET-Plan Study



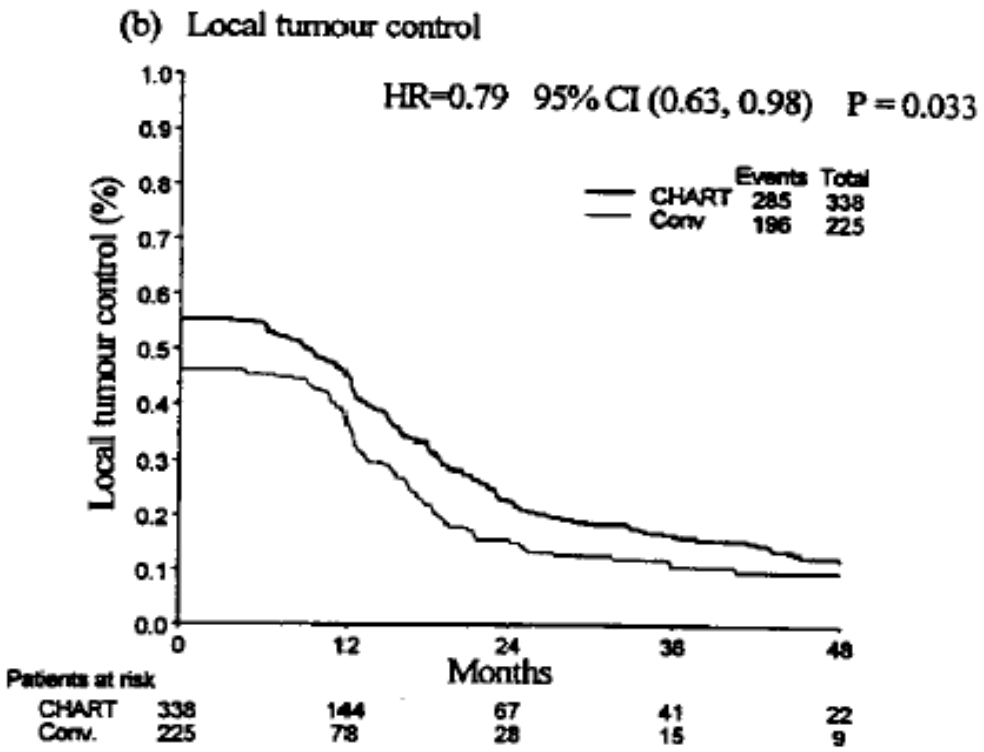
Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.







Risk consideration:
out field recurrence vs. local control



Saunders R&O 1999

>> 50% risk of local progression in advanced NSCLC

possible improvement by dose escalation

must be weighed against

< 10% residual risk of out field recurrence from microscopic nodal spread if no ENI

→ Clinical studies!

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FDG-PET based RT planning in NSCLC: first clinical data

44 pat. NSCLC I-III, 10/44 mediastinal downstaging by PET

Dose escalation to 64,8 Gy/1,8 Gy b.i.d.
GTV = tumor + FDG-PET positive LN-stations

18 local recurrences (41 %)
after median follow up of 16 months
1 isolated out field recurrence
at LN pre treatment N0 in CT and PET

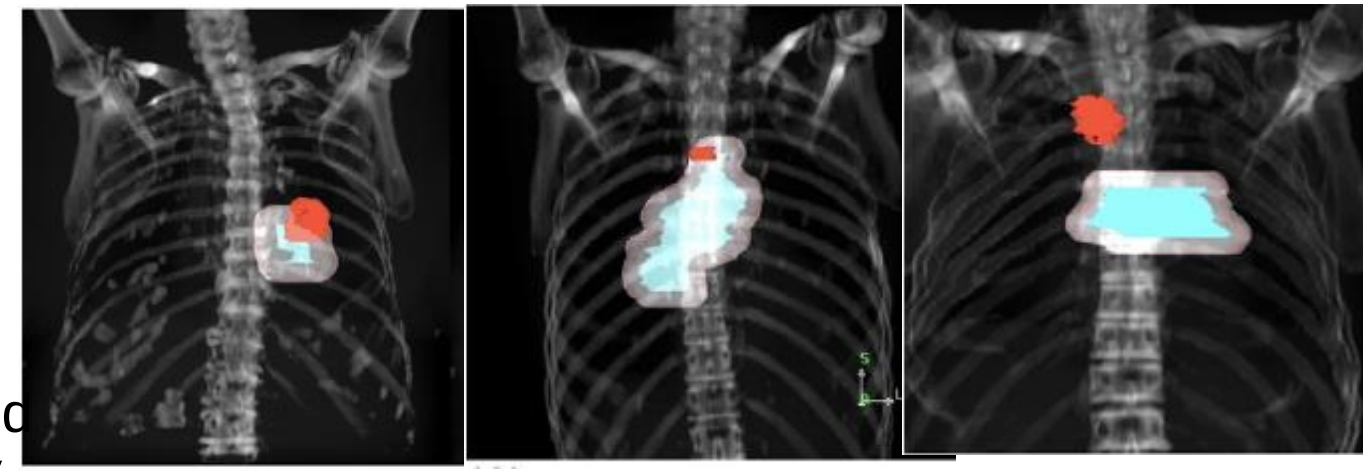
Table 2. Patterns of recurrence

Recurrences	No. of patients (%)
None	26 (59)
In-field	10 (23)
Exclusively in-field	5
In-field and distant	5
Isolated nodal	1 (2)
Nodal (outside of CTV) along with local or distant failure	2 (4.5)
Distant only	7 (16)
Brain only	1

De Ruysscher IJROBP 2005 62; 988-994

Clinical data: risk of marginal miss after FDG based RT planning

26 local recurrences after FDG-based RT planning in advanced NSCLC: after doses >60 Gy 12/18 recurrences located at margin of GTV or PTV



Local failure pattern ($n = 26$)

Dose	Within GTV/PTV	Within GTV/PTV and outward	Marginal miss (within PTV and outward)	Geographic miss (outside but within 1 cm of PTV)
D_{95} <60 Gy	6	2	0	0
D_{prescr} <60 Gy	6	2	0	0
D_{95} ≥60 Gy	6	11	1	0
D_{prescr} ≥60 Gy	6	11	1	0

Sura IJRBOP 2008 70; 1397-1402

When to perform the PET(-CT)?

Table 2. Clinical progression rates at 4, 8, and 16 weeks from the initial staging scans

Event	Number of events	4 week	8 week	16 week	Median interval (range)
Any progression	19	13%	31%	46%	7.6 weeks (1.4–128.3)
Any new site	17	13%	31%	46%	7.1 weeks (1.4–25.0)
Overall stage change	10	3%	13%	21%	16.3 weeks (3.1–128.3)
Distant metastasis	4	3%	13%	13%	5.3 weeks (3.1–7.1)

Advice: >4 weeks interval between PET and planning CT: Repeat PET!

Mohammed et al, IJROBP 2011

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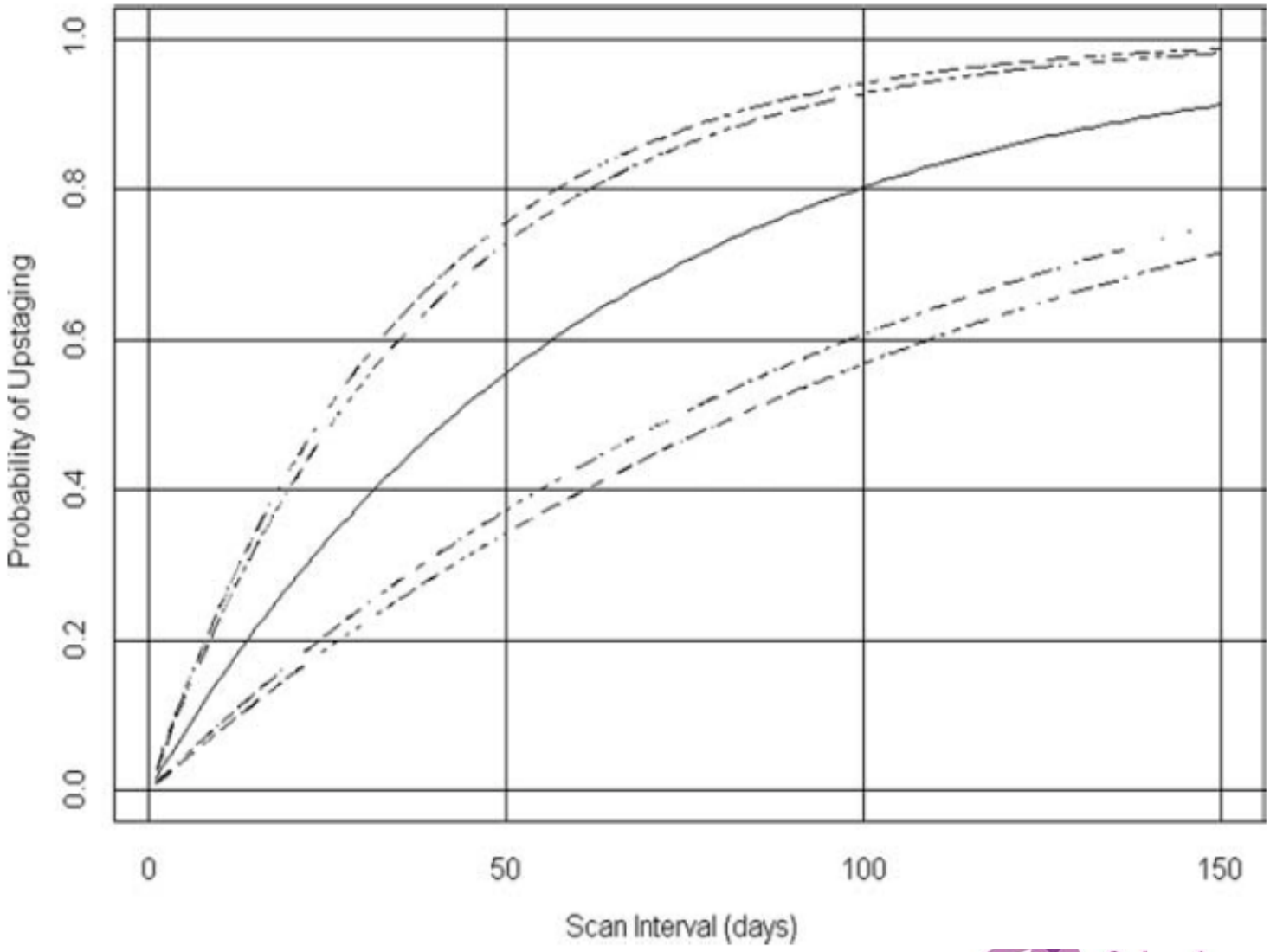
PET for RT-planning: soon before treatment!

82 pts, NSCLC
before radical RT
2 FDG-PET scans
median interval 24 days

progression in 39%

upstaging probability
within 24 days: **32%**

Everitt, S. et al.
Cancer 2010



School

FDG-PET in NSCLC

- Evidence from the literature on PET for RTP
- **PET as a surrogate end point for treatment efficacy**
- **The timing of PET for follow-up of radiation treatment**
- Evolutions

FDG-PET in monitoring radiochemotherapy

Author	n	PET	Criteria	Survival (months)	
				Responder	Non-Responder
MacManus	73	Before/after Rx	Visual	24	4
Hellwig	47	After CRTx	SUV < 4	>56	9
Poettgen	50	Before CTx and after CRTx	ΔSUV> 50%	>36	9
Eschmann	70	Before /after CTx, after CRTx	ΔSUV> 80% ΔSUV> 60%	>60	12

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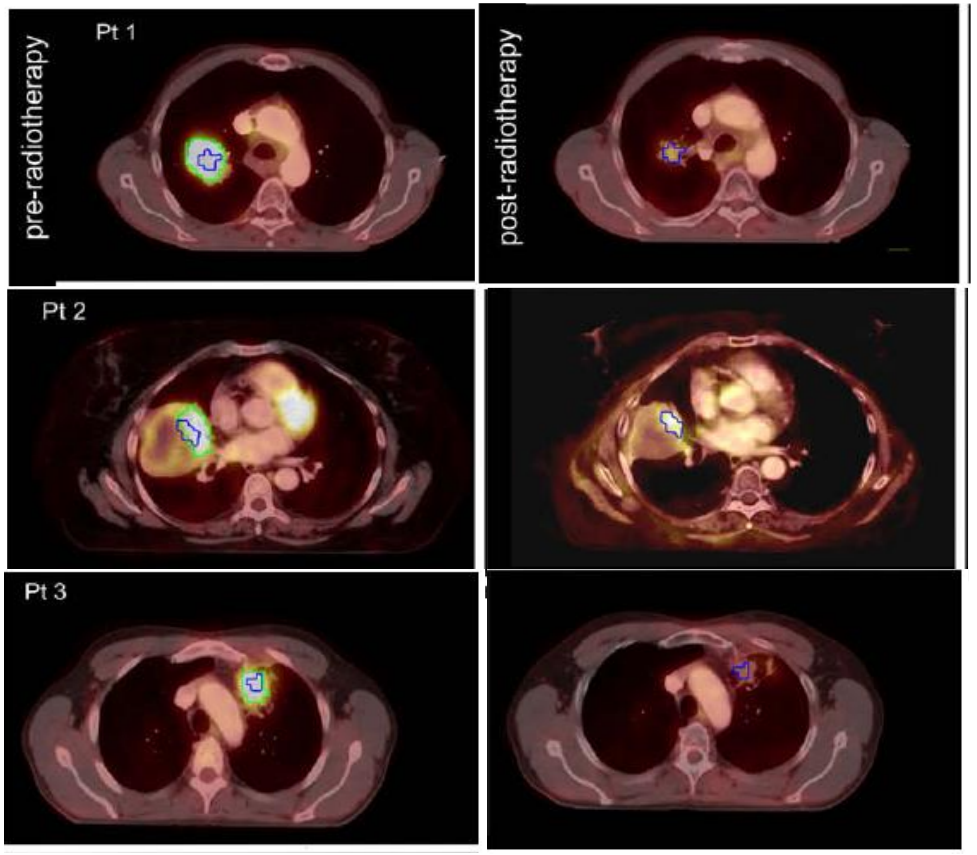
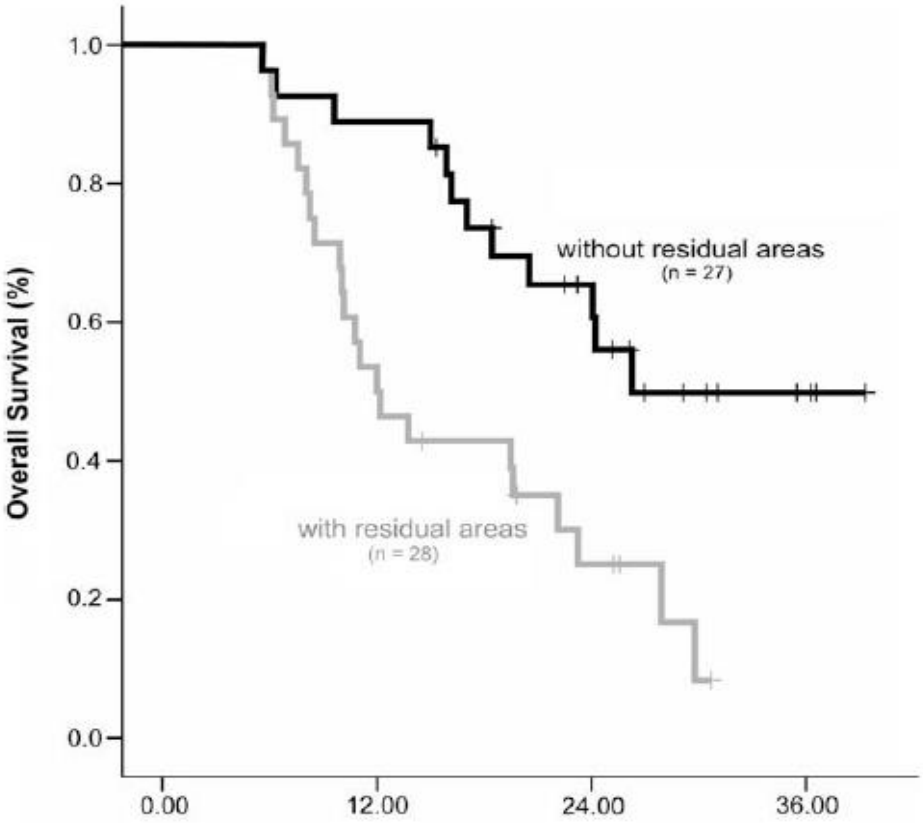
Prediction of local non-response





Aerts, R&O 2009

55 Pat., FDG-PET pre/post RT

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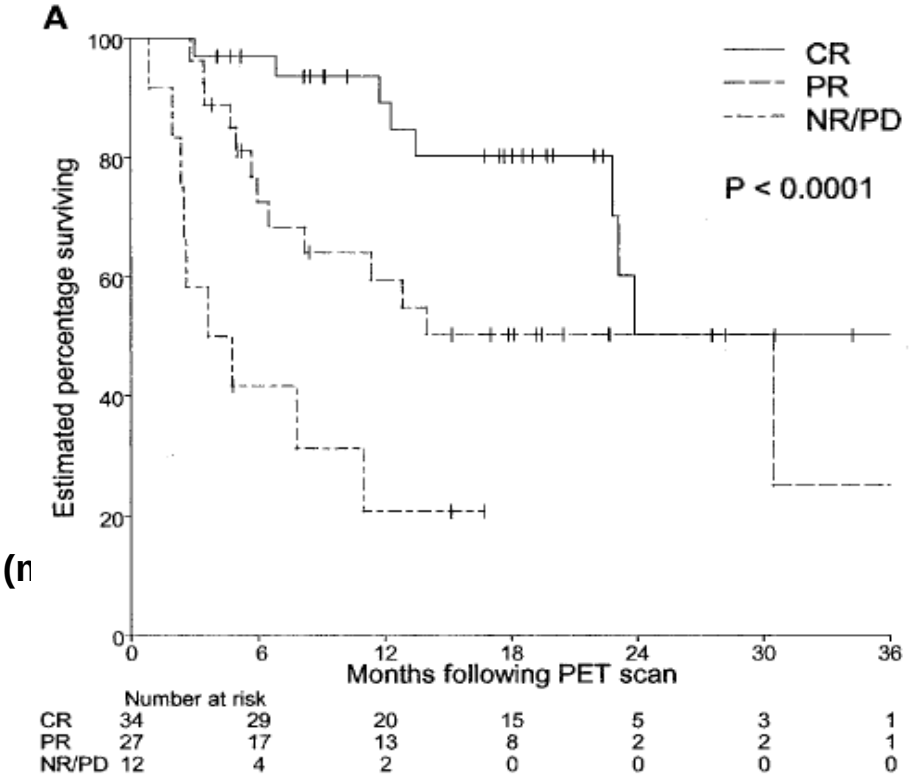
Prediction of survival after radio(chemo)therapy by FDG-PET



73 pts., advanced NSCLC
Radical R(C)T

FDG-PET median 70 days after treatment
Allows better prediction of survival
than stage, CT response or performance

MacManus JCO 2003, 21; 1285-1292

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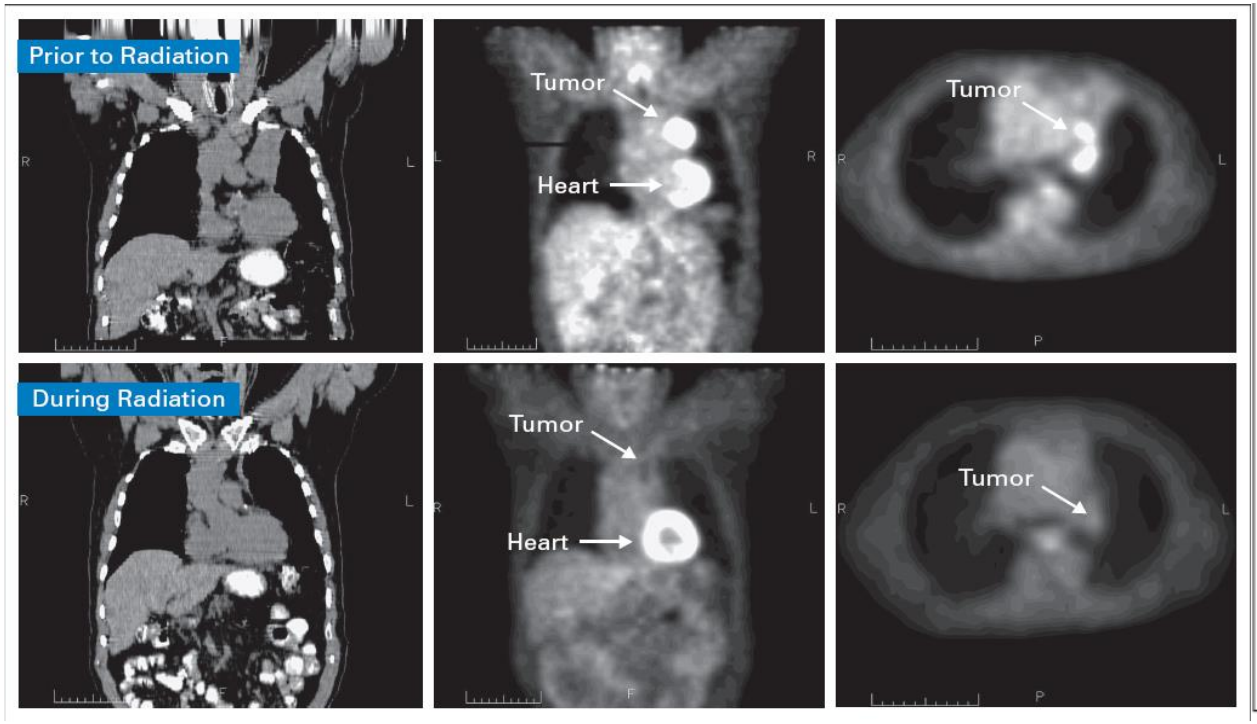
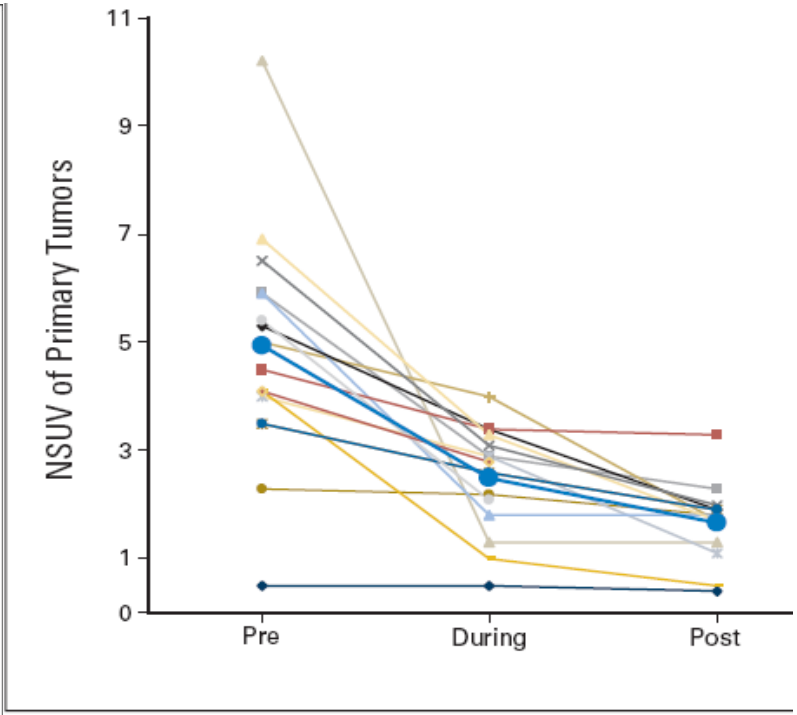
Prediction of response during RT?





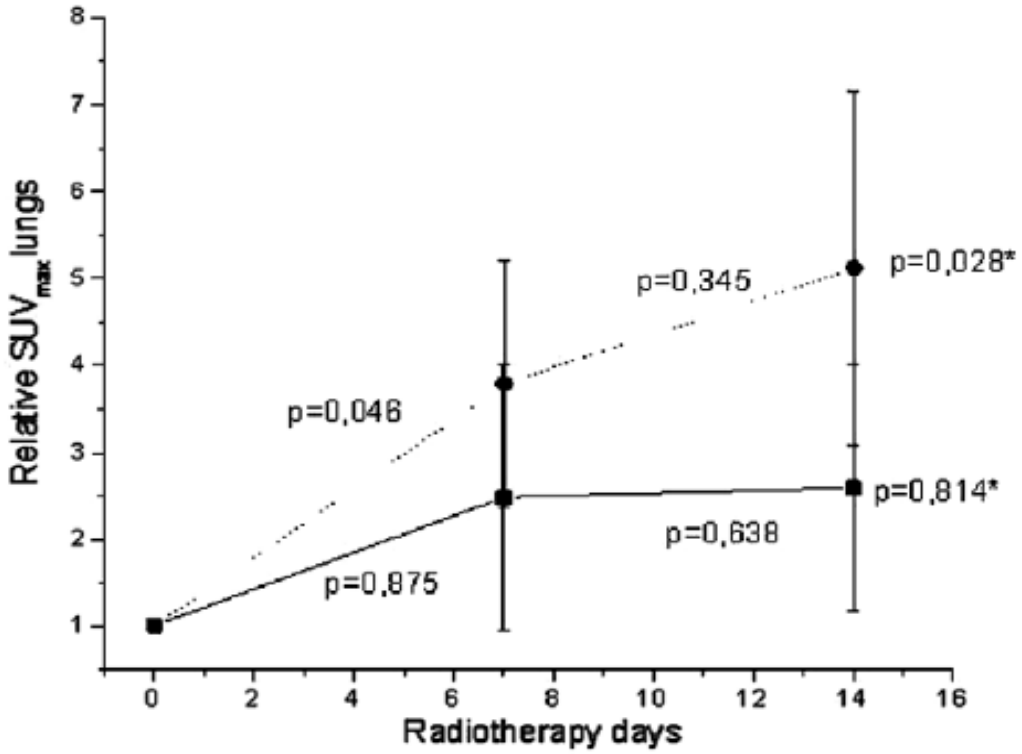
significant correlation
PET-response during vs. after RT

Kong, 2007

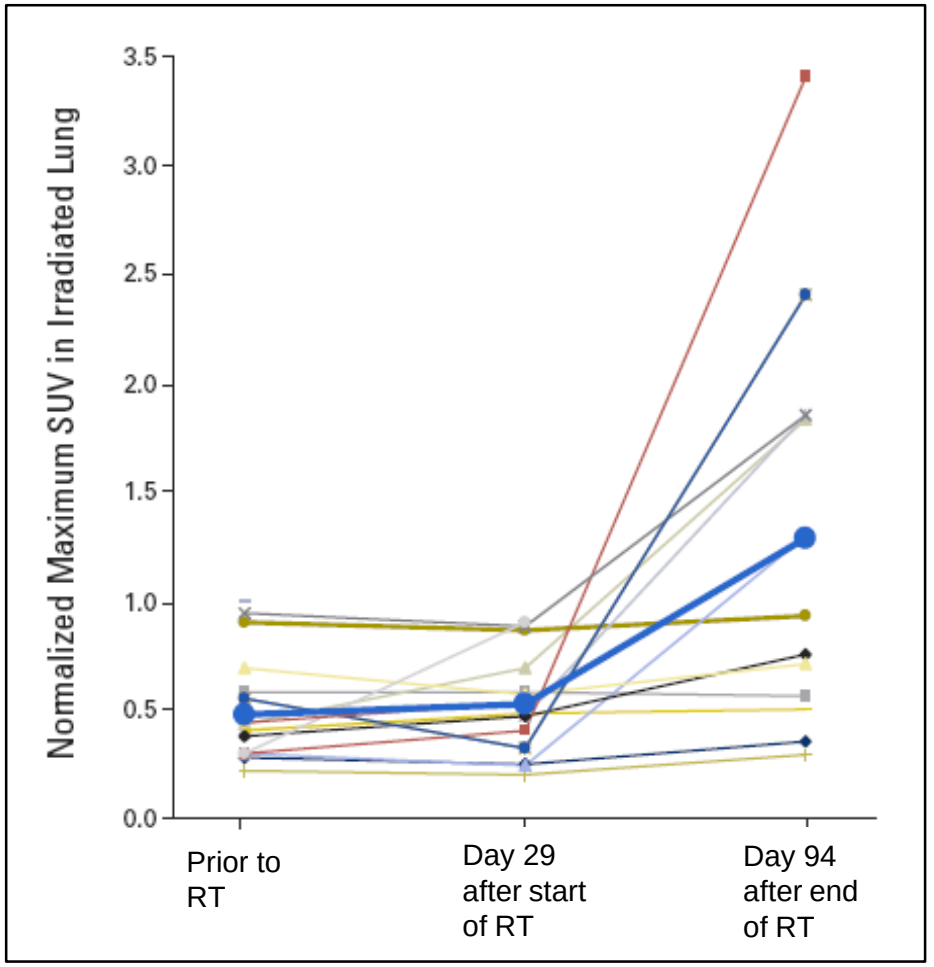
FDG-PET in NSCLC

- Evidence from the literature on PET for RTP
- PET as a surrogate end point for treatment efficacy
- The timing of PET for follow-up of radiation treatment
- **Evolutions**

Prediction of NT-reactions?

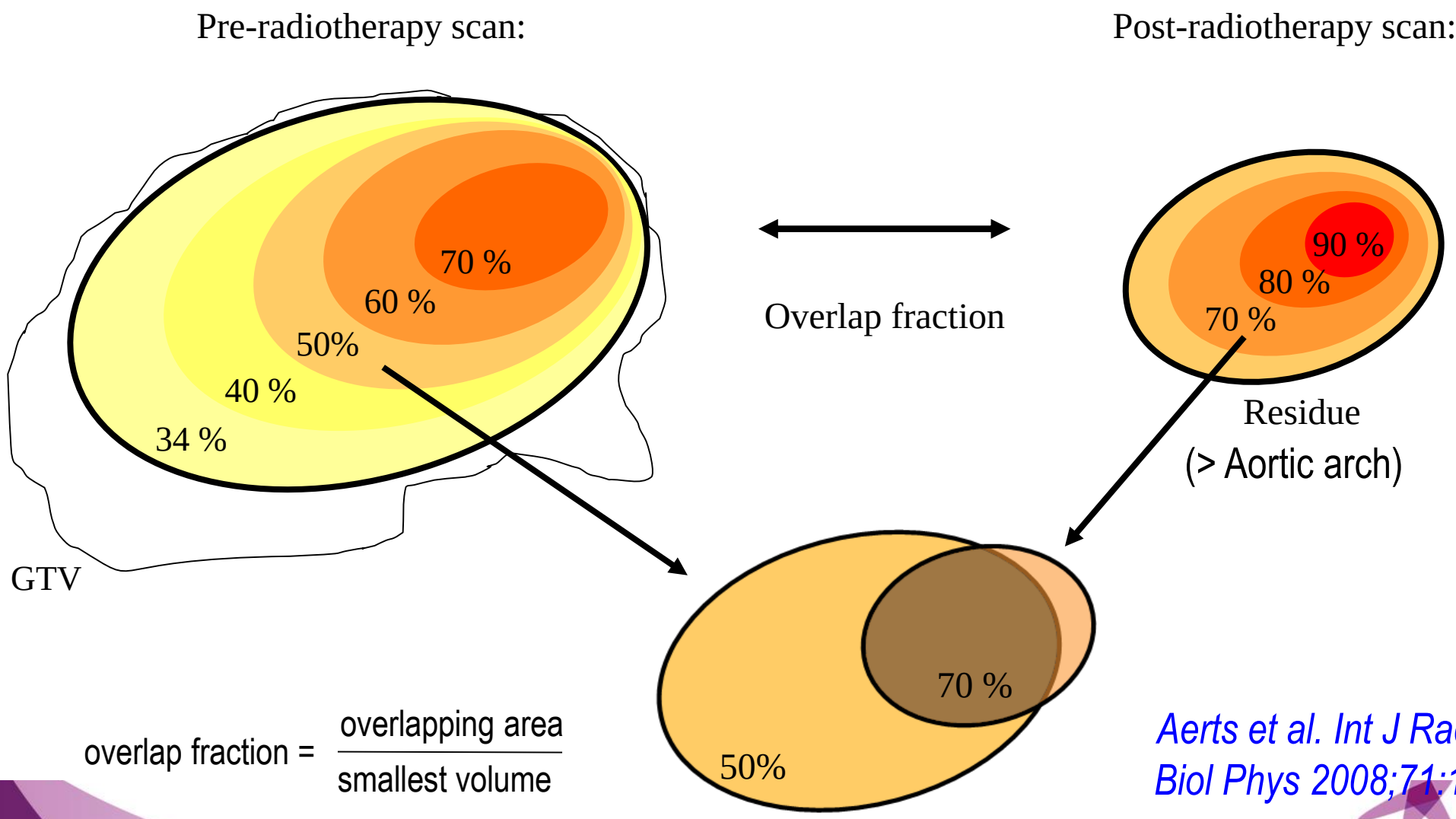


De Ruysscher 2009



Kong, JCO 2007

Question 1: Do the high-uptake areas within the tumor remain at the same location during radiotherapy?

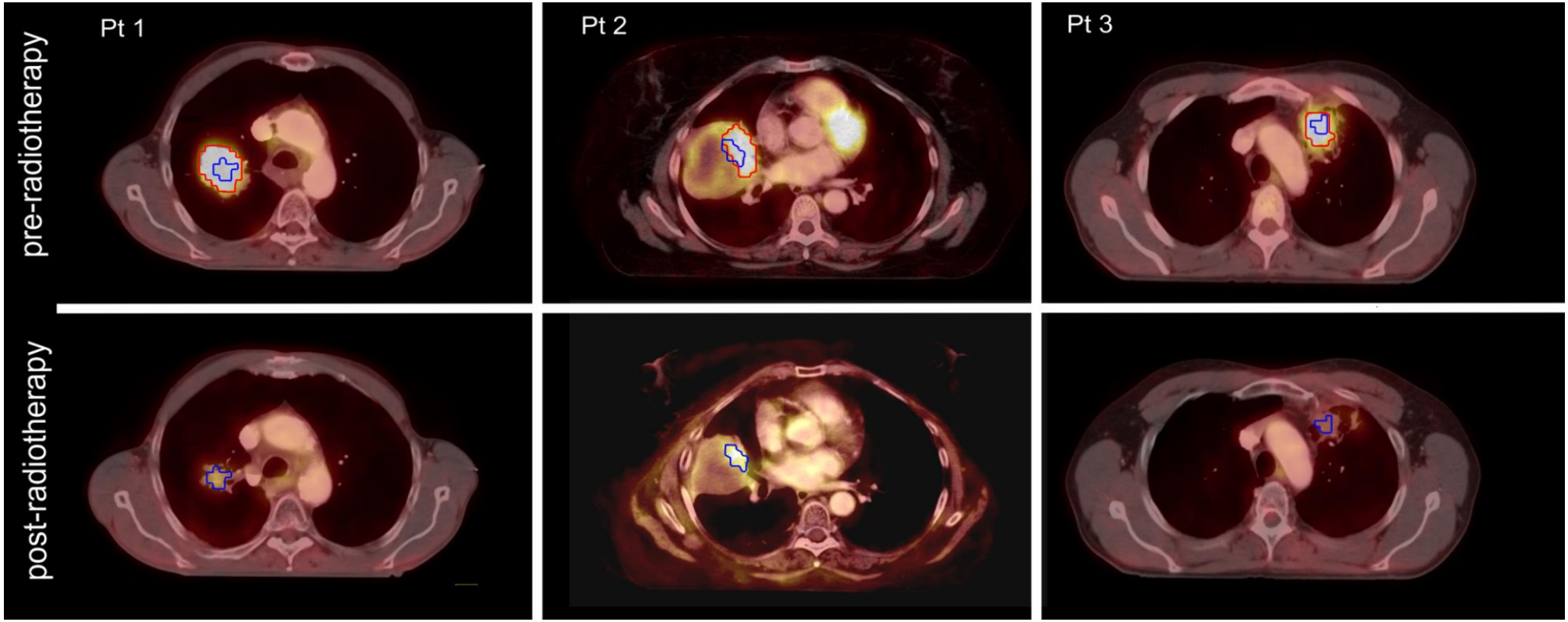


$$\text{overlap fraction} = \frac{\text{overlapping area}}{\text{smallest volume}}$$

Aerts et al. Int J Radiat Oncol Biol Phys 2008;71:1402-1407

Question 2: identify (chemo)-radiation areas within the tumor on the basis of the pre-treatment FDG-PET-CT scan.

Representative FDG-PET-CT images



Aerts et al. Radiother Oncol 2009

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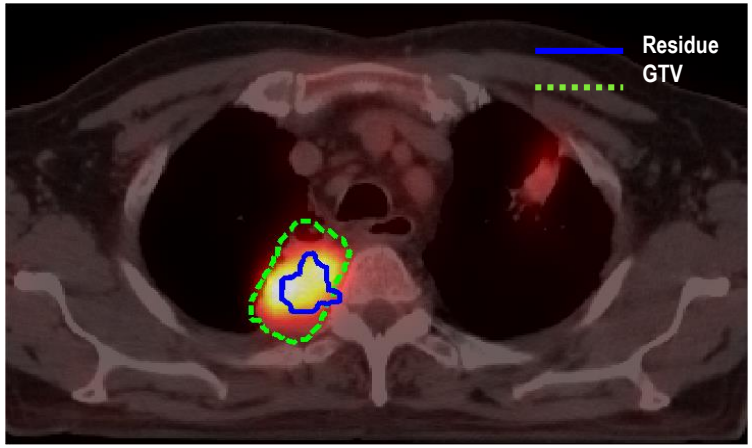
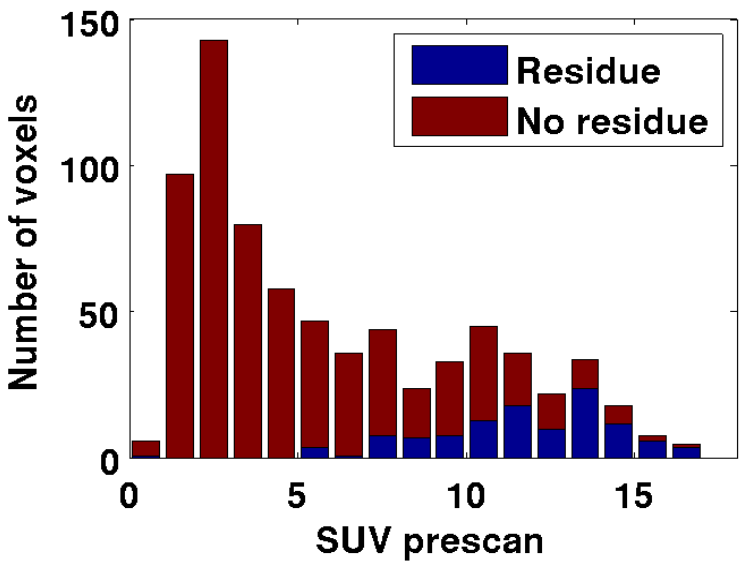
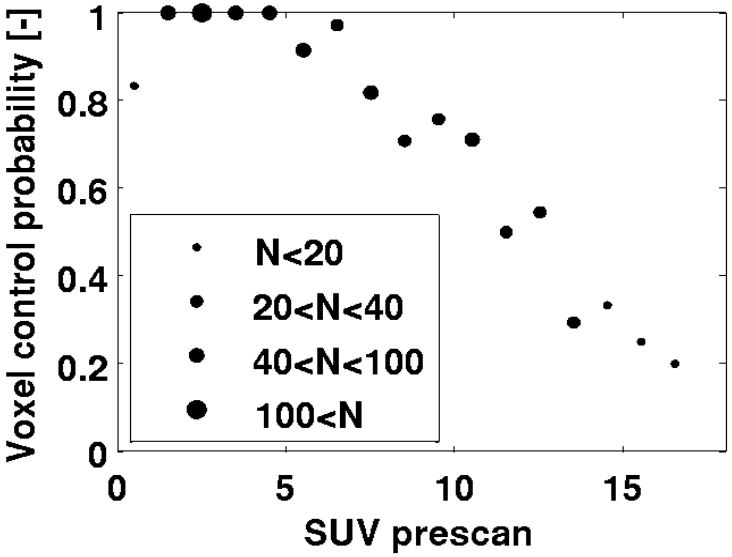
Question 3: Can we quantify the relation between tracer uptake and the “Voxel Control Probability”?

Residue: All voxels with
$SUV > SUV_{aortic\ arch}$
at day 90

Register pre and post CT scan







Petit et al. Radiother Oncol 2009

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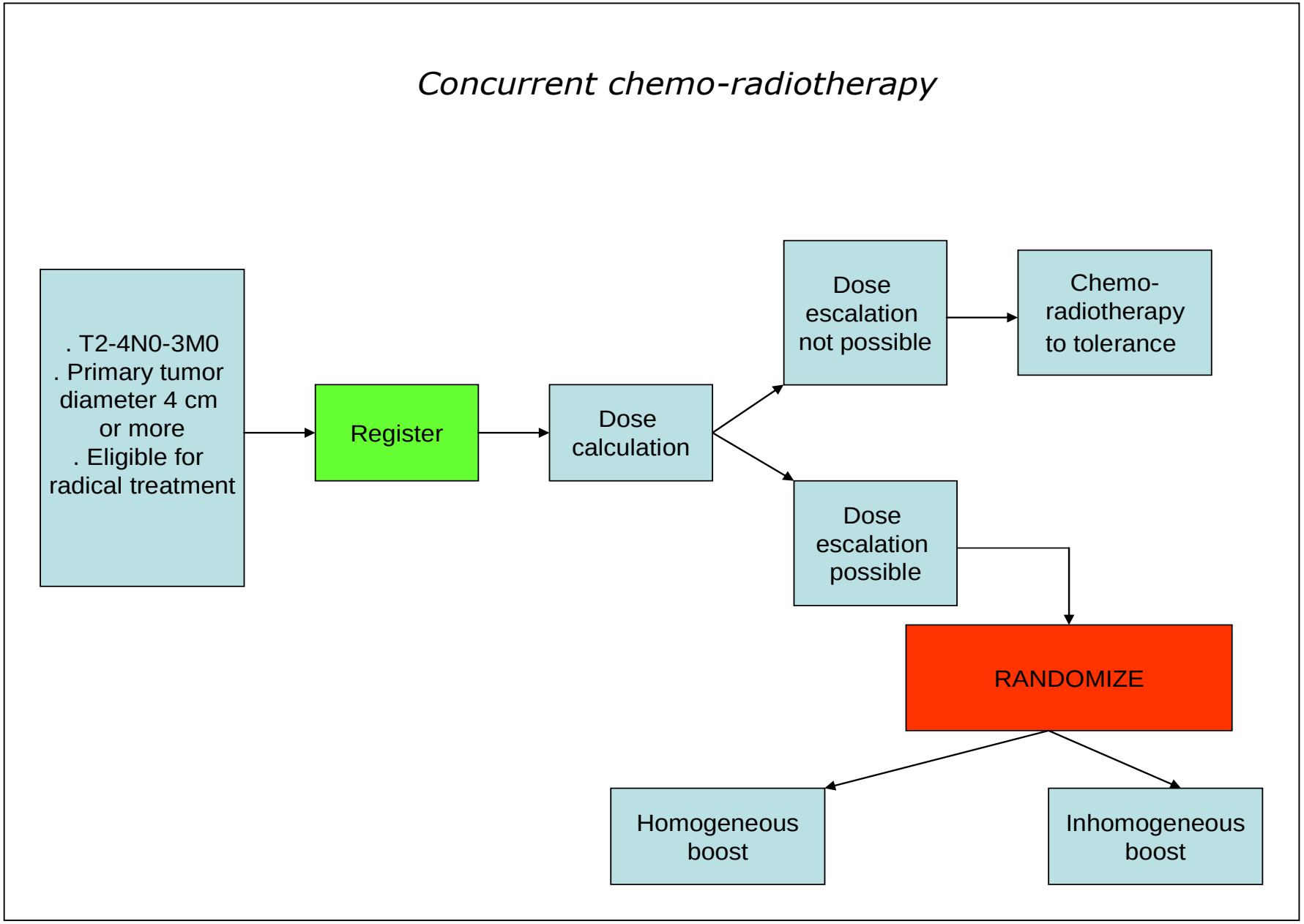
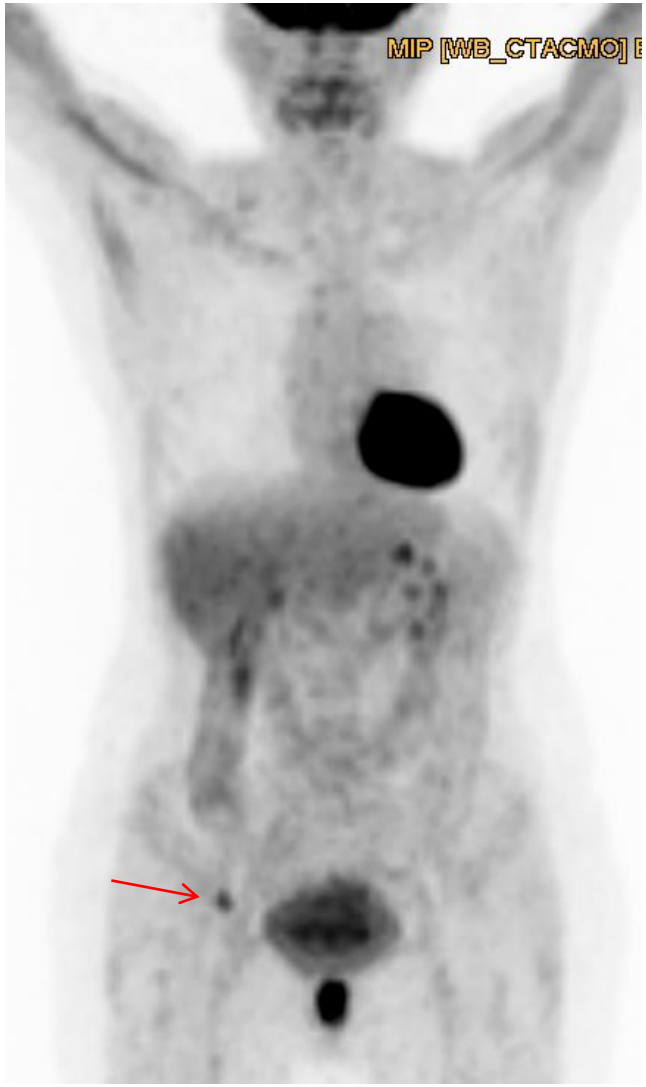
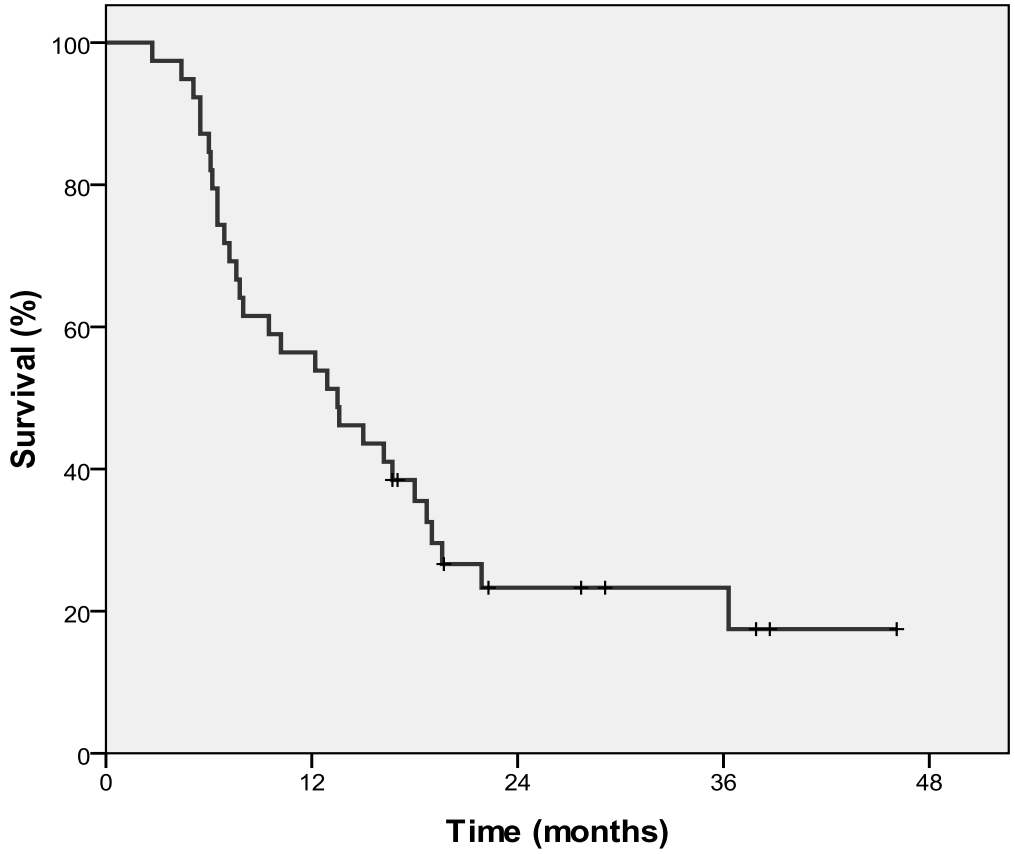
Result: BTV-boost trial



PET/CT based assessment of tumor load: New chance for oligometastatic patients?





n=39, UICC IV, RCT + adj CHT + RT M1

D. DeRuysscher, JTO 2012

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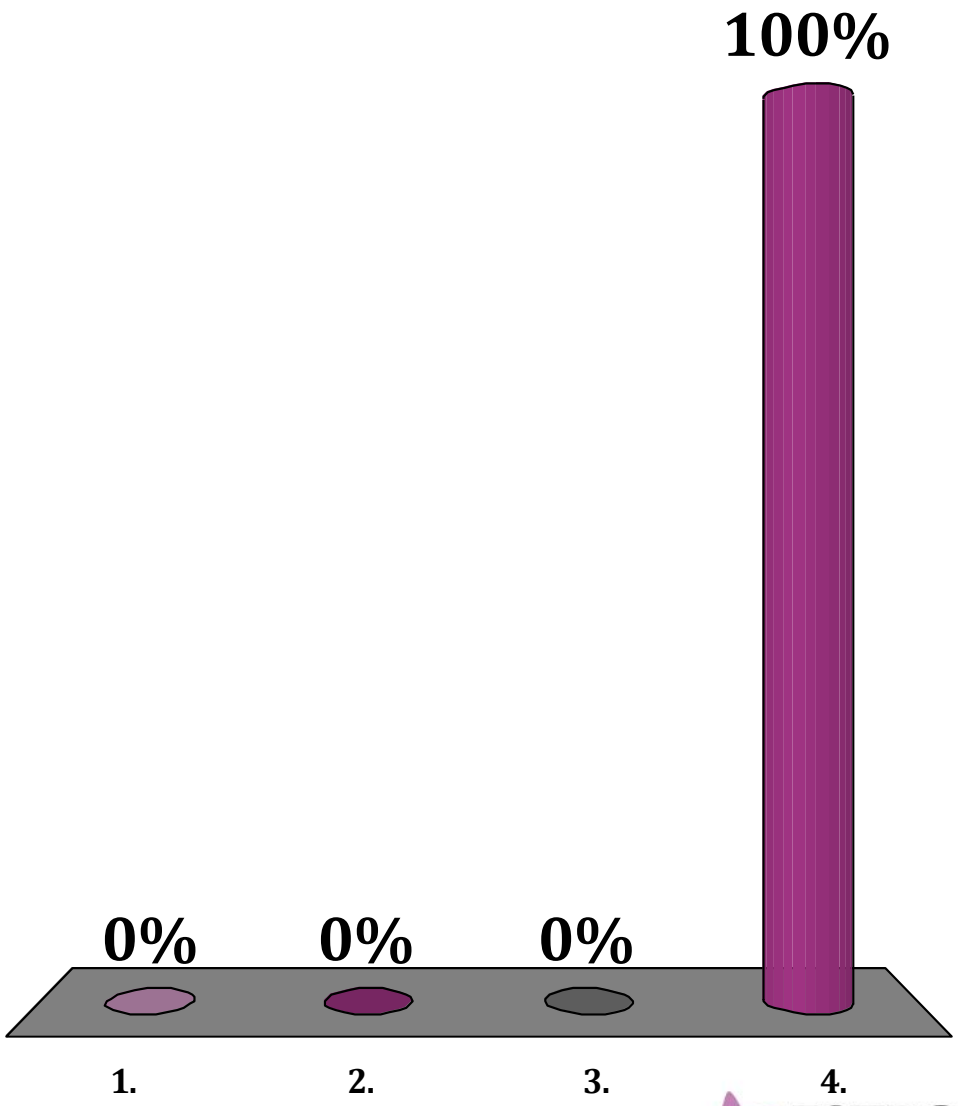
Which is the right answer?

1. Lung cancer ist a domain for MRI
2. FDG-PET/CT has a low diagnostic accuracy for lung cancer
3. With FDG-PET based GTVs, CTV concepts are not necessary anymore
4. There is no right answer



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NSCLC: Summary

Evidence from the literature on PET for RTP:

- **feasible with small residual risk for out-field recurrences**
- **technical problems to be solved**
- **clinical studies needed to demonstrate patients' benefit**

PET as a surrogate end point for treatment efficacy

- **demonstrated under chemotherapy**
- **possible after radiotherapy**

PET for follow-up of radiation treatment

- **bears potential for adaptive RT and early assessment of response**

PET tracers beyond FDG

- **Hypoxia imaging and imaging of proliferation possible**
- **Use for RT planning to be determined**

ESNM/ESTRO COURSE
MOLECULAR IMAGING & RADIATION ONCOLOGY
10-13 APRIL BORDEAUX

MRI of Rectal Cancer

Professor Vicky Goh
Division of Imaging Sciences & Biomedical Engineering, Kings College London
Department of Radiology, Guy's & St Thomas' NHS Trust
London, UK

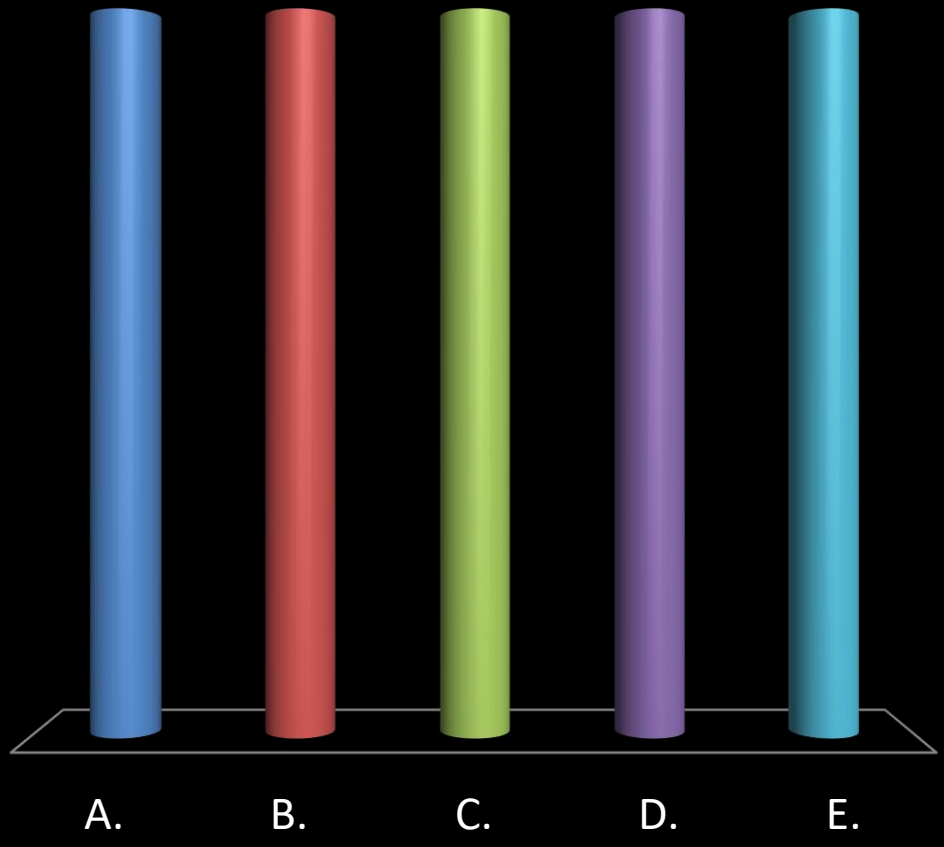
Email: vicky.goh@kcl.ac.uk

Learning Objectives

- To understand the advantages of MRI for imaging rectal cancer
  - Staging
  - Resectability
  - Pre-operative response assessment

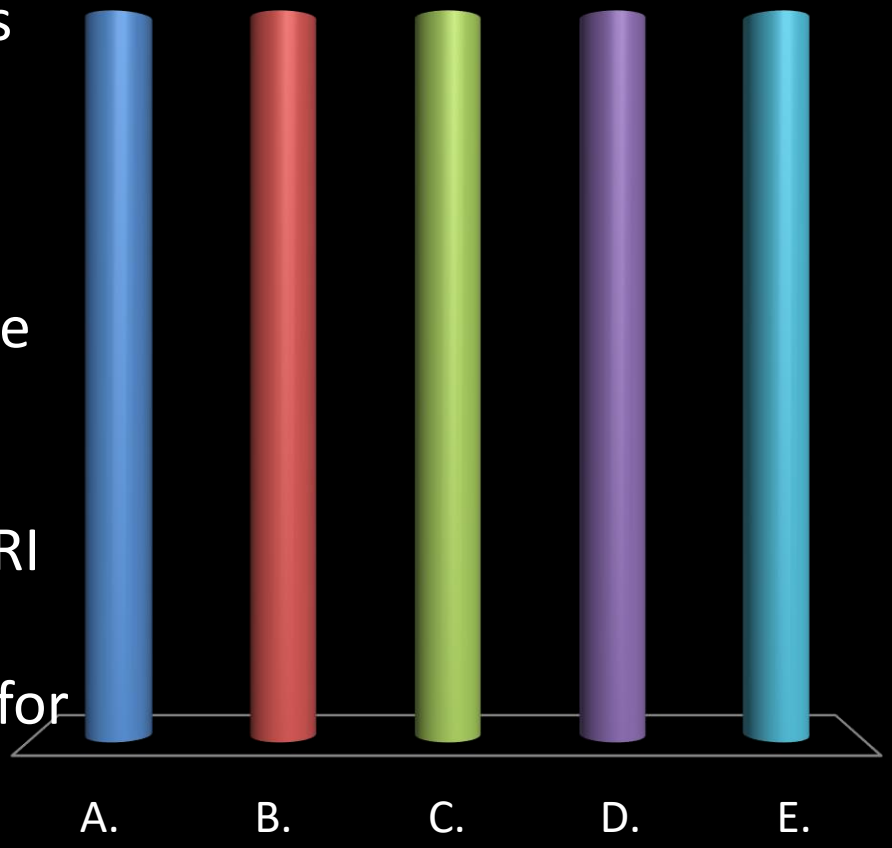
Test: Where are we?

A. Bordeaux
B. London
C. Paris
D. Rome
E. Amsterdam



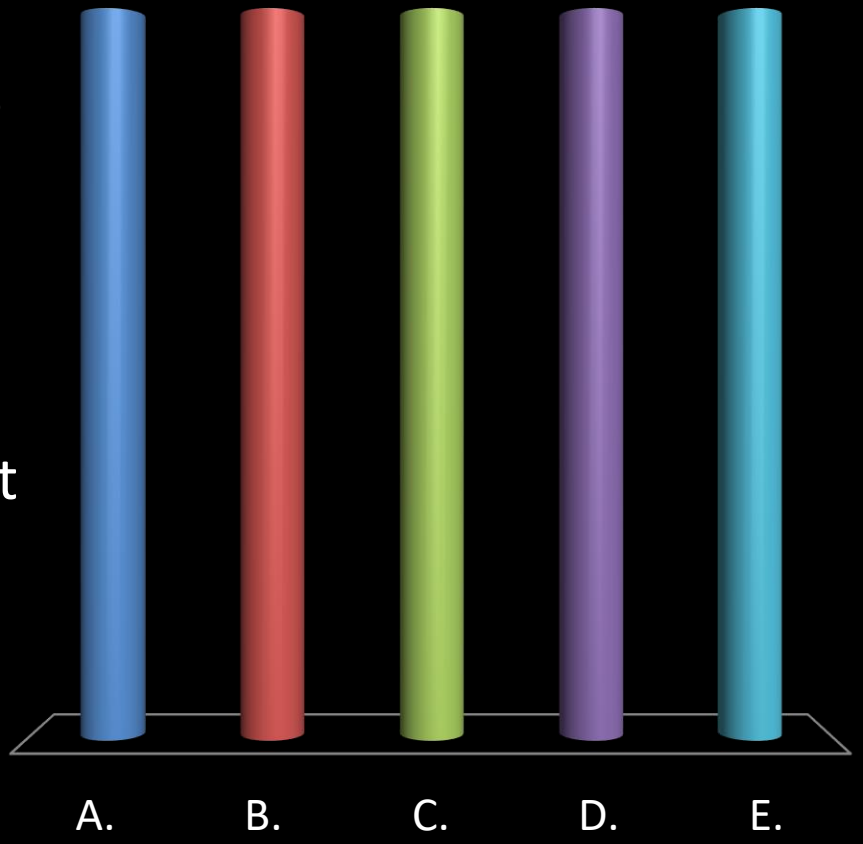
With respect to the following regarding MRI of rectal cancer, which is correct?

A. T2-W MRI has high sensitivity & specificity for nodal metastases
B. MRI is superior to PET/CT for radiotherapy planning
C. MRI has high accuracy for delineating the tumour distance from the potential resection margin
D. Dynamic contrast enhanced MRI is essential for staging
E. PET/MRI is better than PET/CT for staging

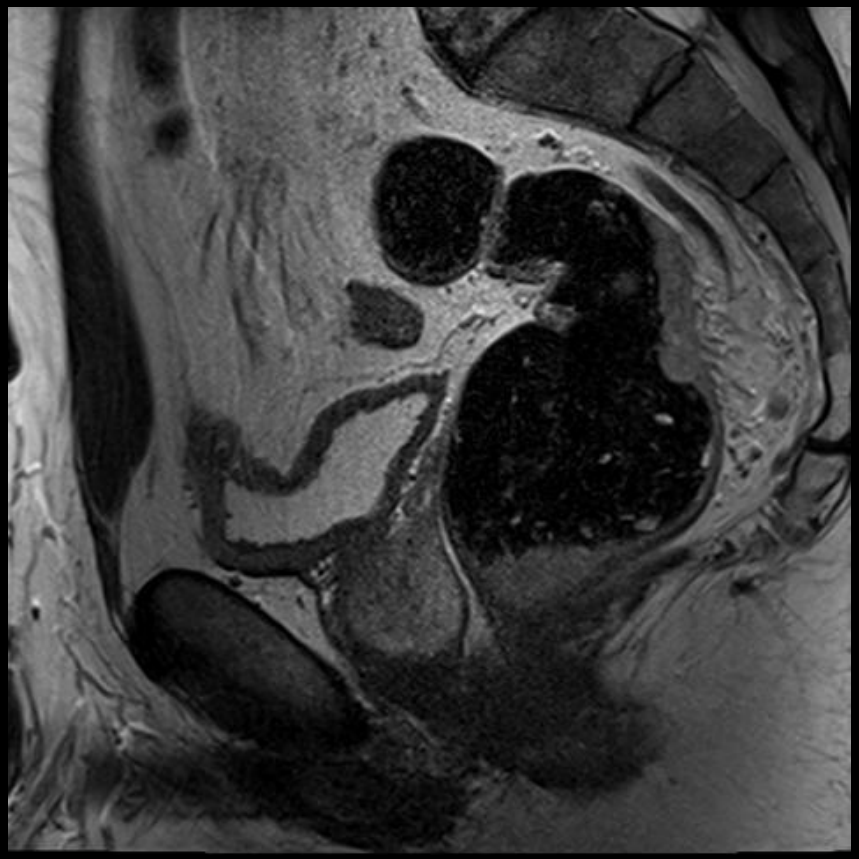


With respect to the following regarding MRI of rectal cancer, which is correct?

A. MRI tumour regression grading (TRG) has prognostic value
B. MRI TRG 4 is a good response to therapy
C. The presence of rectal wall diffusion signal is indicative of residual tumour
D. Colonoscopic confirmation is not required if MRI indicates complete response
E. Fibrosis demonstrates high T2 signal



Imaging Rectal Cancer



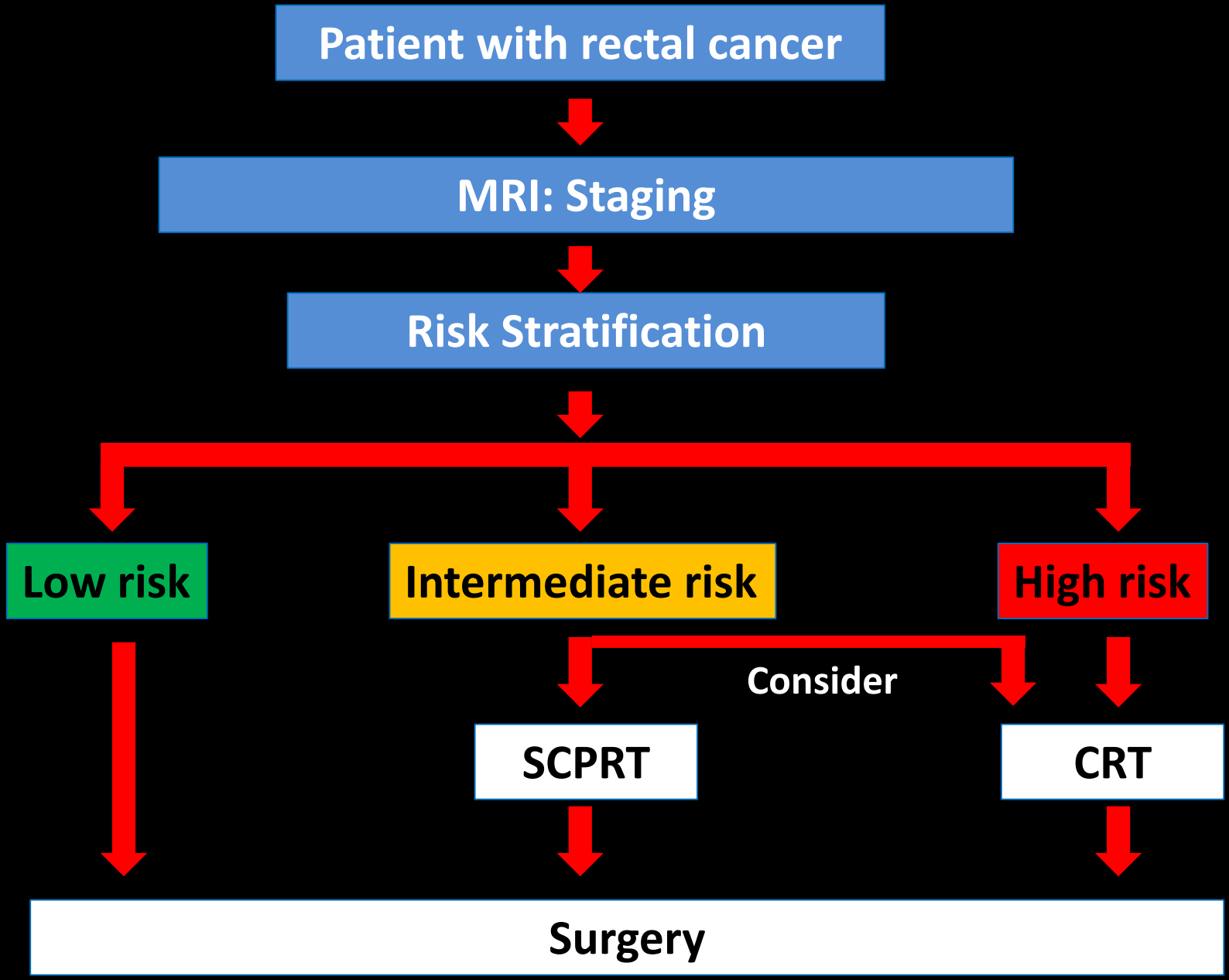
MRI: Standard of Care

- Staging & treatment planning
- Response assessment

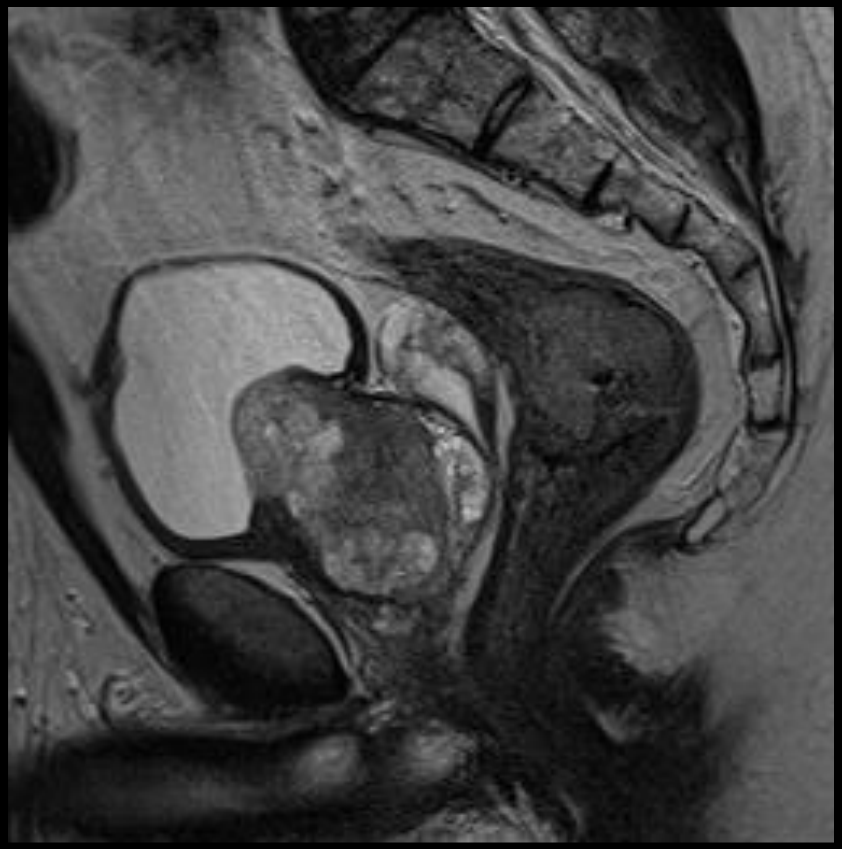
ESGAR Consensus. Beets-Tan et al. Eur Radiol. 2013; 23: 2522-31
EURECA-CC2 . Valentini et al. Radiother Oncol. 2009;92:148-63

KING'S College LONDON

KING'S HEALTH PARTNERS


Patient with rectal cancer
MRI: Staging
Risk Stratification
Low risk
Intermediate risk
High risk
Consider
SCPRT
CRT
Surgery

MRI Evaluation



Systematic review and meta-analysis:
N=21 studies

Parameter	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	DOR (95% CI)
T category	87 (81–92)	75 (68–80)	20.4 (11.1–37.3)
Lymph node involvement	77 (69–84)	71 (59–81)	8.3 (4.6–14.7)
CRM involvement	77 (57–90)	94 (88–97)	56.1 (15.3–205.8)

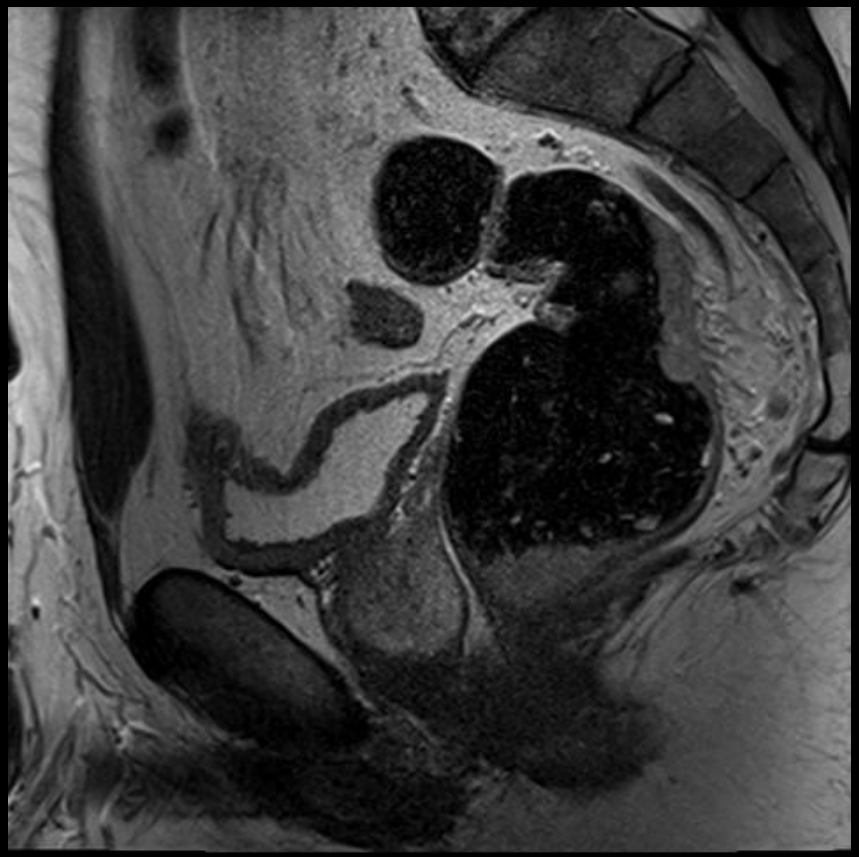
CI confidence interval, *CRM* circumferential resection margin, *DOR* diagnostic odds ratio

$$DOR = \frac{\frac{TP}{FN}}{\frac{FP}{TN}}$$

Higher value = better test performance

DOR: Ratio of the odds of positivity in disease relative to the odds of positivity in non-diseased

Imaging Rectal Cancer



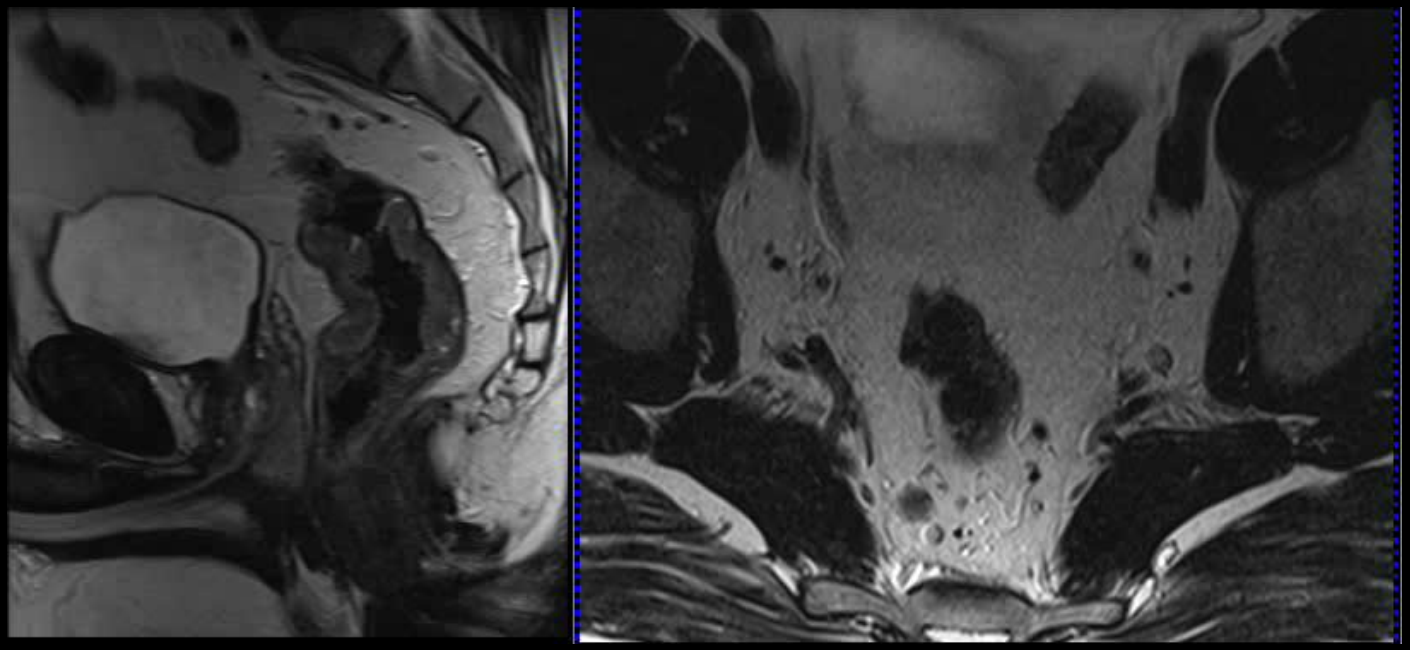
Advantages of MRI:

- Excellent tissue contrast
- Good spatial resolution
- Multiplanar imaging
- Anatomical & physiological imaging
- No radiation burden

Impact of MRI

Source	Patients	No	CRM +ve rate
Leeds cohort 1986-1997	All rectal cancers	561	27%
Dutch TME trial 1996-2000	Mobile rectal cancers	180	22%
MERCURY trial 2002-2003	All rectal cancers	428	16%

Tumour Appearances & Local Extent



MRI demonstrates:

- Primary tumour extent
- Relationship to potential resection margin
- Vascular invasion
- Locoregional lymph nodes

MRI Acquisition

Anatomical:

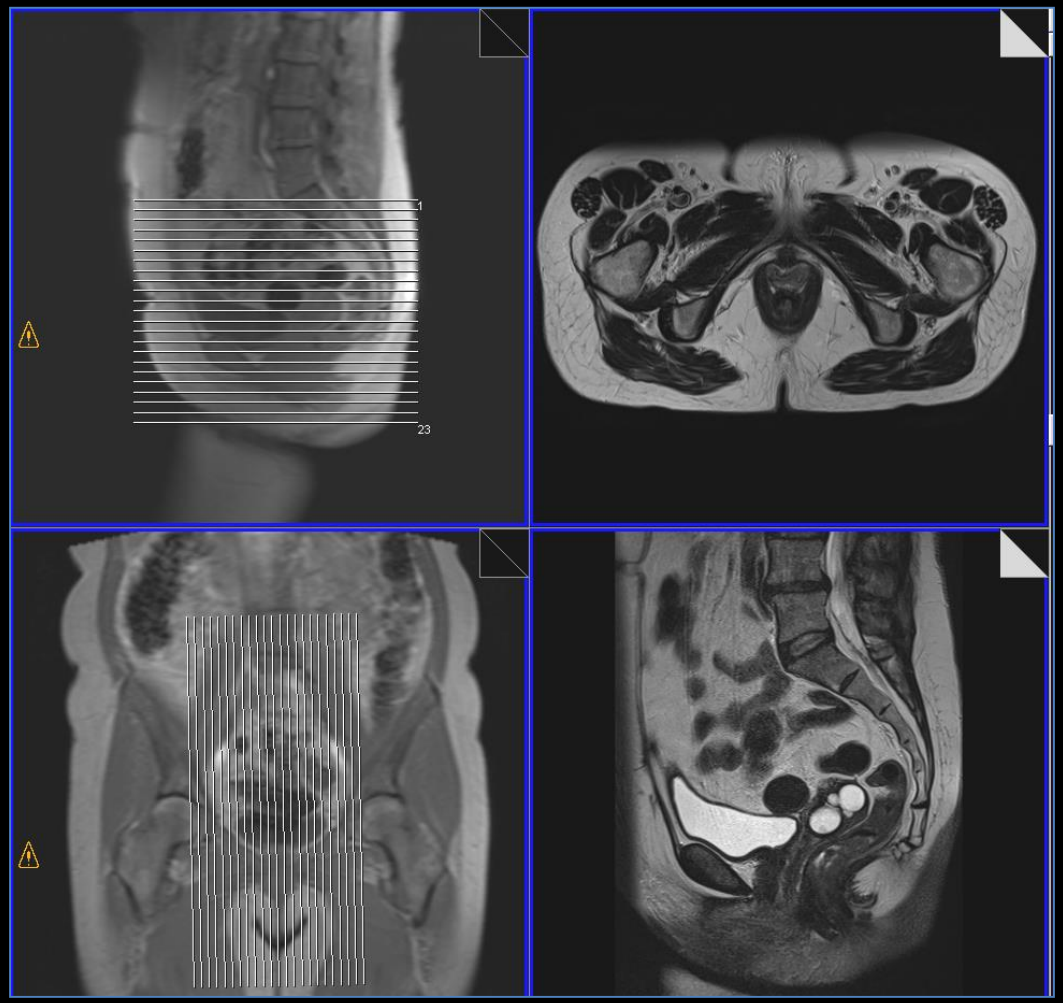
1.5 or 3-Tesla

Region	Sequence
Pelvis	T1 TSE axial
	T2 TSE axial
Tumour	T2 TSE sagittal
	T2 TSE coronal oblique*
	T2 TSE axial oblique*

*Parallel & perpendicular to tumour long axis

Patient preparation:

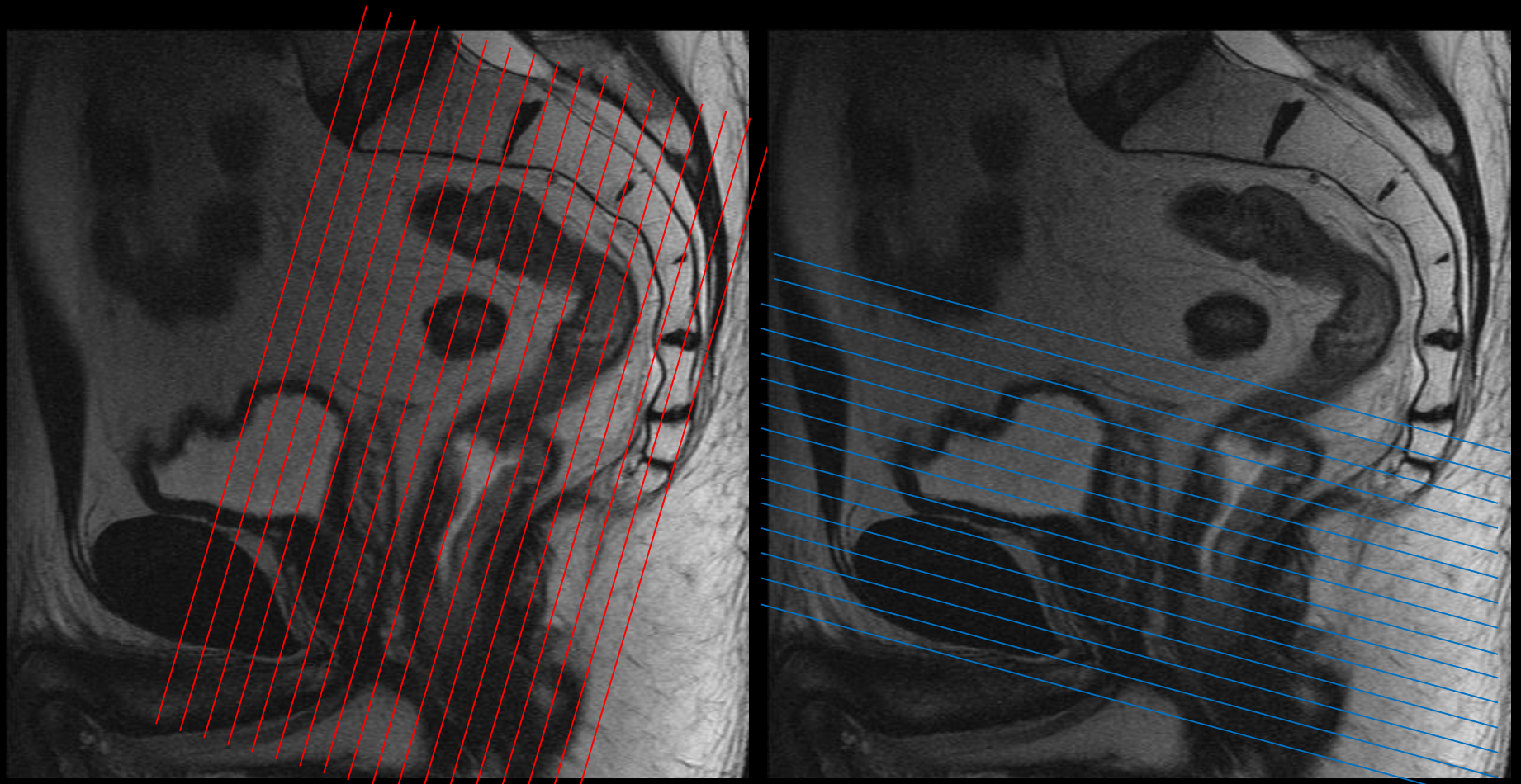
- No prior bowel preparation
- No rectal distension
- Emptying the bladder prior to MRI & anti-peristaltic (Buscopan IM) may improve imaging by reducing artefact



- Phased surface array coils centred for good SNR at anorectal junction
- Anatomical coverage: Sacral promontary to below symphysis pubis

T2 Coronal

T2 Axial

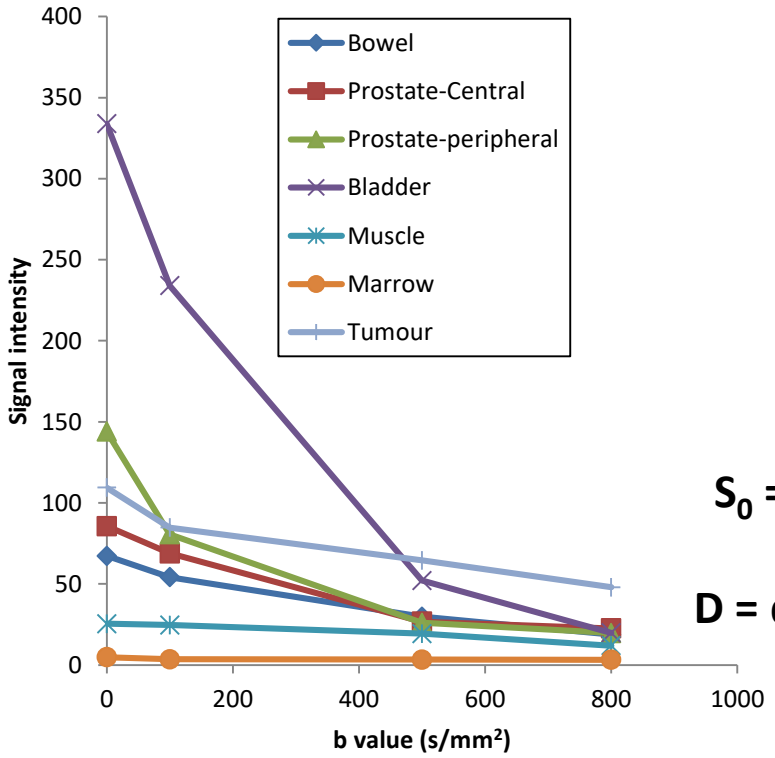


Acquisition Planes: Parallel & Perpendicular to Tumour

Anatomical Sequences

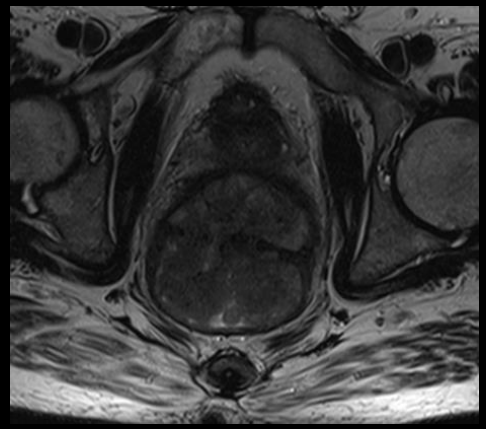
Sequence	TR	TE	NEX	FOV	Matrix	ST (mm)	IPAT	BW
T1 axial TSE	450-600	15-20	1	350	512*282	6	-	90
T2 axial TSE	4000-6500	140-180	1	350	512*282	6	-	195
T2 sagittal TSE	4000-6500	140-180	1	200	384*239	4	-	195
T2 axial oblique TSE	4000-6500	140-180	1	200	512*278	3	-	195
T2 coronal oblique TSE	4000-6500	140-180	1	200	512*414	4	-	195

Sequence	TR	TE	NEX	FOV	Matrix	ST (mm)	IPAT	BW
Diffusion Weighted SS-EPI SPAIR	5000-6000	65-80	>4	260	256*256	4-6	2	2200
	Pelvis: b=0, 1200 s/mm^2 Rectum: b=0, 100, 500, 800 s/mm^2							

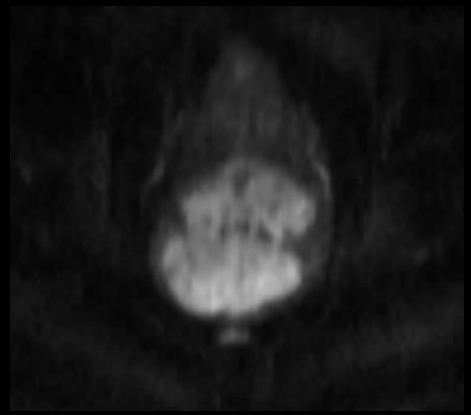


$$\frac{S}{S_0} = e^{-bD}$$

S = DW signal
S_0 = signal without DW
b=diffusion factor
D = diffusion coefficient



T2



DWI b800

MRI Assessment

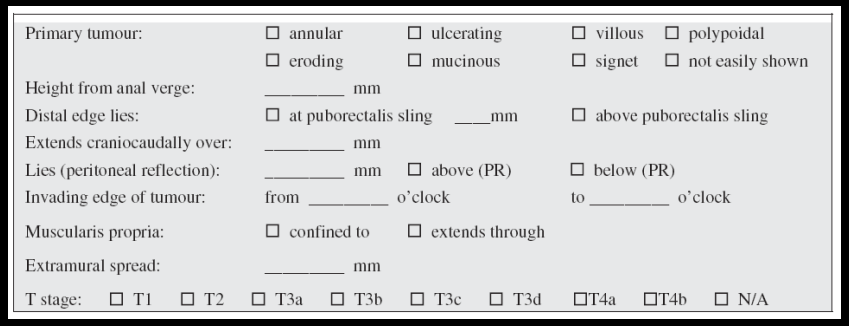
Systematic approach to MRI assessment:

Have you checked your DISTANCE ?

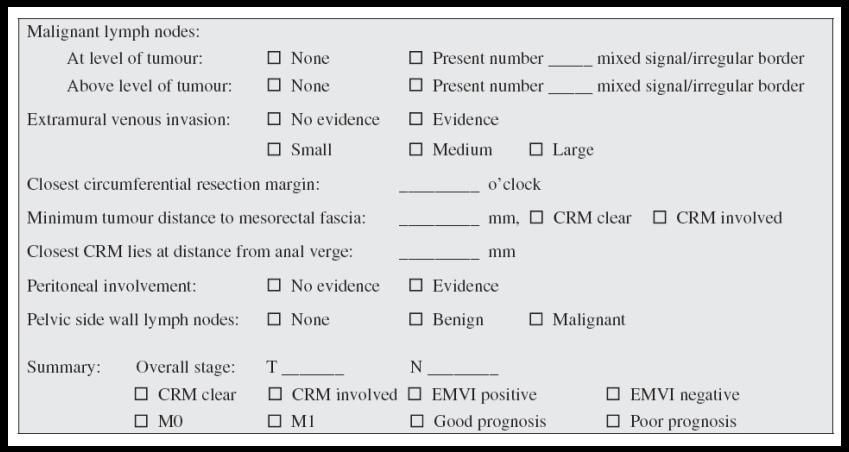
- Dis: Distance from inferior part of tumour to transitional skin
- T: T staging
- A: Anal complex
- N: Nodal Staging
- C: Circumferential resection margin
- E: Extramural vascular invasion

Nougaret et al. Radiology 2013; 268:330-44.

Proforma Reporting



Primary tumour:	☐ annular	☐ ulcerating	☐ villous	☐ polypoidal
	☐ eroding	☐ mucinous	☐ signet	☐ not easily shown
Height from anal verge:	_____ mm			
Distal edge lies:	☐ at puborectalis sling	___mm	☐ above puborectalis sling	
Extends craniocaudally over:	_____ mm			
Lies (peritoneal reflection):	_____ mm	☐ above (PR)	☐ below (PR)	
Invading edge of tumour:	from _____ o'clock		to _____ o'clock	
Muscularis propria:	☐ confined to	☐ extends through		
Extramural spread:	_____ mm			
T stage:	☐ T1 ☐ T2 ☐ T3a ☐ T3b ☐ T3c ☐ T3d ☐T4a ☐T4b ☐ N/A			



Malignant lymph nodes:				
At level of tumour:	☐ None	☐ Present number ____ mixed signal/irregular border		
Above level of tumour:	☐ None	☐ Present number ____ mixed signal/irregular border		
Extramural venous invasion:	☐ No evidence	☐ Evidence		
	☐ Small	☐ Medium	☐ Large	
Closest circumferential resection margin:	_____ o'clock			
Minimum tumour distance to mesorectal fascia:	_____ mm,	☐ CRM clear	☐ CRM involved	
Closest CRM lies at distance from anal verge:	_____ mm			
Peritoneal involvement:	☐ No evidence	☐ Evidence		
Pelvic side wall lymph nodes:	☐ None	☐ Benign	☐ Malignant	
Summary: Overall stage:	T _____	N _____		
☐ CRM clear	☐ CRM involved	☐ EMVI positive	☐ EMVI negative	
☐ M0	☐ M1	☐ Good prognosis	☐ Poor prognosis	

Taylor FJ et al. Cancer Imaging 2010; Spec no A:S142-50. Taylor F et al. AJR Am J Roentgenol. 2008;191 (6):1827-35.

- Introduction of standardized reporting may improve report quality compared to free text:
  - Pre-operative risk assessment
  - Staging

Pedersen BG et al . Dis Colon Rectum 2011;54(3):328–334

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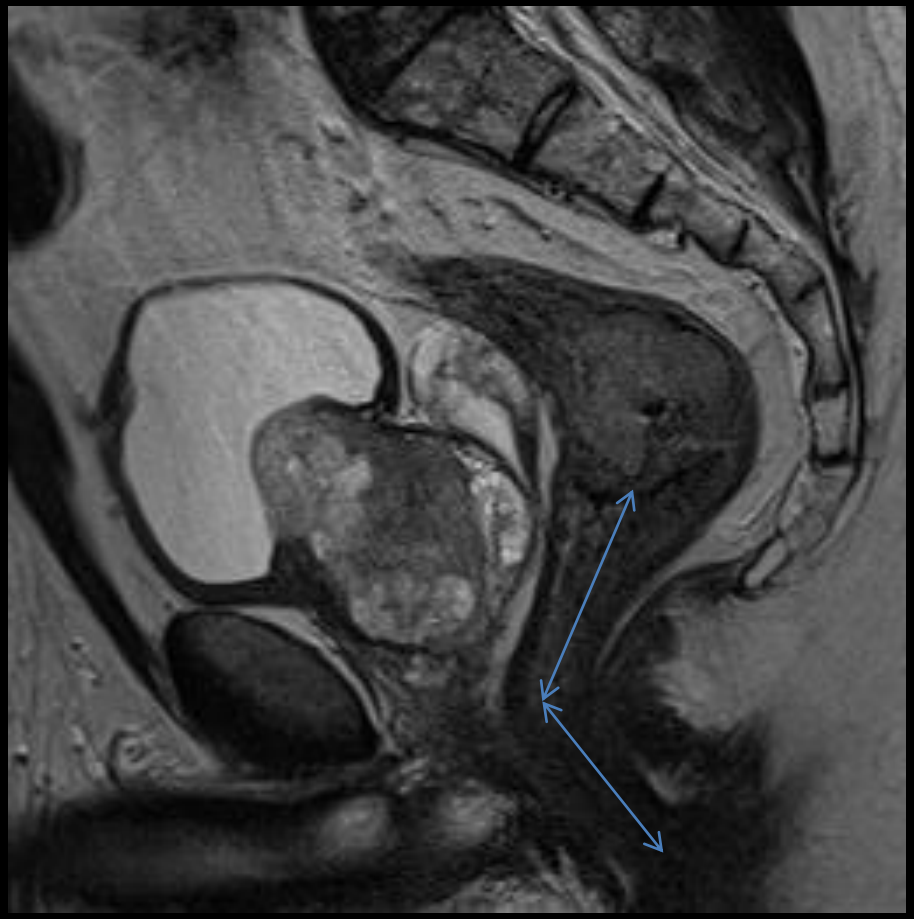
Tumour Site

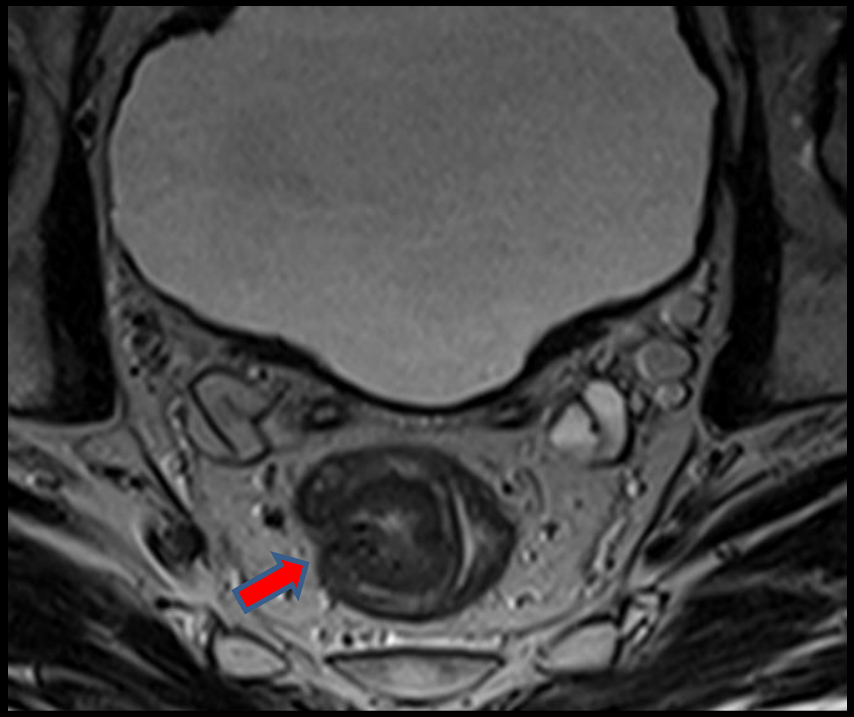


Distance of inferior margin from anal verge:

- Lower rectum: ≤5cm
- Mid rectum: 5-10cm
- Upper rectum: >10cm

Rectum: Runs from rectosigmoid junction (S2/S3) to ano-rectal junction

Tumour Morphology

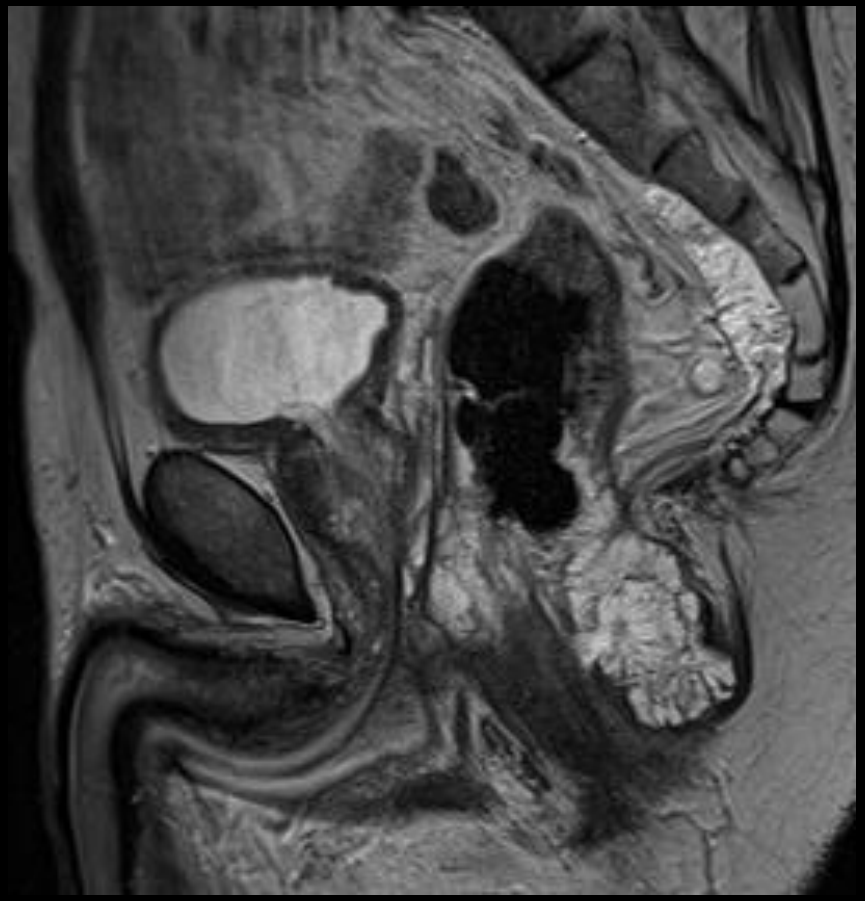


Polypoidal tumour:
Smaller invasive front extending through wall through stalk

Morphological characteristics:

- Annular
- Semi-annular
- Polypoidal
- Ulcerating
- Mucinous
- Invading edge
- Size

Tumour Morphology



- Intramural spread is rare with the exception of mucinous tumours
- If present, important consideration for superior – inferior resection margin

Madsen PM et al. Dis Colon Rectum 1986; 29:279-82.
Sidoni A et al. Tumori 1991; 77: 514-17

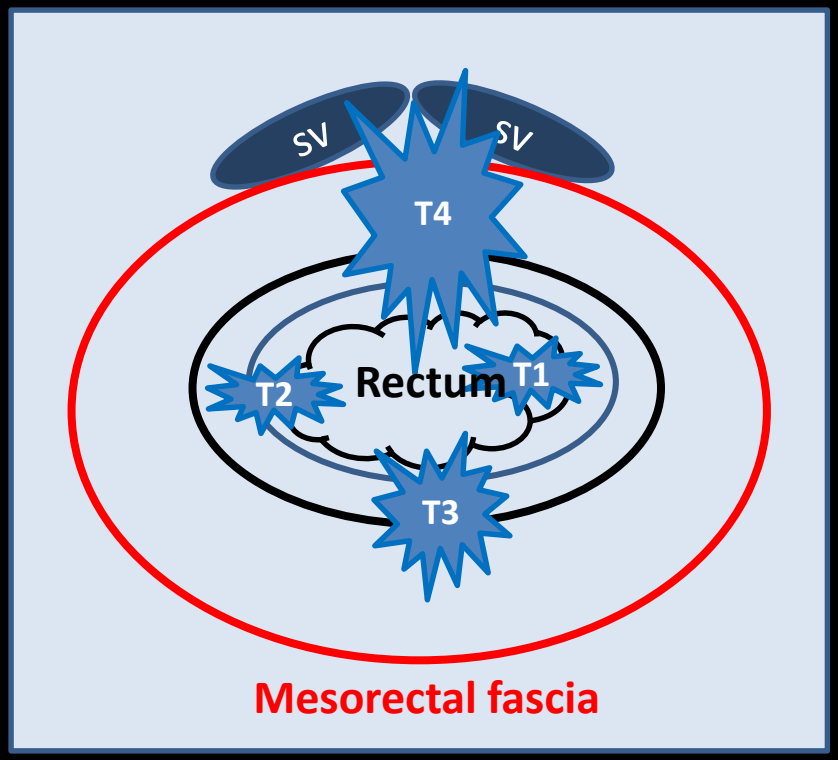
T Stage

T staging:

- T1: Extending to submucosa
- T2: Extending to muscularis propria
- T3: Extending beyond muscularis propria

  T3a <1mm T3b 1-5mm
  T3c 5-15mm T3d >15mm

- T4: a. Involvement of the visceral peritoneum
  b. Invasion of pelvic organs



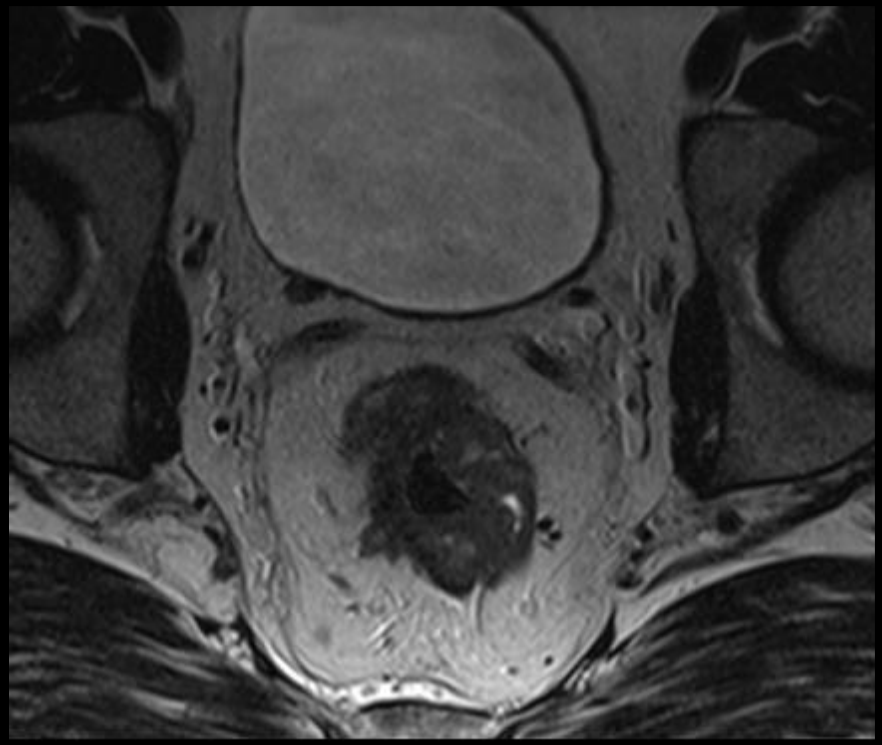
T Stage

Extension beyond MP:

- Independent risk factor for recurrence-free survival:
- HR: 2.186 (1.336-6.577)
- Recurrence-free survival rate:
  - T3a: 86%
  - T3b: 69%
  - T3c: 43%

Cho SH et al. AJR 2014; 202(6): 1238-44

T Stage: Example



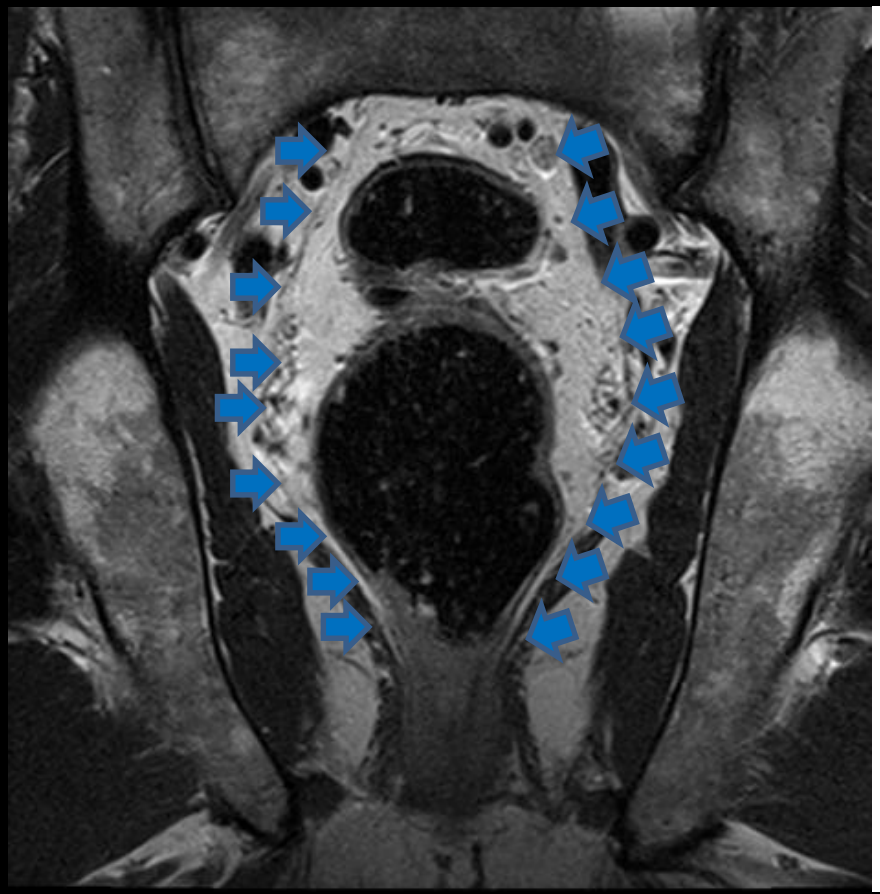
T staging:

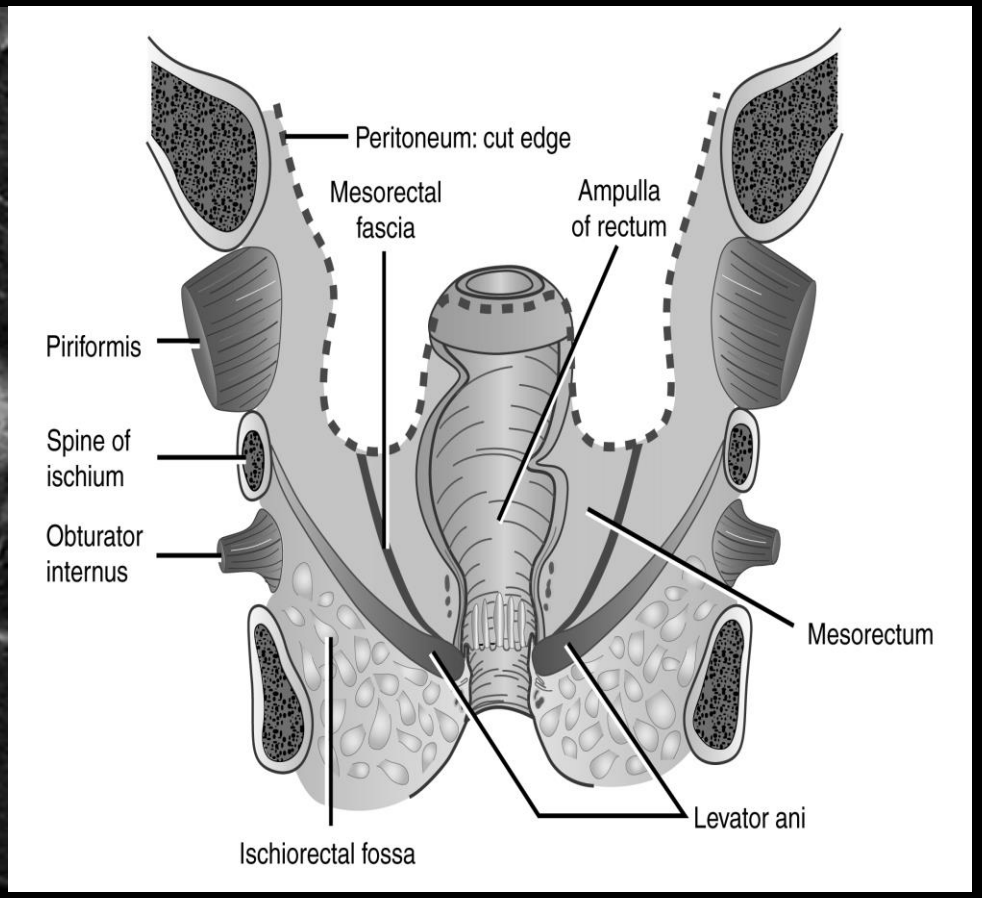
- T1: Extending to submucosa
- T2: Extending to muscularis propria
- **T3: Extending beyond muscularis propria**

  T3c 5-15mm

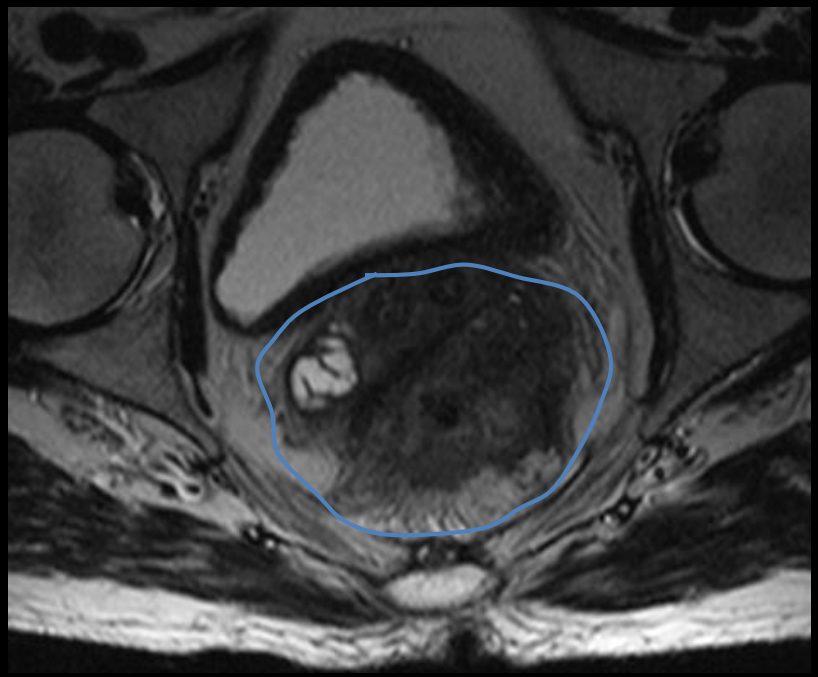
- T4: a. Involvement of the visceral peritoneum
  b. Invasion of pelvic organs

Relationship to Circumferential Resection Margin





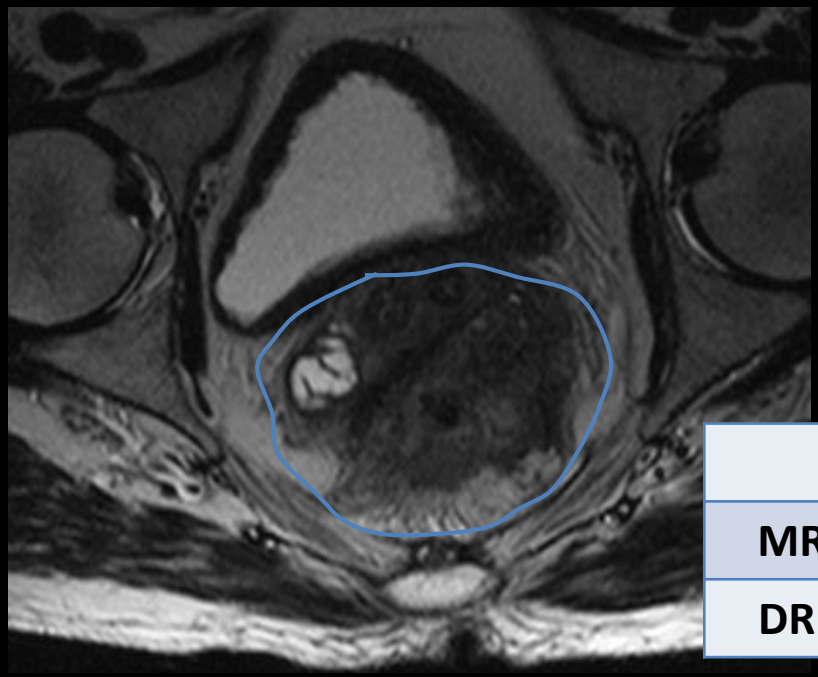
Relationship to Circumferential Resection Margin



- MRI-defined MRF corresponds to CRM*
- Distance to MRF predicts CRM involvement
  - ≥5mm distance good predictor of at least 1mm histological margin+
  - < 1mm cutoff : potentially involved margin++

*Bissett IP et al. Dis Colon Rectum 2001; 44: 259-65; + Beets-Tan RG et al. Lancet 2001; 357: 497-504; ++ Mercury study group. BMJ 2006; 333: 779.

Relationship to Circumferential Resection Margin

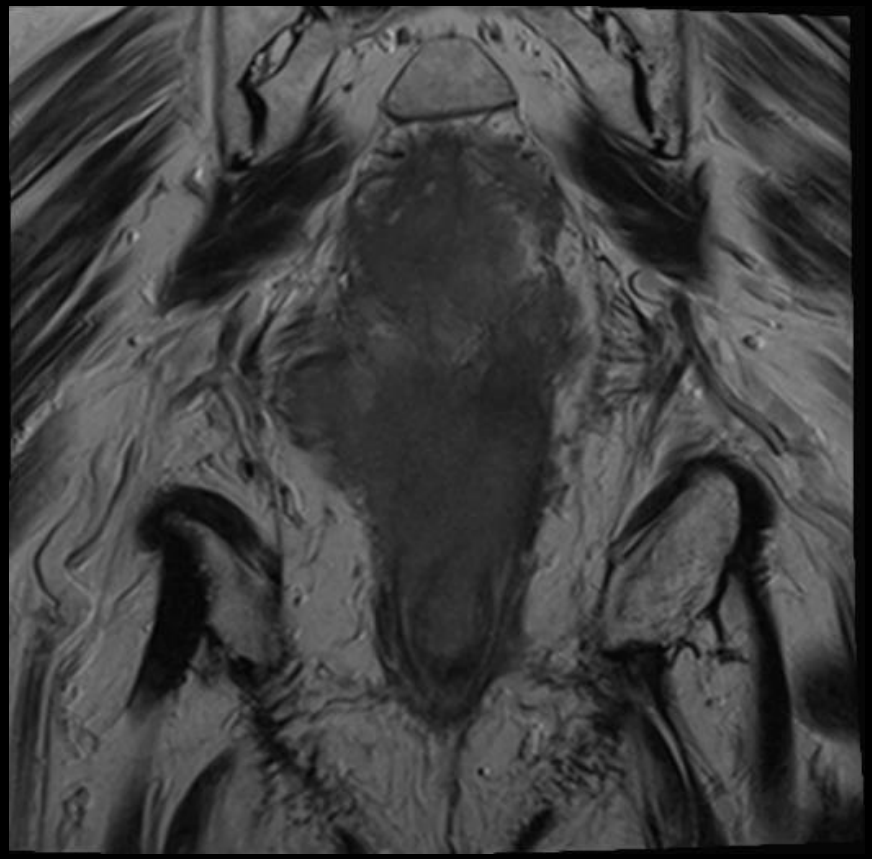


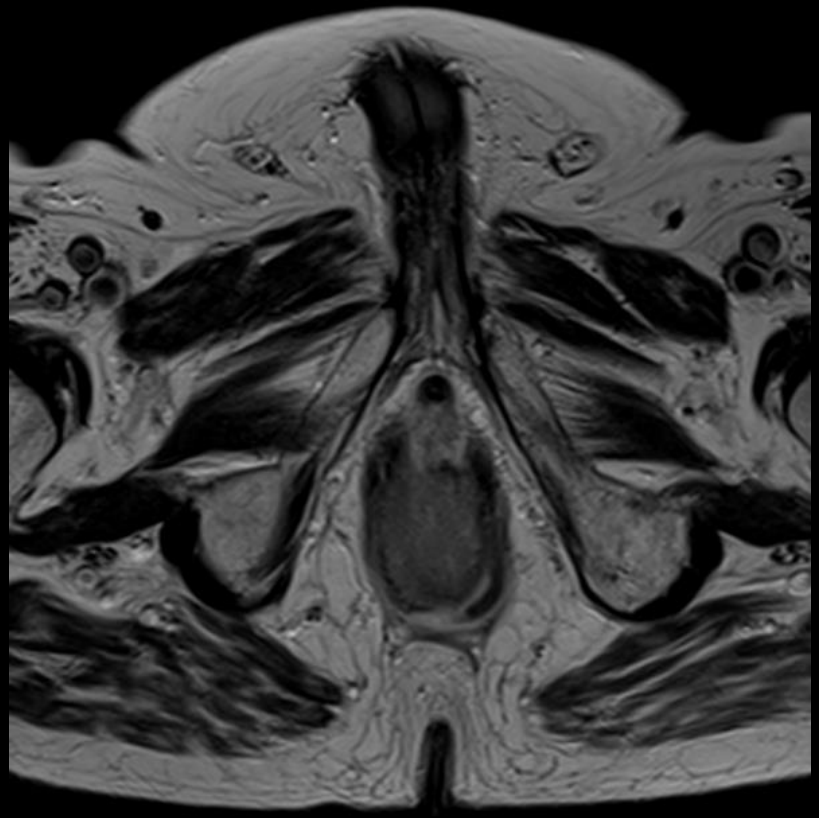
	Clear	Involved	Grand total
MRI prediction at circumferential resection margin:			
Clear	215	15	230
Involved	4	11	15
Grand total*	219	26	245
Digital rectal examination:			
Mobile	161	16	177
Fixed/tethered	58	10	68
Grand total†	219	26	245

	Sens	Spec	Acc	PPV	NPV
MRI	42	98	92	73	93
DRE	38	74	70	15	91

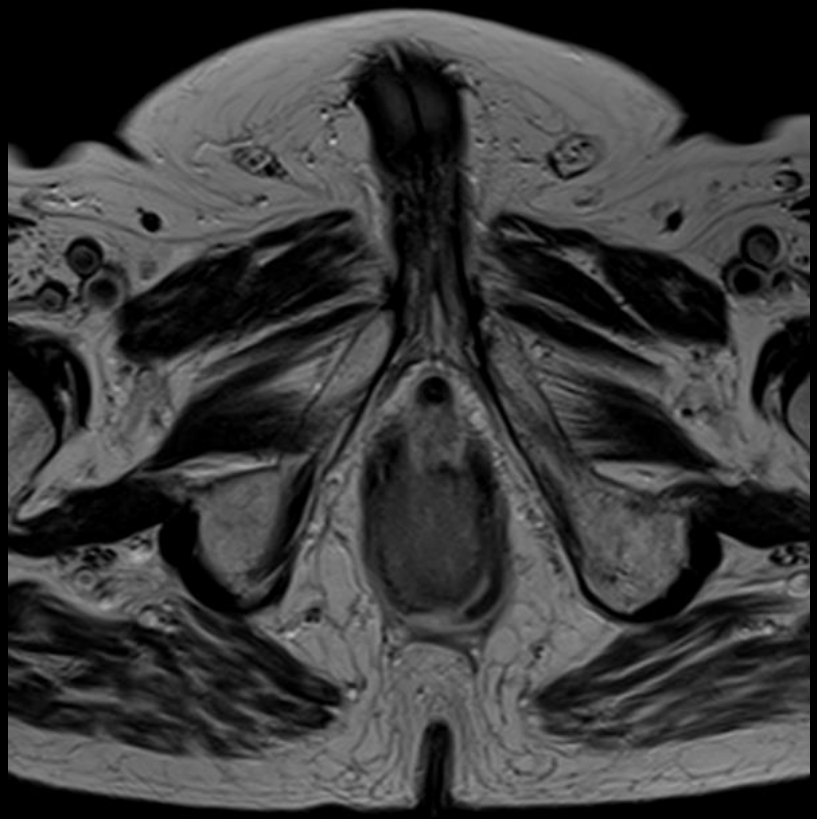
Mercury study group. BMJ 2006; 333: 779

Relationship to Anal Sphincter Complex: Low Rectal Cancers





Low Rectal Cancers



- **Low rectal cancer has higher CRM positivity rate with APER vs low AR with TME**
  - MERCURY: 33% vs 13%
  - Leeds: 36.5% vs 22.3%
  - MRC CLASICC: 21% vs 10%
  - Dutch TME: 30.4% vs 10.7%

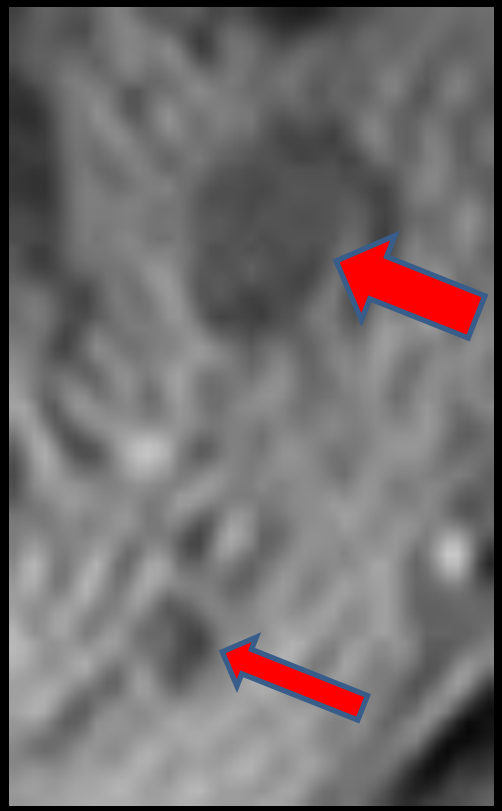
Shihab OC et al. Lancet Oncol 2009; 10: 1207-11; Ann Surg Oncol 2011; 18(12): 3278-84

Level	Tumour extension	Operative plane
1: Levator origin to top of puborectalis	Confined to muscle coat	LAR Intersphincteric APE
	Beyond muscle coat	LAR Intersphincteric APE
	Extending <1mm from levator/mesorectal fascia	Extra-levator APE
	Extending into/beyond levator	Extra-levator APE
2: Below puborectalis	Extending into submucosa/ muscularis propria well defined	LAR Intersphincteric APE
	Extending full thickness of muscularis propria	Extra-levator APE
	Extending into intersphincteric plane	Extra-levator APE
	Extending into external sphincter	Extra-levator APE
	Beyond external sphincter into schiorectal tissue	Pelvic exenteration

Nodal Assessment

Involvement based on:

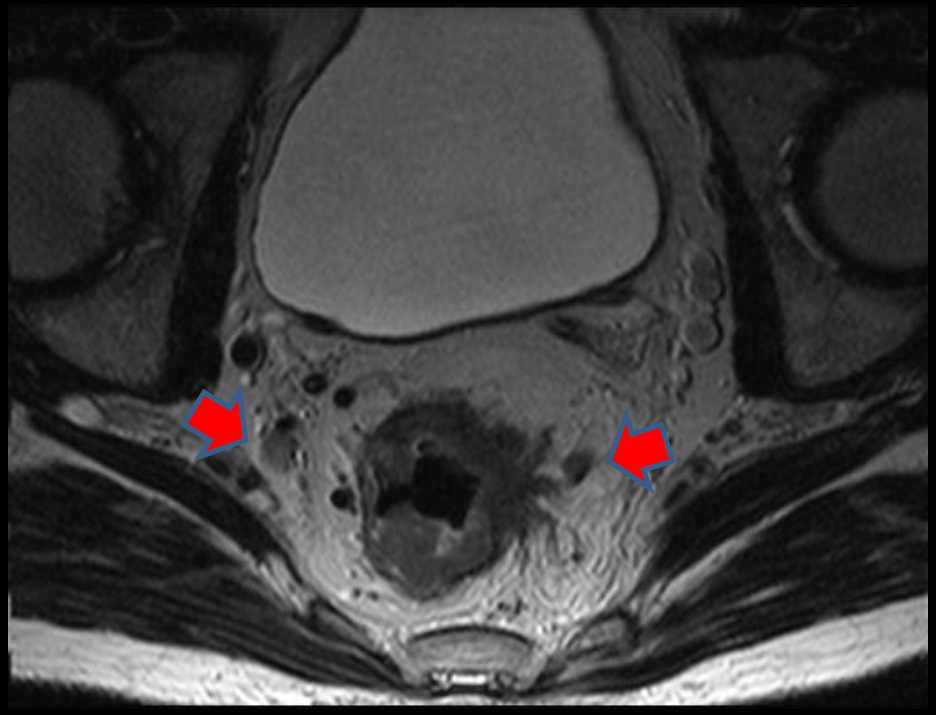
- **Size (short axis)**
  - Mesorectal ≥5mm:
    Sens 81%, Spec 68% (vs 3% & 100% for ≥10mm)
  - Internal iliac: ≥8mm
  - Other nodes ≥10mm
- **Morphology:**
  - Mixed signal characteristics
  - Irregular border
    Sensitivity 85%, Specificity 97%*



*Brown et al. Radiology 2003;227:371-377

Nodal Assessment

- **Regional lymph nodes:**
  - Mesorectal
    - 99% within 5cm proximal to tumour
    - 78% at level of tumour*
  - Sigmoid mesenteric
  - Inferior mesenteric
  - Lateral sacral, pre-sacral
  - Internal iliac
  - Superior, middle or inferior rectal

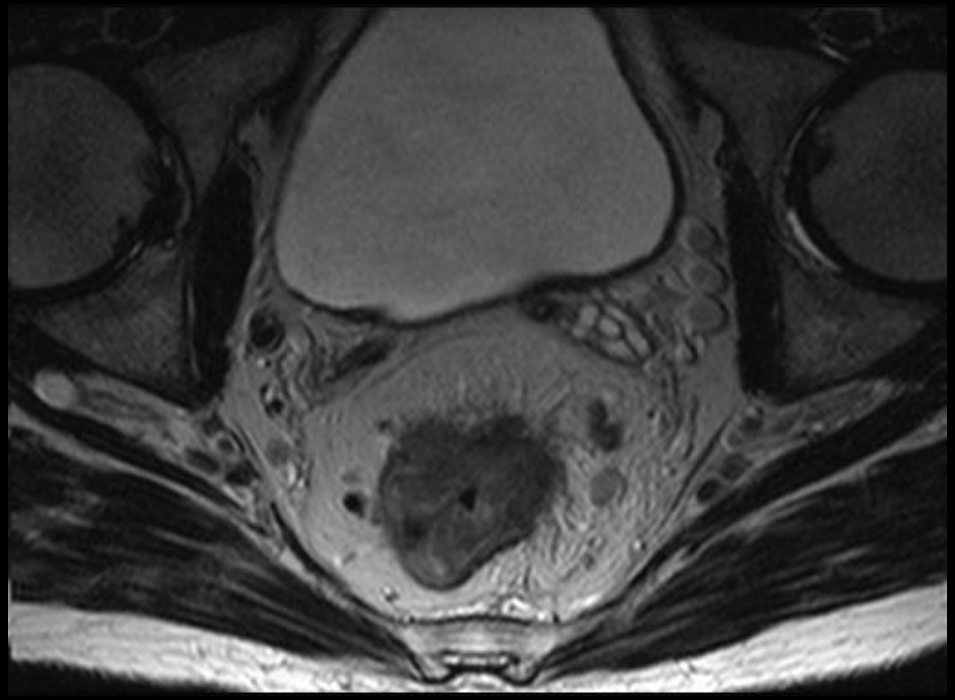


Right internal iliac node & mesorectal node

*Koh DM et al. Eur Radiol 2005; 1650-7

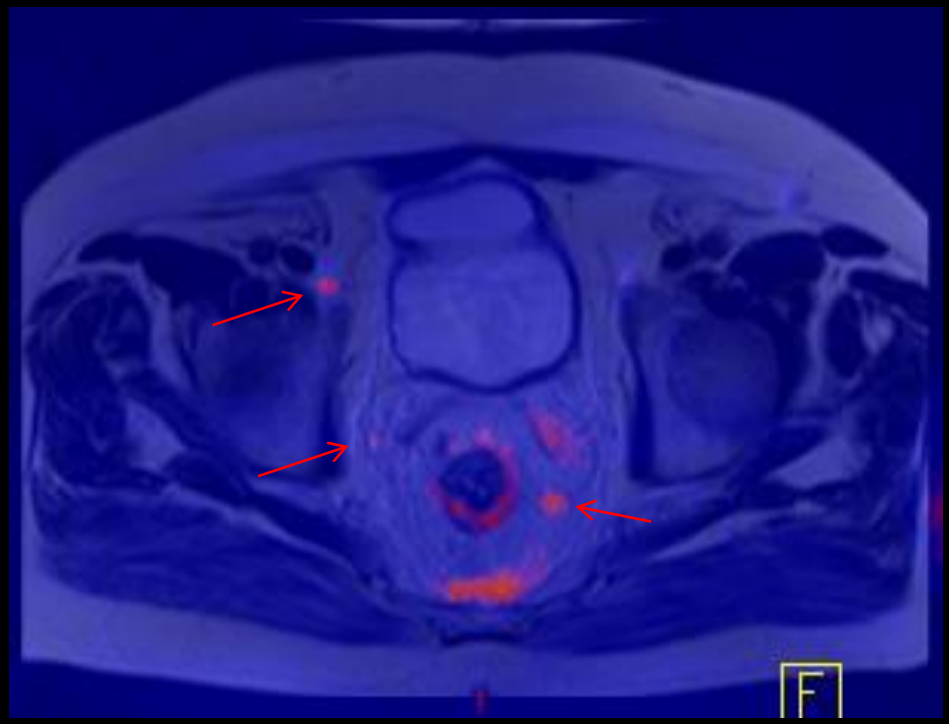
Nodal Assessment

- **Number of regional nodes**
  - N0: No nodes
  - N1: 1-3 regional nodes
    - N1a 1 node
    - N1b 2-3 nodes
    - N1c tumour deposit
  - N2: 4 or more nodes
    - N2a 4-6 nodes
    - N2b ≥7 nodes



N1a

Nodal Assessment: Additional Benefit of Diffusion-Weighted MRI ?



Lambregts DM et al. Eur Radiol 2011; 21 (2): 256-73;
Mir et al. J Med Imaging Radiat Oncol 2010; 54:358-64*

DWI improves nodal detection+

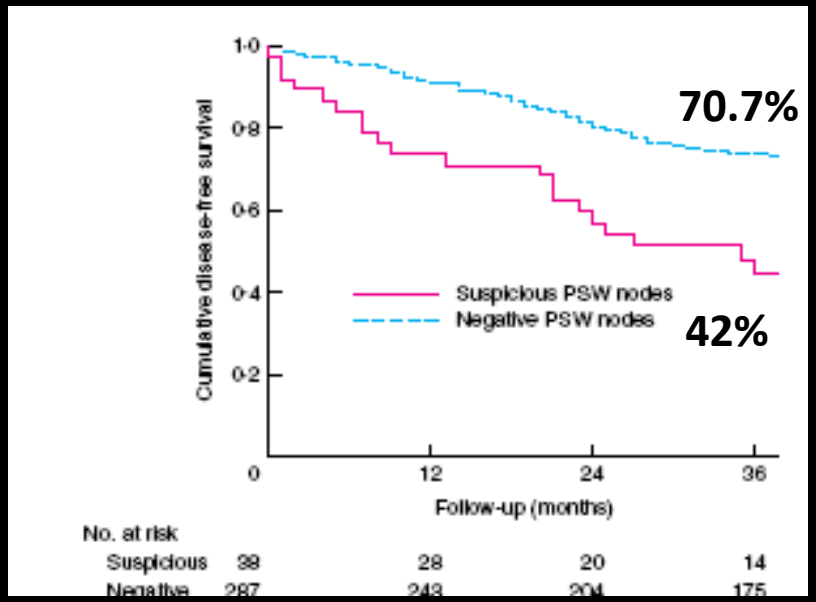
- **T2 vs DW-MRI$_{0, 500,1000}$**
  - 101 / 222 nodes on T2; median 4mm: 27 N+
  - **157/222 (71%) on DWI; median 3mm: 37 N+**
- **Fusion of T2 & high DWI improves nodal identification***
  - 47 additional nodes identified
  - 114 (T2) vs 161 (fused) nodes
- **Qualitative signal intensity not different between normal & metastatic nodes**

Can ADC differentiate malignant from benign nodes?

Author, Yr	Pts	B values	Nodes	Findings: ADC
Surgery alone				
Heijnen et al 2013	n=21	1.5T: 0,500,1000	Total: 212 Met: 16	NM: 1.04 ± 0.22; M: 1.15± 0.24 $X10^{-3}$ Cut off 1.07 $X10^{-3}$: Sn 67%, Sp 60%, PPV 18%, NPV 93%
Cho et al 2013	n=34	1.5T: 0,1000	Total: 114 Met: 46	NM: 1.1 ± 0.22; M: 0.9± 0.15 $X10^{-3}$ Cut off 1 $X10^{-3}$: Sn 78%, Sp 67%, PPV 61%, NPV 82%
Pre-operative chemoradiation therapy				
Lambregts et al 2011	n=30	1.5T: 0,500,1000	Total:222 Met: 34	NM: 1.19 ± 0.27; M: 1.43 ± 0.38 $X10^{-3}$ Cut off 1.25 $X10^{-3}$: Sn 53%, Sp 82%, PPV 35%, NPV 91%
Kim et al 2014	n=59	1.5T: 0,1000	Total: 115 Met: 29	NM: 1.13 ± 0.23; M: 1.36 ± 0.27 $X10^{-3}$ Cut off 1.25 $X10^{-3}$: Sn 66%, Sp 72%, PPV 46%, NPV 87%

Heijnen LA et al. Eur Radiol 2013; 23(12): 3354-60; Cho EY et al. Eur J Radiol 2013; 82 (11): 662-8; Lambregts DM et al. Eur Radiol 2011; 21 (12): 2567-74; Kim SH et al. Acta Radiol 2014; Nov 25 Epub

Relevance of Pelvic Side Wall Nodal Involvement



MERCURY study, n=325, 11.7% with MRI suspicious PSW nodes

- Lower DFS in patients with suspicious PSW nodes BUT
- Presence of suspicious nodes had no impact in patients undergoing pre-operative CRT
- Presence of suspicious PSW nodes not an independent prognostic variable

MERCURY study group. Br J Surg 2011; 98: 1798-804

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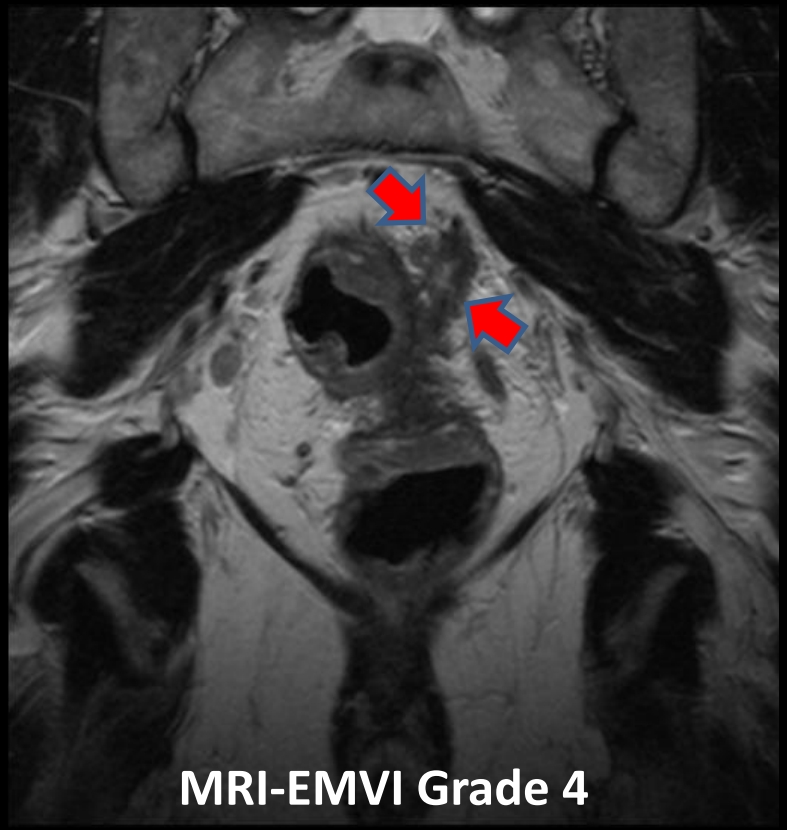
Vascular Invasion



Grade	Definition
0	Normal vessel calibre, No vessel adjacent to tumour penetration
1	Normal vessel calibre, No vessel adjacent to nodular tumour extension
2	Normal vessel calibre, Nodular tumour adjacent to vessel
3	Intermediate signal tumour within vessel; no expansion
4	Nodular vessel expansion by tumour

Smtih NJ et al. Br J Surg 2008; 95: 229-36; Smith NJ et al. AJR 2008; 191(5): 1517-22

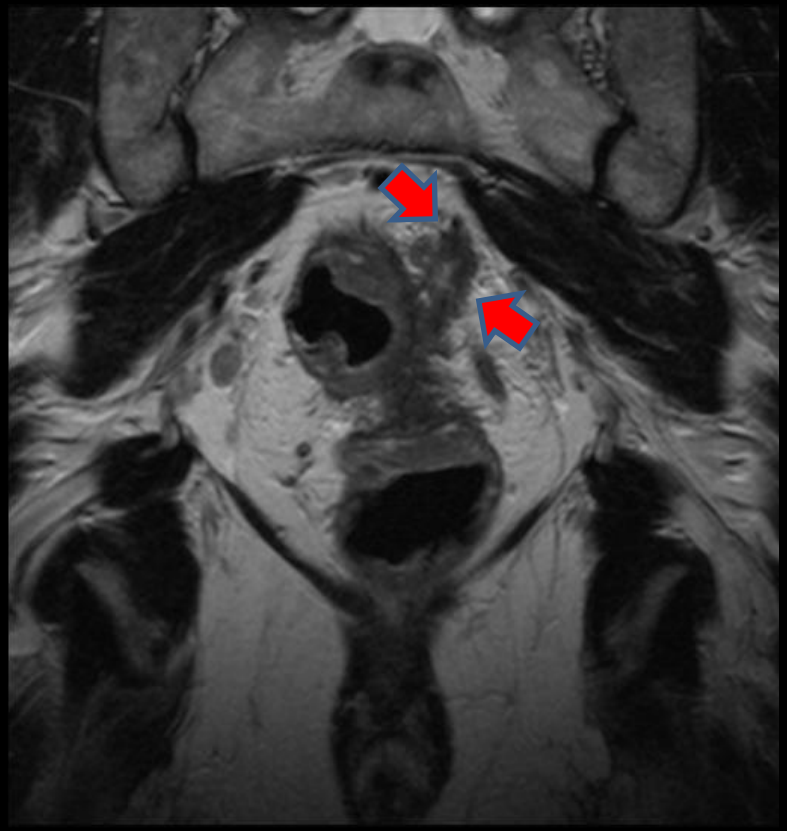
Vascular Invasion: Prognostic Significance

Author, Yr	Patients	Metastases	Findings
Sohn et al. 2014	447	79 (17.7%)	Positive EMVI: Independent risk factor for synchronous metastases (OR 3.02)
Bugg et al. 2014	202 53 EMVI +	24.5%	Positive EMVI: 3.7X increased relative risk for metachronous metastases

Sohn B et al. Eur Radiol 2014 {Dec 13 Epub}; Bugg WG et al. Clin Radiol 2014; 69: 619-23

Independent risk factor for synchronous & metachronous metastases

Vascular Invasion

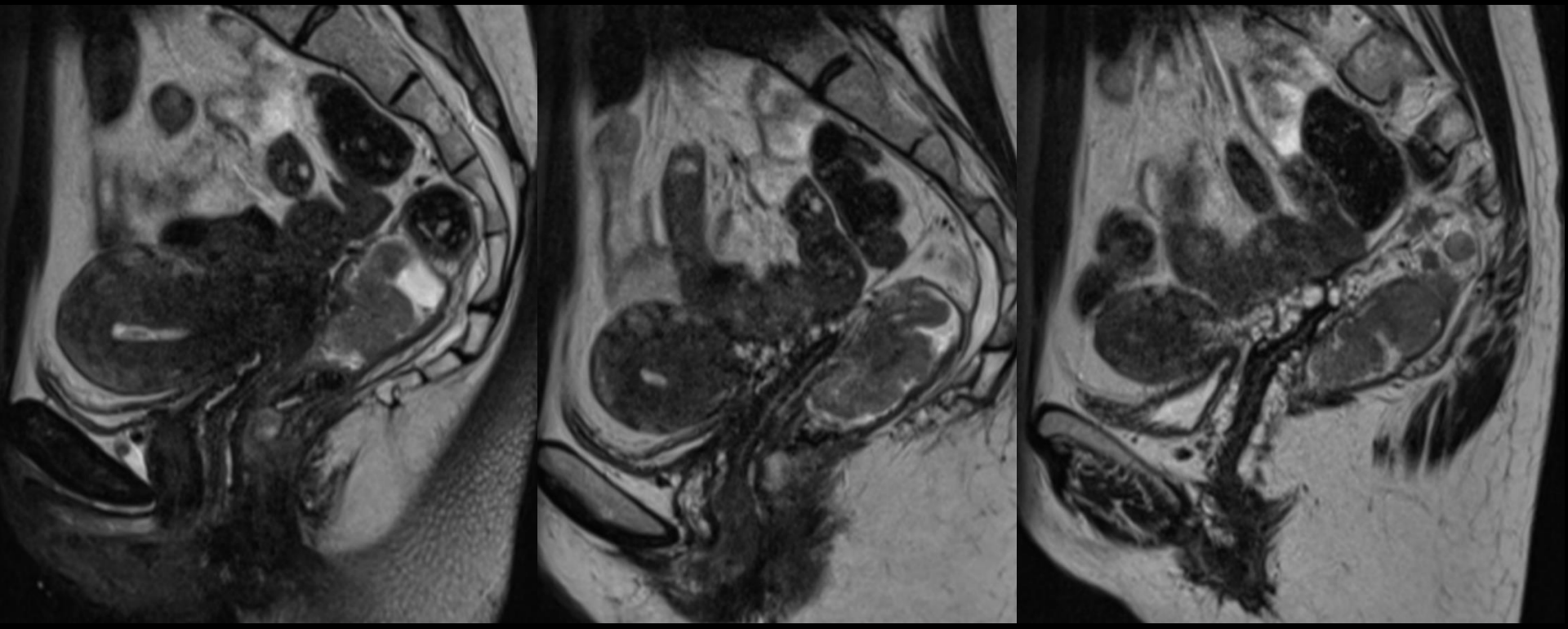


MRI-detected EMVI:

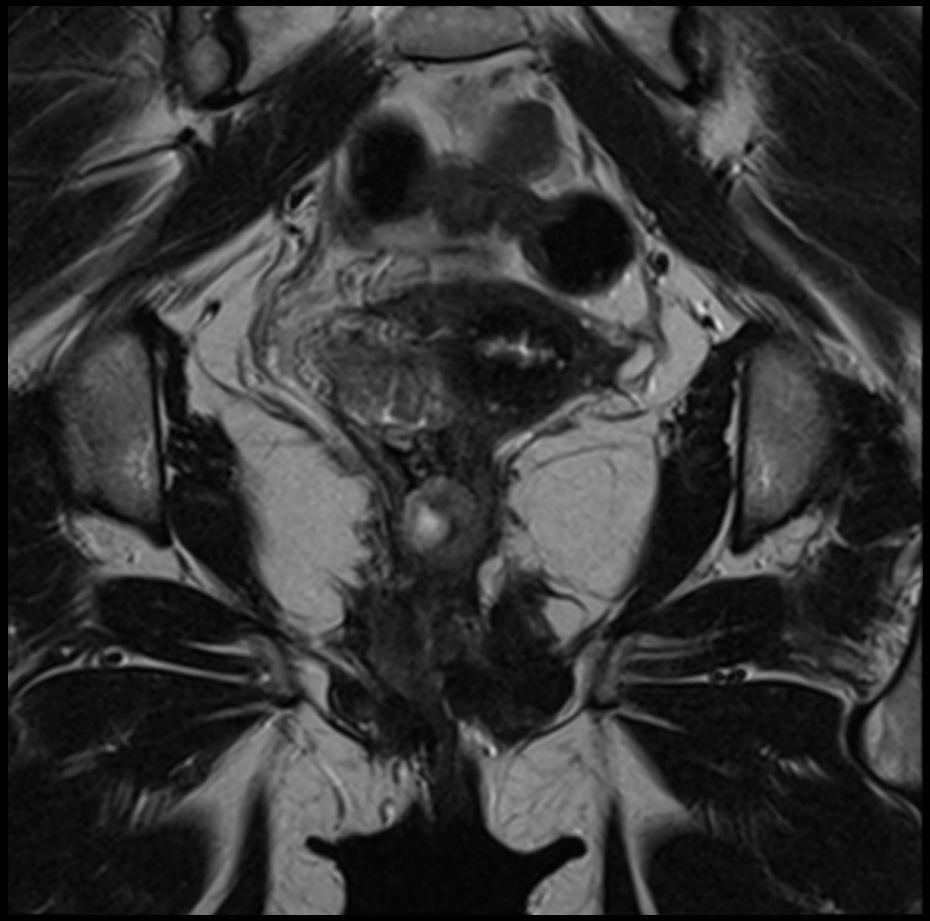
- Sensitivity, Specificity (n=94 surgical patients): 62%, 88%
- Sensitivity, Specificity, Accuracy (n=447): 28%, 94%, 80%*

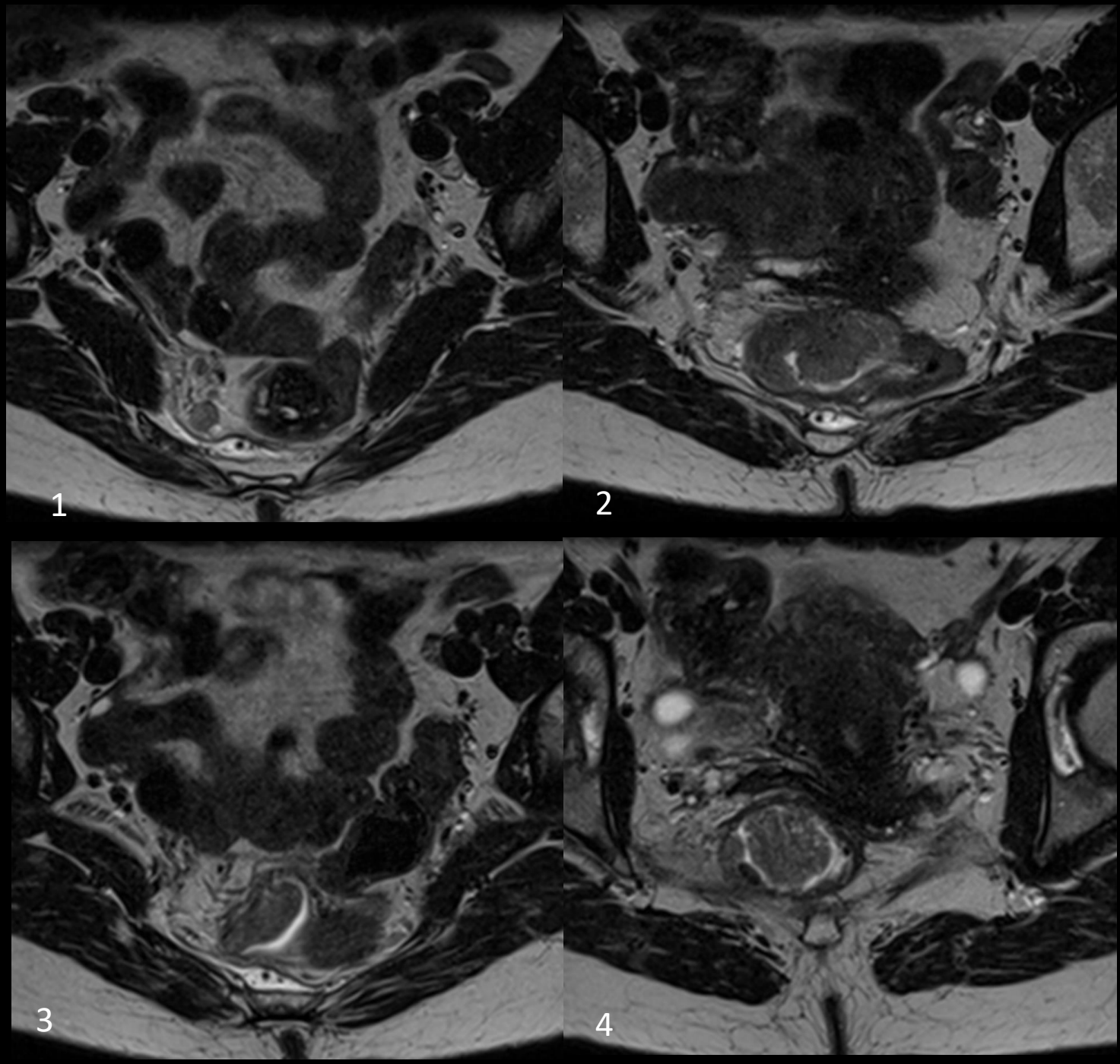
Smith NJ et al. Br J Surg 2008; 95: 229-36 ; *Sohn B et al. Eur Radiol 2014 {Dec 13 Epub}

Case example



Case example




1
2
3
4

Case example

Mid rectal cancer

Polypoid

T3aN1aM0

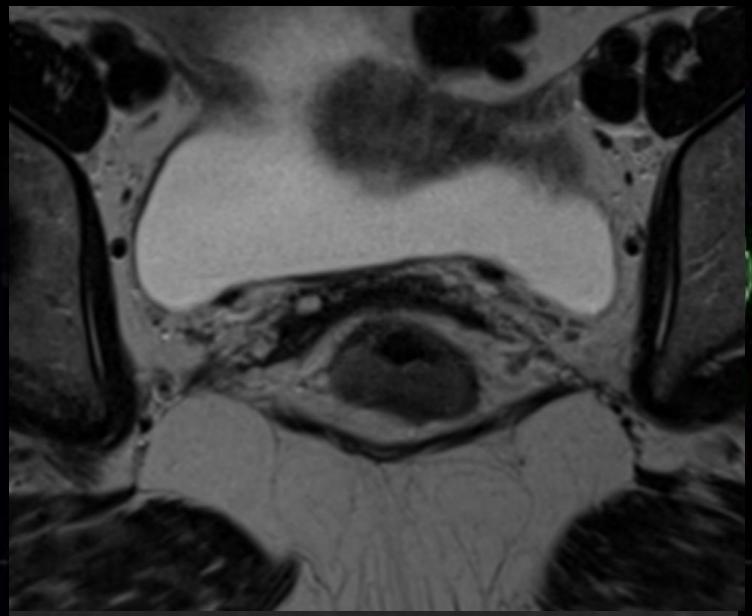
Additional discrete component at anorectal junction

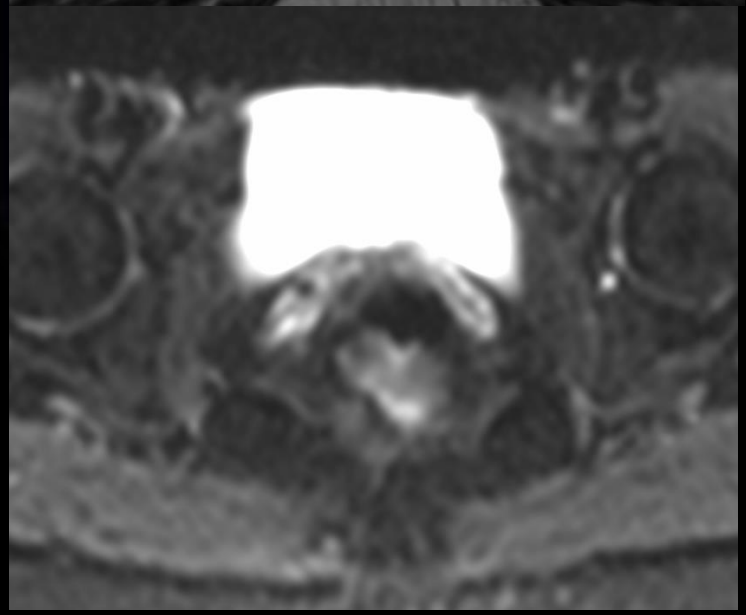
MRI: Planning

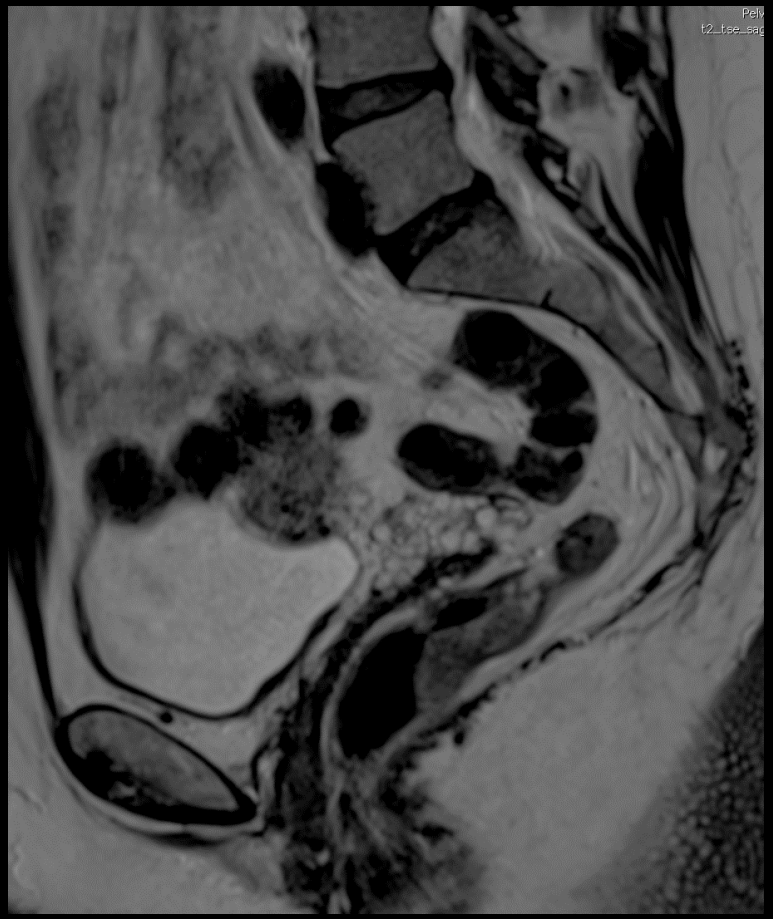
Advantages

- Improved characterization of soft tissues compared with CT
- MR distortion assessment/correction algorithms/co-registration/fusion can improve these technical issues
- DCE-MRI & diffusion MRI may contribute to characterization of tumour sub-regions
- Ultrafast cine MR sequences may define temporal patterns of target & organ at risk deformity and variations in spatial location
- PET/MRI GTV combined may be provide a more accurate assessment of tumour burden. (New lesions in 15%/Stage chane in 12% of the patients by PET/CT).

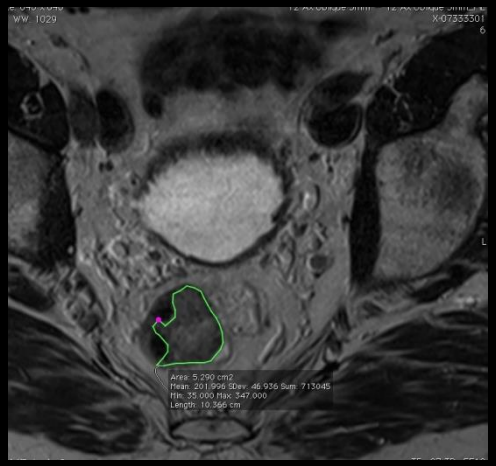
Brændengen et al. Int J Radiat Oncol Biol Phys. 2011;81(4):e439-4
Bassi et al. Int J Radiat Oncol Biol Phys 2008;70(5):1423-6

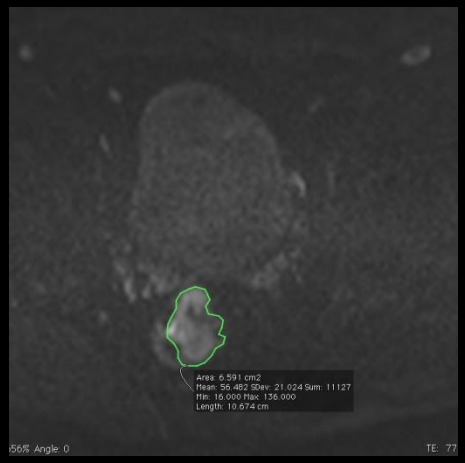


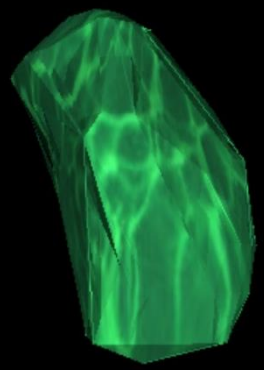


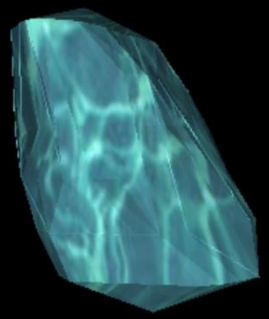


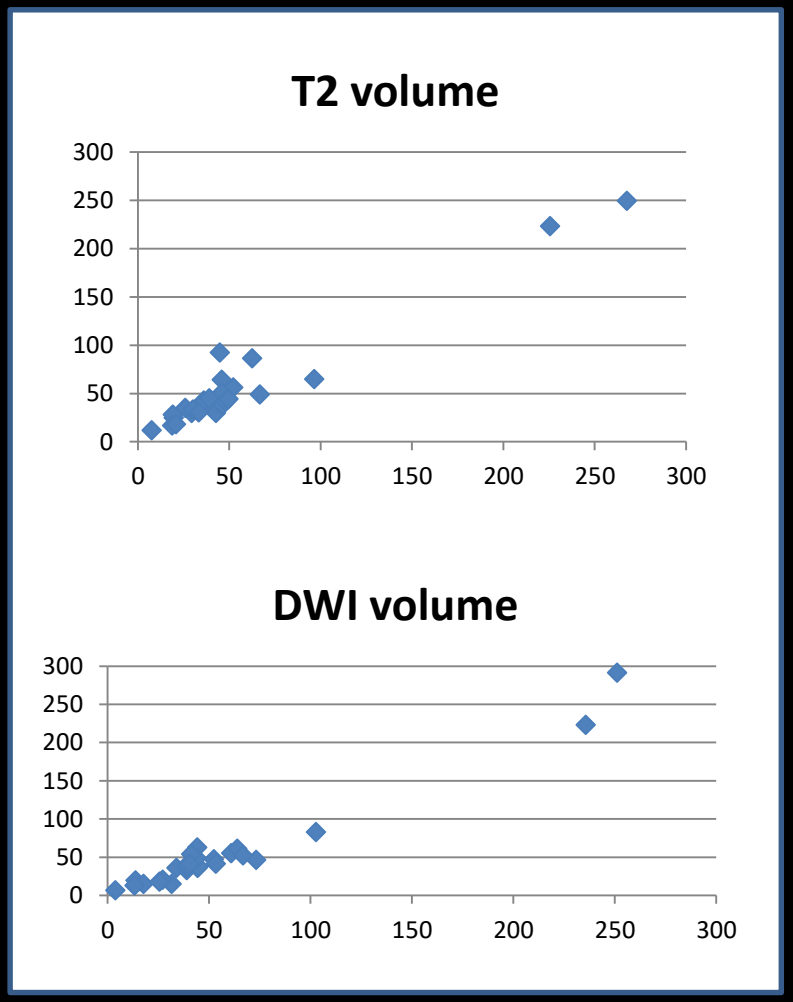
Tumour Delineation: DWI reduces Observer Discordance







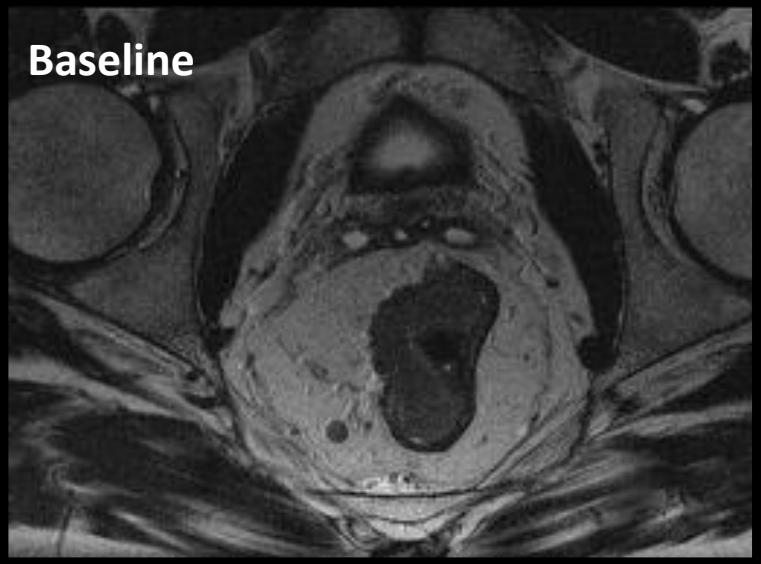


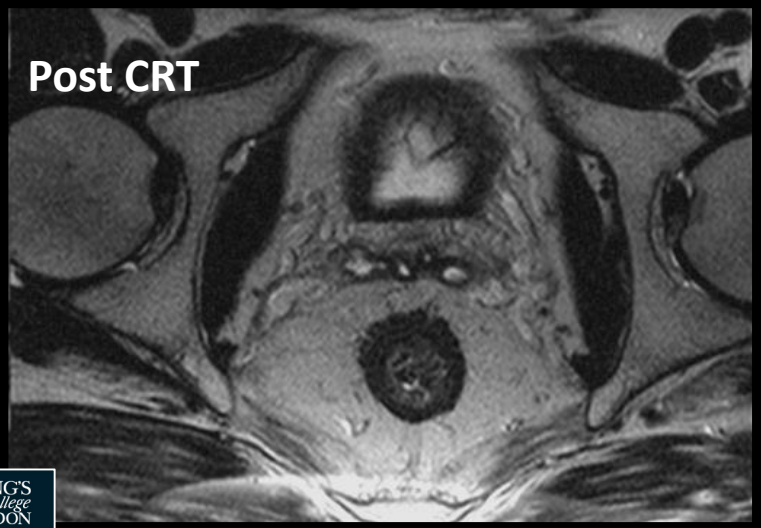


Burbach et al .Radiother Oncol. 2016;118(2):399-407

Regini et al. Eur J Radiol 2014; 83 (5), 768-72

Therapy Response Assessment

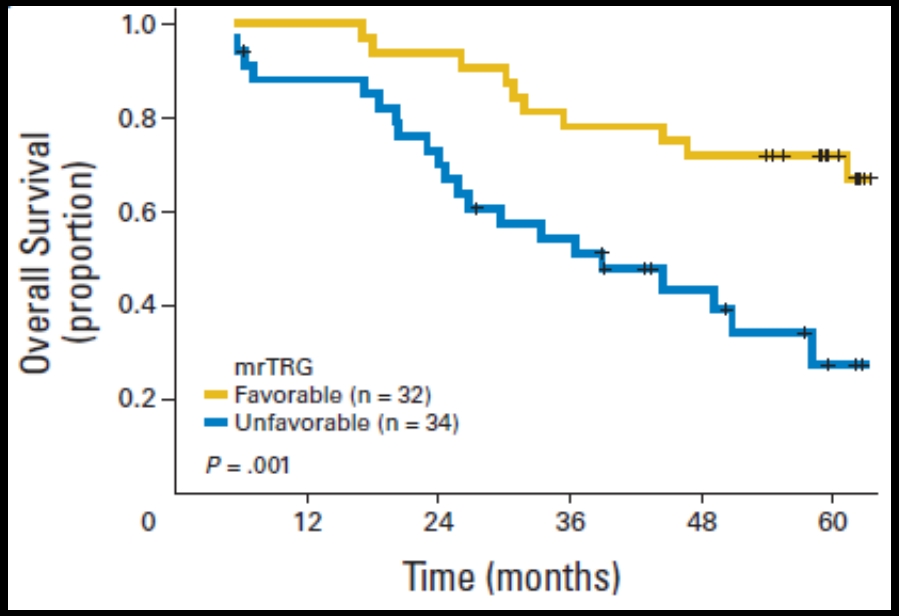




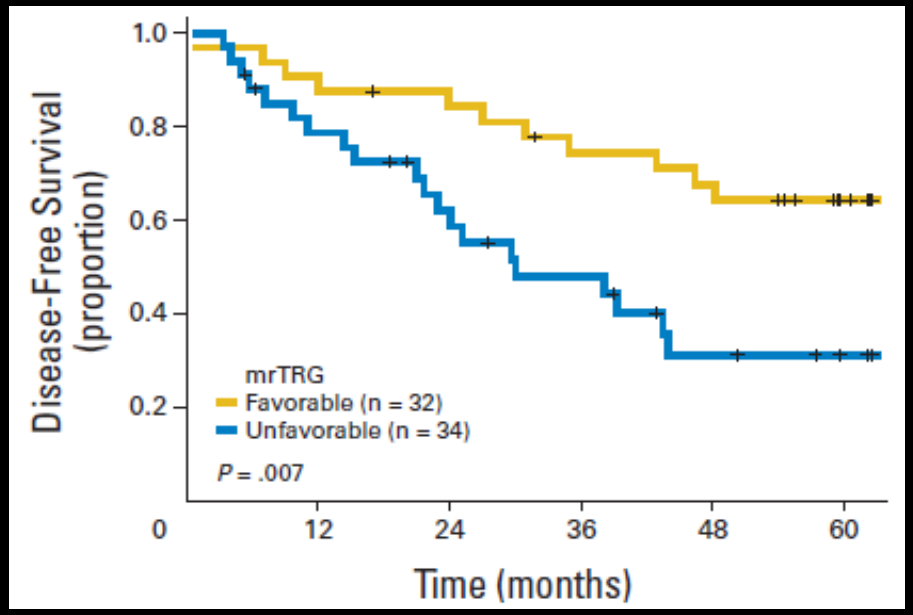
- MRI provides objective response assessment & judgement of whether R0 resection is viable following pre-operative therapy
- Up to 25% patients have a pCR following pre-operative therapy

Chawla S et al. Am J Clin Oncol 2014

Response Assessment: MRI



MERCURY study



Patel et al J Clin Oncol 2011 29:3753-60

MRI response assessment has prognostic value

Response Assessment: MRI

Restaging:

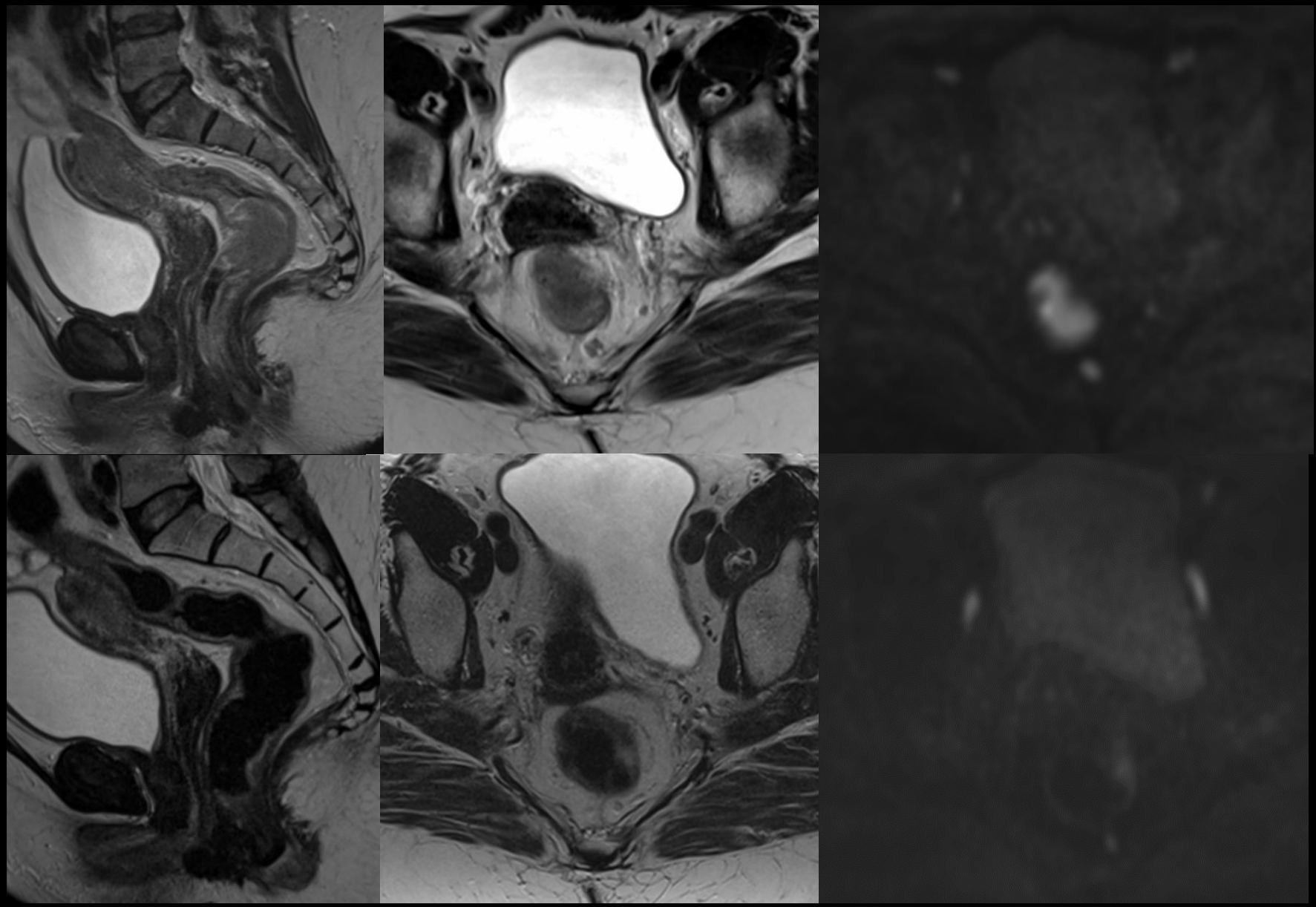
- Presence/absence of tumour
  - Distance from anal verge
  - Tumour length
  - Location
  - Extramural extension (mm), location & distance to CRM
- Presence/absence of fibrosis
- Presence/absence of suspicious mesorectal lymph nodes
- Presence/absence of suspicious extra- mesorectal lymph nodes
- yTNM staging

ESGAR Consensus. Beets-Tan et al. Eur Radiol. 2013; 23: 2522-31

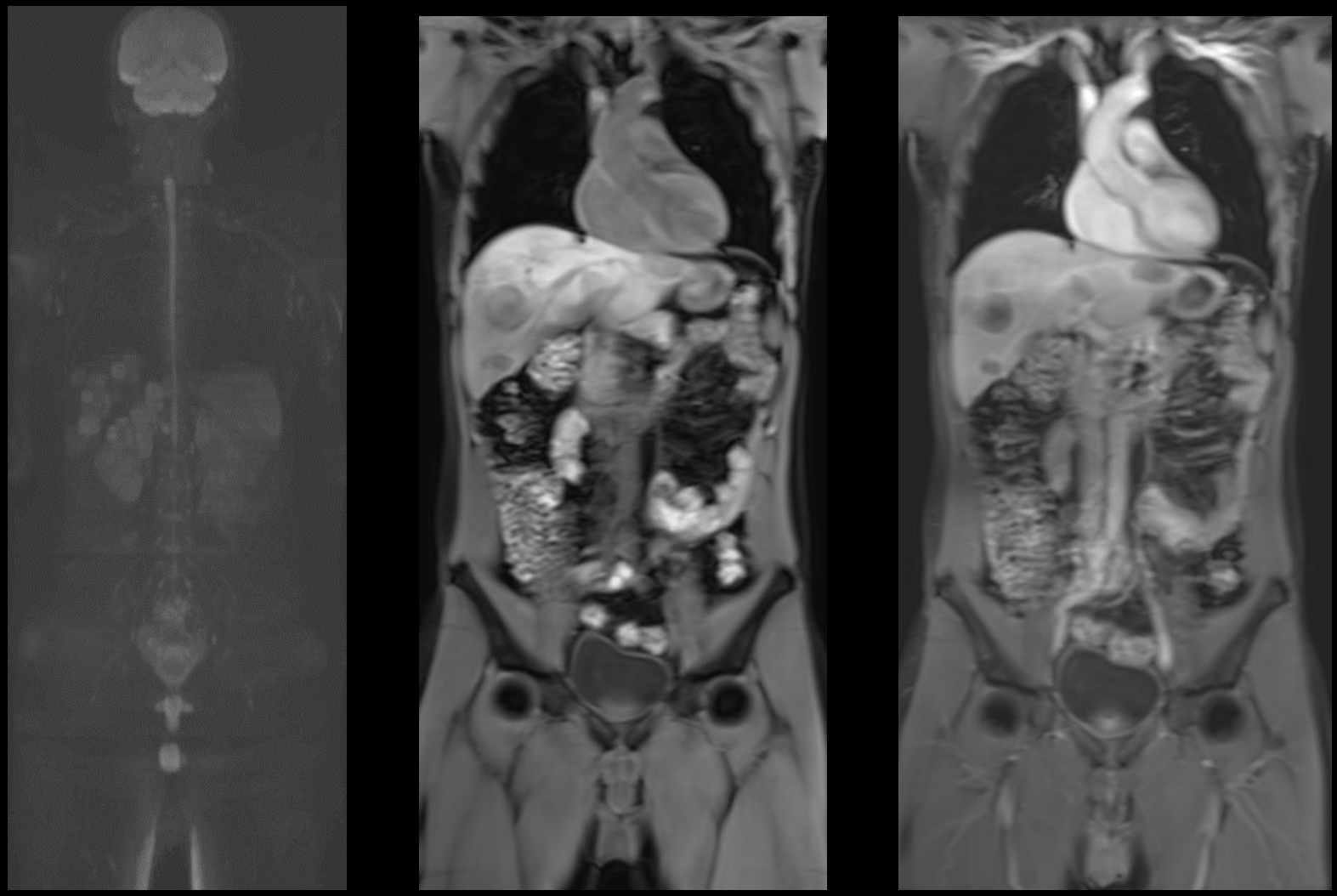
Response Assessment: MRI

MRI Tumour Regression Score:

1	Complete response	No visible tumour
2	Excellent response	Predominantly fibrosis, small amount of viable tumour
3	Good response	Mixed areas of fibrosis and tumour
4	Moderate response	More tumour than fibrosis
5	Poor or no response	No fibrosis, only tumour signal visible



Whole Body MRI



Metastatic Rectal Cancer

Whole Body MRI

Paucity of published data:

Author, Yr	MRI	Compartor	Pts	Tumour	Findings
Squillaci E et al. 2008	3T: STIR, T2, T1 ±C	18-F FDG PET-CT	20	Colon cancer: Staging	Detected >liver (27 vs 23) but < lung metastases (19 vs 25) vs PET/CT
Schmidt GP et al. 2009	1.5/3T: STIR, T1 Locoregional T1 +c, T2	18-F FDG PET-CT	24	Colorectal cancer (Re)-Staging	MRI: Sn 72%, Sp 93%, Ac 83% PET/CT: Sn 86%, Sp 96%, Ac 91%

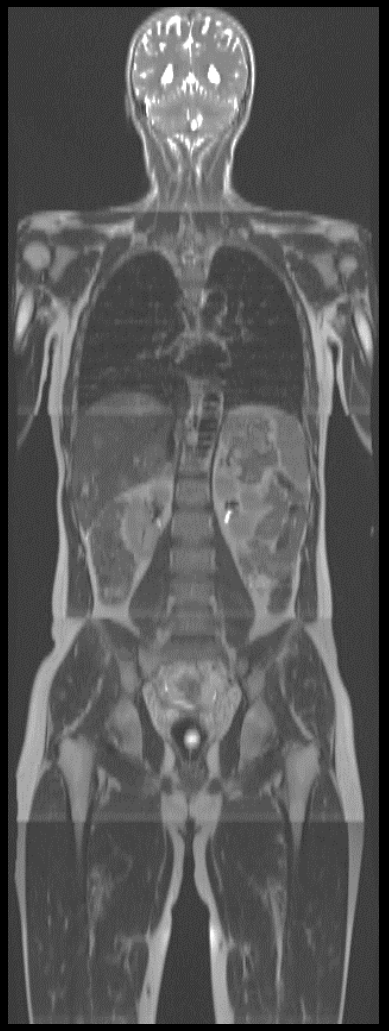
Potential advantages WB-MRI:
Detection of liver, brain & bone metastases

Squillaci E et al. Abdom Imaging 2008; 33(6): 676-88; Schmidt GP et al Eur Radiol 2009; 19(6): 1366-78

Whole Body MRI

Streamline–C Trial: UK NIHR HTA

- Target recruitment: 322
- Aim: To evaluate whether early WB-MRI increases detection rate for metastasis in colorectal cancer compared to standard pathways
- Primary outcome: Detection rate of metastasis by WBMRI vs standard staging pathways in newly diagnosed colorectal cancer

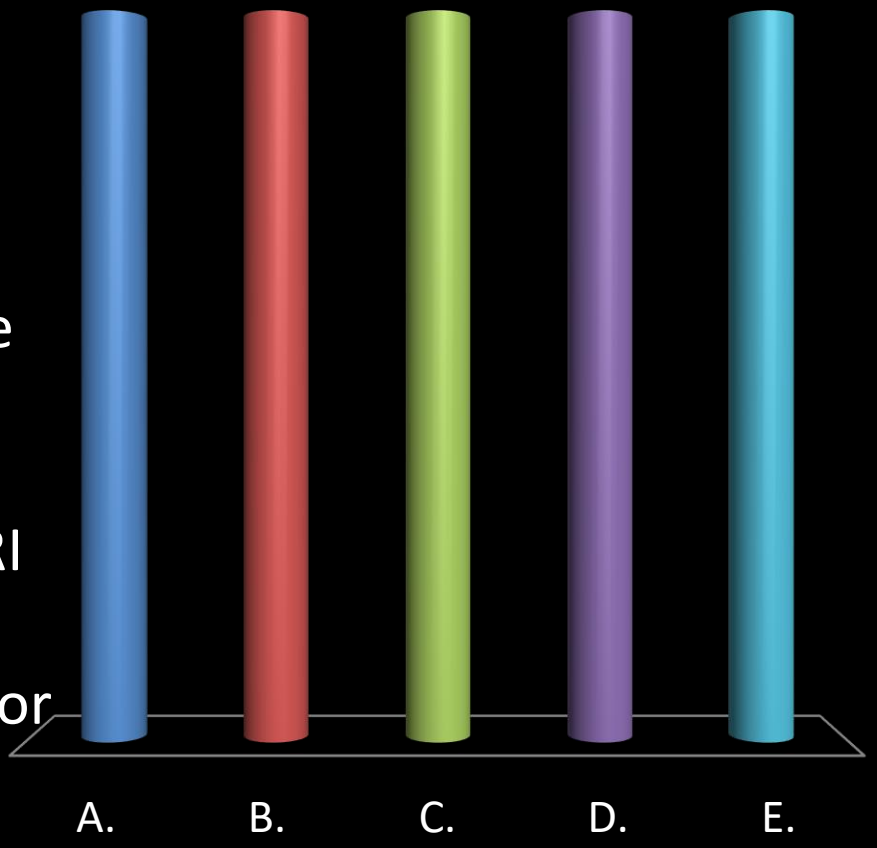


Summary

- MRI is advantageous for imaging rectal cancer
  - Resectability & staging: Improved therapeutic triage
  - Assessment of pre-operative therapy : Deferral of surgery
- MRI remains limited for nodal characterisation
- MRI may improve tumour delineation for radiotherapy planning
- Newer techniques being explored:
  - Whole body MRI for staging

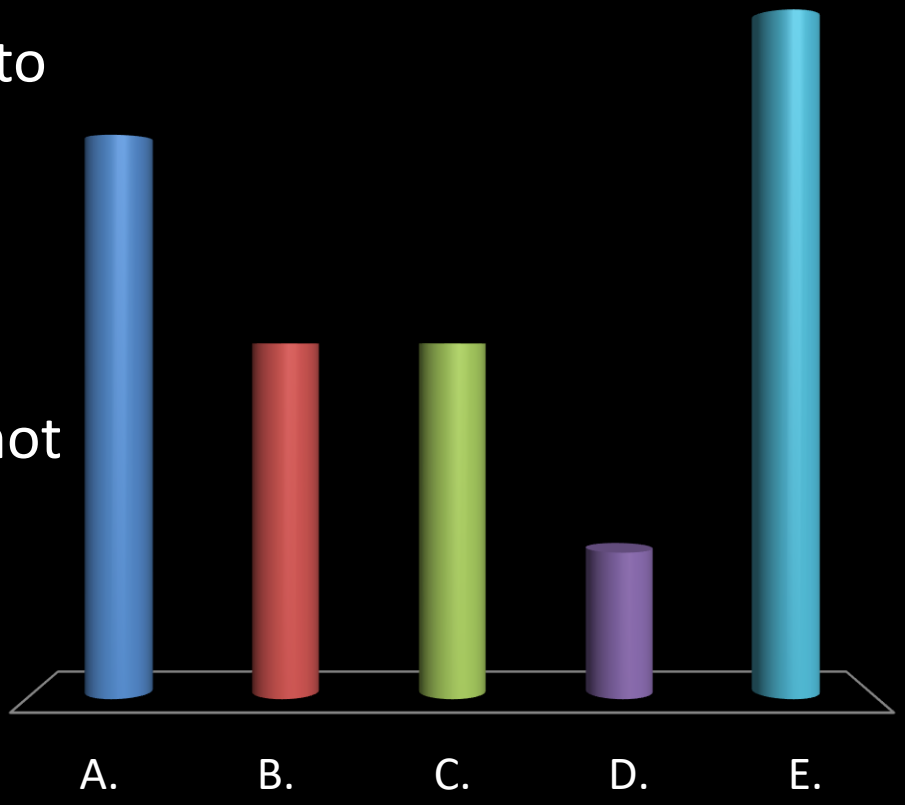
With respect to the following regarding MRI of rectal cancer, which is correct?

A. T2-W MRI has high sensitivity & specificity for nodal metastases
B. MRI is superior to PET/CT for radiotherapy planning
C. MRI has high accuracy for delineating the tumour distance from the potential resection margin
D. Dynamic contrast enhanced MRI is essential for staging
E. PET/MRI is better than PET/CT for staging



With respect to the following regarding MRI of rectal cancer, which is correct?

A. MRI tumour regression grading (TRG) has prognostic value
B. MRI TRG 4 is a good response to therapy
C. The presence of rectal wall diffusion signal is indicative of residual tumour
D. Colonoscopic confirmation is not required if MRI indicates complete response
E. Fibrosis demonstrates high T2 signal



ESTRO School

ESMIT

ESTRO/ESMIT Course on

Molecular Imaging and Radiation Oncology

Bordeaux, France - 10-13 April, 2017

FDG-PET/CT and Anal Cancer

A radiation oncologist's point of view

CHU Hôpitaux de Bordeaux

Dr Véronique Vendrely

Radiotherapy department-Bordeaux University Hospital

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université de BORDEAUX

No Conflict of interest to disclose

Plan

- Introduction
- A few things you should know

1. FDG-PET/CT in the initial staging
2. FDG-PET/CT for delineation
3. FDG-PET/CT as prognostic factor
4. FDG-PET/CT in response assessment
5. What’s next ?

Introduction

- < 1 % of all K

but incidence is increasing
(X 4 in the last decades)

- 4 à 6 % GI K

- Age : around 60-70 years

- Risk Factors
  - Cigarette smoking
  - HPV (benign lesions : genital warts)
  - Immunosuppression : HIV+
    - CD4<200 vs >500
    - MSM HIV+

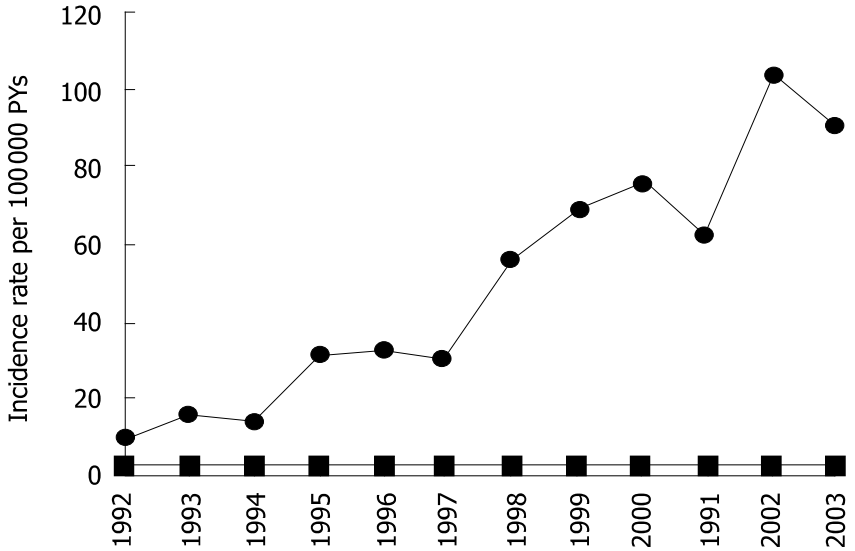
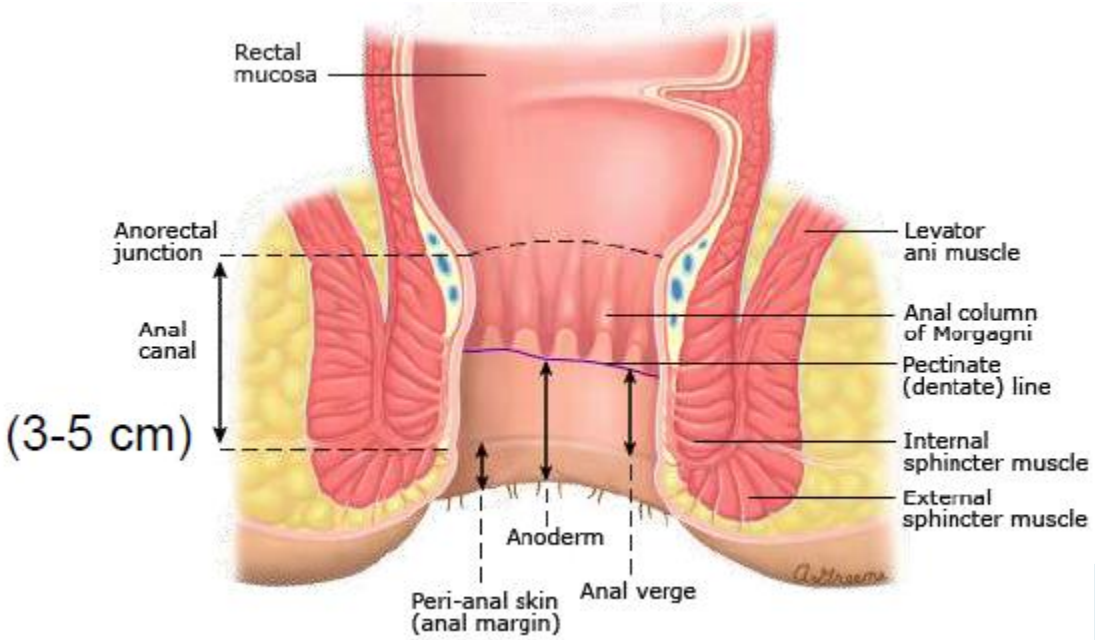
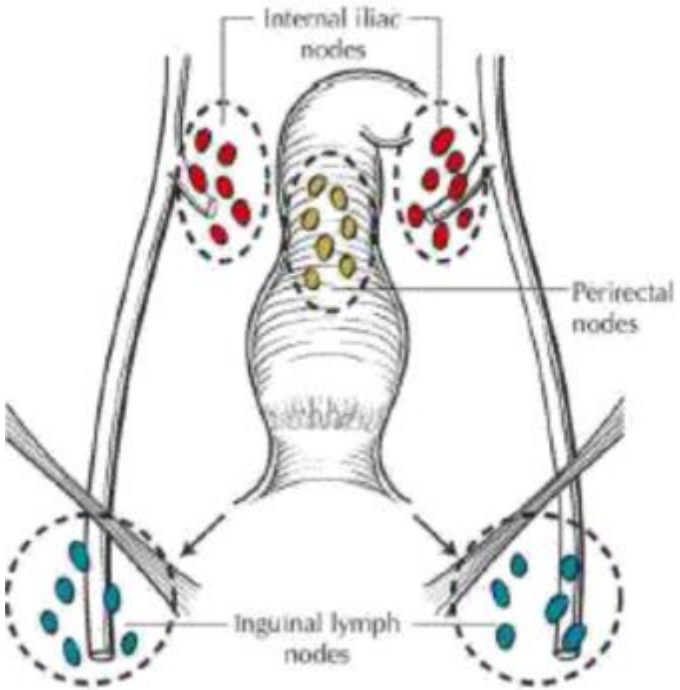


Figure 1 Annual incidence rates of anal cancer among HIV-infected persons (circles) and the general population (squares), USA 1992-2003.

HIV+ dramatically increases risk

Anal Cancer





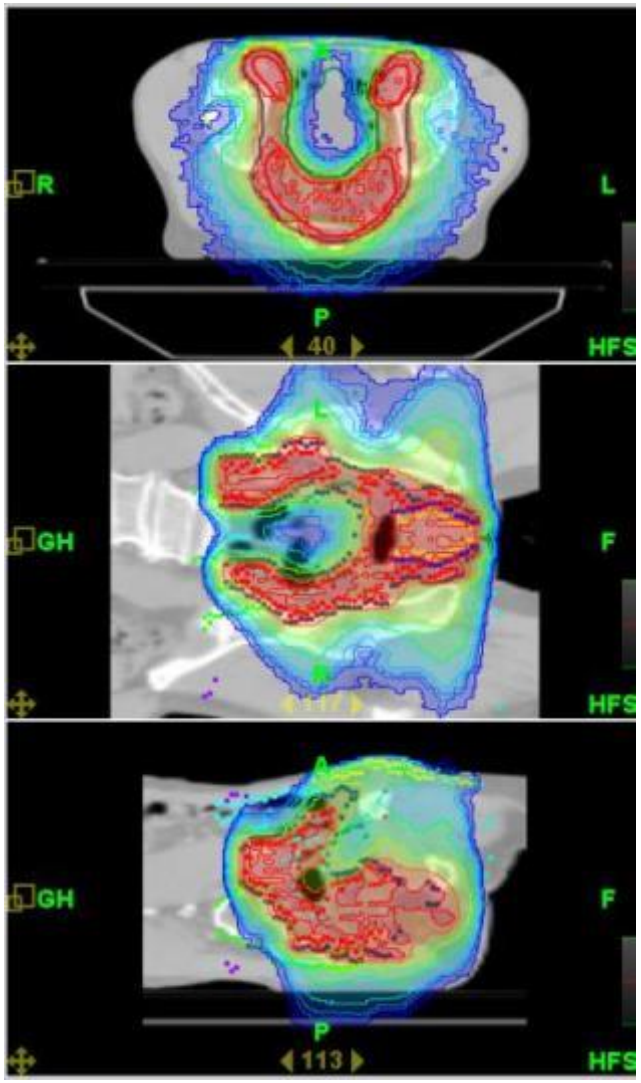
Histology: Squamous Cell Carcinoma (>80 %)

Nodal spread is frequent

- inguinal and external iliac nodes
- hemorroïdal internal iliac nodes
- Primitiv iliac nodes

Standard of care: general agreement

- Exclusive Radiochemotherapy
  - MMC/5FU (or capecitabine)
  - (CDDP/5FU)
  - No benefit for neoadjuvant chemotherapy
  - No benefit for maintenance
- IMRT
  - Can reduce acute toxicity
  - High gradient dose between tumor and normal tissue
  - Needs accurate delineation and control
- No Gap
- Good outcomes: 5-year survival=70 %

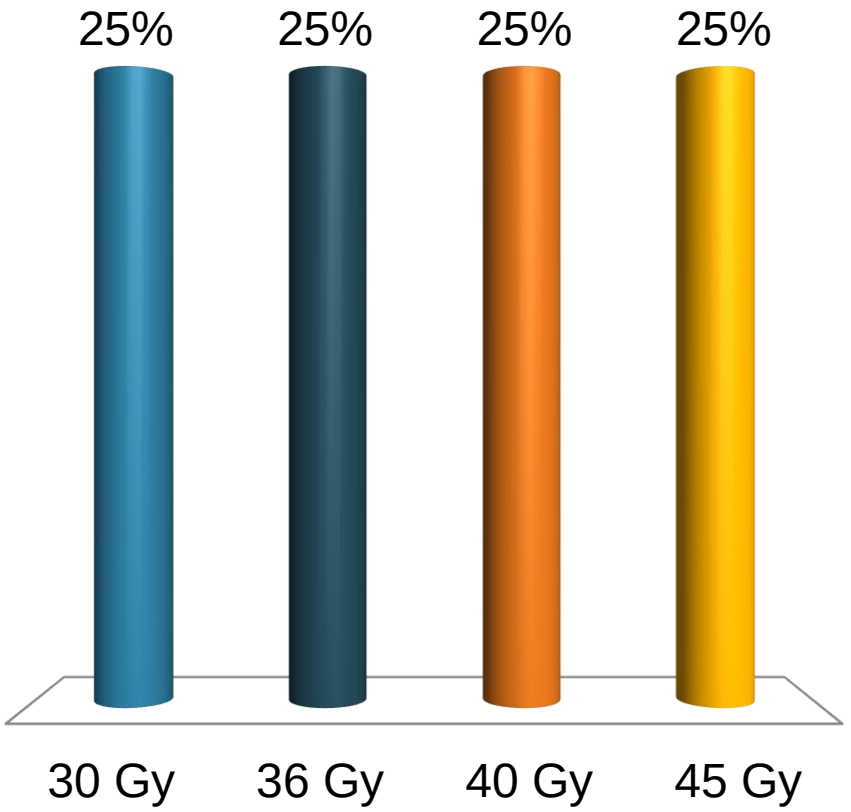


But doses : somewhat heterogeneous !

Dose	Recorad		RTOG		UK		ATGIT	
	Option 1	Option 2	T2N0	T3-4, N+	T1-2	T3-4	T1-2	T3-4
Prophylactic N	45	36	42	45	40	40	30	36
Involved N	60-65	59.4	na	50.4	na	53.2	na	54
T	60-65	59.4	50.4	54	50.4	53.2	50.4	60

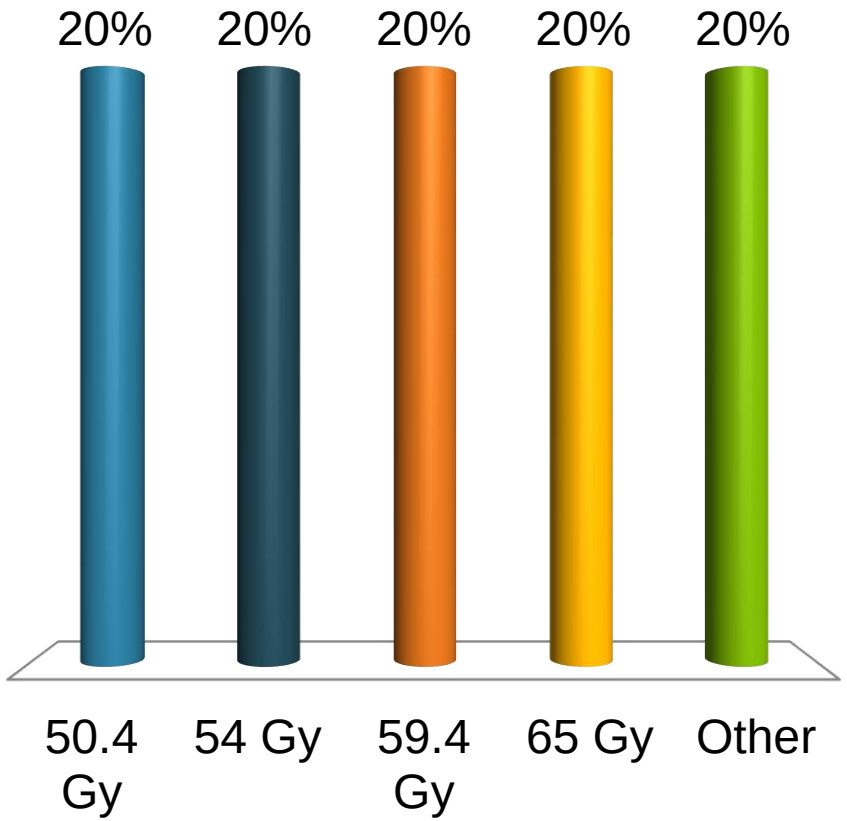
But doses : somewhat heterogeneous !
What are your prescribed doses ?
Prophylactic nodal dose

A. 30 Gy
B. 36 Gy
C. 40 Gy
D. 45 Gy



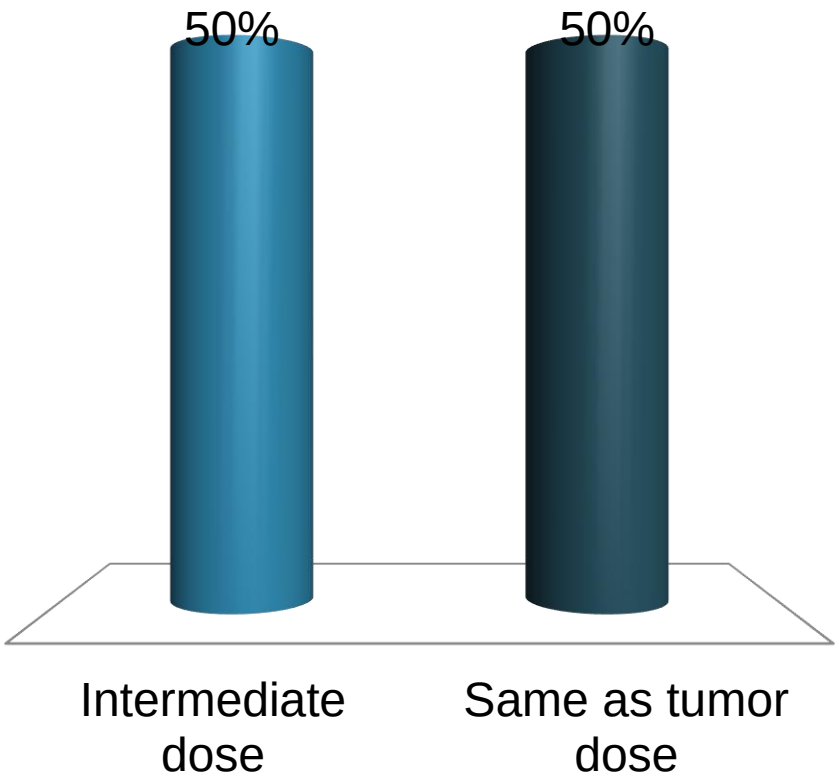
But doses : somewhat heterogeneous !
What are your prescribed doses ?
Prophylactic nodal dose

A. 50.4 Gy
B. 54 Gy
C. 59.4 Gy
D. 65 Gy
E. Other



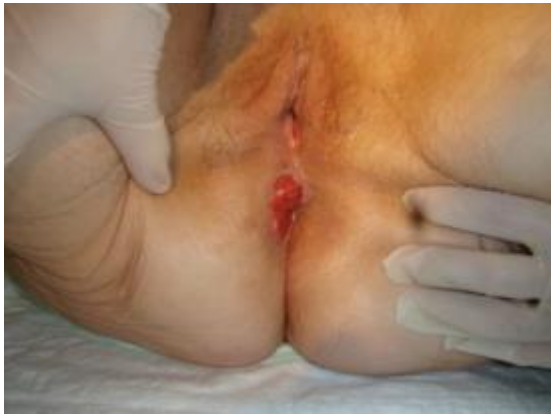
But doses : somewhat heterogeneous !
What are your prescribed doses ?
Involved nodal dose

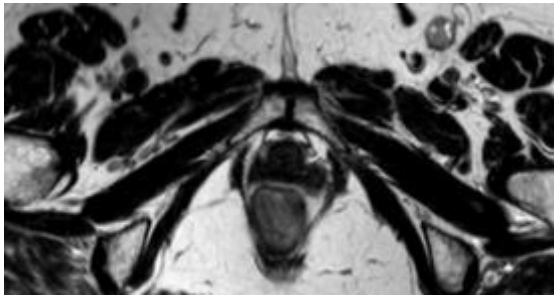
A. Intermediate dose
B. Same as tumor dose

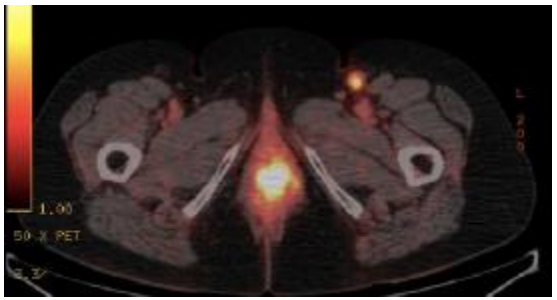


Workup

- Clinical Exam
  - anoscopy
  - DRE
  - Biopsy
  - Inguinal node evaluation
  - Gynecologic exam
  - Performance status, comorbidity
  - Continence evaluation (Jorge Wexner score)
- MRI +/- Echoendoscopie anale (plus fiable pour les petites tumeurs)
- FDG-PET/CT
- HIV/CD4







FDG-PET/CT in the initial staging

FDG-PET/CT should be part of the initial staging workup

According to

- NCCN guidelines (strongly recommended)
- ESMO/ESTRO guidelines (optional)
- TNCD french guidelines (strongly recommended)
- Can adress all 3 staging criteria of TNM

Moureau-Zaboutto et al. «Cancer du canal anal ». Thésaurus National de Cancérologie Digestive, 11-2016, http://www.tncd.org 6.1.

FDG-PET/CT vs conventionnal imaging

Ann Surg Oncol (2015) 22:3574–3581
DOI 10.1245/s10434-015-4391-9

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – COLORECTAL CANCER

The Role of FDG-PET in the Initial Staging and Response Assessment of Anal Cancer: A Systematic Review and Meta-analysis

Michael Jones, BSc, BE (Hons), MBBS, MPHTM[1], George Hruby, BHB, MBChB, FRANZCR[1], Michael Solomon, MBBCh, BAO (Hons), MSc, LRCPI, FRACS, FRCSI (Hon)[2], Natalie Rutherford, BMed, BMedSci, FRACP[3], and Jarad Martin, BSc, MBChB, DMed (Research), FRANZCR, GAustMS[4]

12 studies
FDG-PET/CT vs CT or MRI

High sensitivity
High NPV

FDG-PET/CT vs conventionnal imaging

TABLE 1 Clinical characteristics and imaging performed in selected studies

Authors	Year	Origin	No. of patients	Age		Gender			Imaging		Treatment
				Range	Median	M	F	% *F*	Conventional	PET	
Trautmann and Zuger[11]	2005	US	21	37–81	52	6	15	71	CT	PET	CRT
Cotter et al.[12]	2006	US	41	30–89	52	18	23	56	CT	PET/CT	CRT
Nguyen et al.[13]	2008	AUS	50	36–85	58	19	31	62	CT	PET or PET/CT	CRT/BT
Winton et al.[14]	2009	AUS	61	27–88	57	27	34	56	CT, MRI or both	PET or PET/CT	CRT
Iagaru et al.[15]	2009	US	8	33–60	44	6	2	25	CT	PET	CRT
Kidd et al.[16]	2010	US	77	30–89	53	33	44	57	NA	PET/CT	CRT
Day et al.[17]	2011	AUS	48	35–87	56	22	26	54	NA	PET or PET/CT	CRT
Bannas et al. [18]	2011	GER	22	39–79	61	13	9	41	CT	PET	CRT
Engledow et al.[19]	2011	UK	40	38–87	57	24	16	40	CT + MRI	PET/CT	CRT
Bhuva et al.[20]	2012	UK	30	NR	NR	NR	NR	NR	CT + MRI	PET/CT	CRT
Wells and Fox[21]	2012	UK	43	NR	NR	NR	NR	NR	CT + MRI	PET/CT	CRT/S
Mistrangelo et al.[10]	2012	ITA	53	32–75	57	19	34	64	CT	PET/CT	CRT/RT/S
Total			494	27–89	44–61			56			

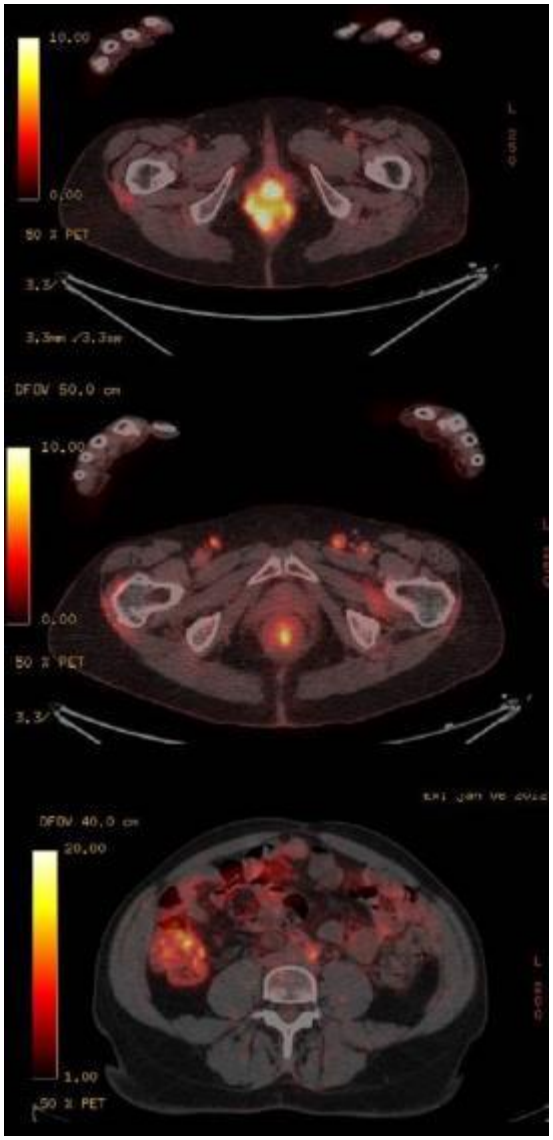
M male, *F* female, *PET* positron emission tomography, *CT* computed tomography, *MRI* magnetic resonance imaging, *CRT* chemoradiotherapy, *BT* brachytherapy, *RT* radiotherapy, *S* surgery, *NR* not reported, *NA* not available, *US* United States, *AUS* Australia, *GER* Germany, *UK* United Kingdom, *ITA* Italy

FDG-PET/CT vs conventionnal imaging

- Primary Disease
  - PET/CT : 99 % (95%CI: 96-100)VS
  - CT: 60 % (95%CI: 46-75)
- Nodal disease:

alteration in nodal stage 28 %

  - Nodal upstaging: 15 %
    - 16 % /CT
    - 15 %/ MRI
  - Nodal downstaging: 15 %
    - 17% vs CT
    - 14% vs MRI
  - Distant metastases : 3 %



Inguinal nodes :PET/CT versus sentinel node biopsy

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 1, pp. 73–78, 2010

0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.04.020

CLINICAL INVESTIGATION **Anus**

COMPARISON OF POSITRON EMISSION TOMOGRAPHY SCANNING AND SENTINEL NODE BIOPSY IN THE DETECTION OF INGUINAL NODE METASTASES IN PATIENTS WITH ANAL CANCER

Massimiliano Mistrangelo, Ph.D., M.D.,*‖ Ettore Pelosi, M.D.,† Marilena Bello, M.D.,† Isabella Castellano, M.D.,‡ Paola Cassoni, Ph.D., M.D.,‡ Umberto Ricardi, M.D.,§ Fernando Munoz, M.D.,§ Patrizia Racca, M.D.,** Viviana Contu, M.D.,** Giancarlo Beltramo, M.D.,§ Mario Morino, M.D.,* and Antonio Mussa, M.D.¶

Table 2. PET-CT performance vs. SNB: estimated midpoints and 95% CI

	PET-CT
Sensitivity (95% CI)	100 (30–100)
Specificity (95% CI)	83 (62–94)
Positive predictive values (95% CI)	43 (12–80)
Negative predictive values (95% CI)	100 (80–100)

High sensitivity
High NPV (negative predictive values)

But moderate PPV (positive predictive values): beware of the risk of false positive

FDG-PET/CT Limits: false positive

Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 3, pp. 720–725, 2006

0360-3016/06/$–see front matter
doi:10.1016/j.ijrobp.2006.01.009

CLINICAL INVESTIGATION **Anus**

FDG-PET/CT IN THE EVALUATION OF ANAL CARCINOMA

Shane E. Cotter, B.S.,*¶ Perry W. Grigsby, M.D.,*†‖ Barry A. Siegel, M.D.,†‖
Farrokh Dehdashti, M.D.,†‖ Robert S. Malyapa, M.D.,*# James W. Fleshman, M.D.,‡‖
Elisa H. Birnbaum, M.D.,‡‖ Xia Wang, M.D.,† Elliot Abbey, M.D.,§‖ Benjamin Tan, M.D.,§‖
Ira J. Kodner, M.D.,‡‖ Steven R. Hunt, M.D.,‡ Jennifer K. Lowney, M.D.,‡
Matthew G. Mutch, M.D.,‡‖ David W. Dietz, M.D.,‡‖ and Robert J. Myerson, M.D.*‖

- Increased risk of false positive for HIV+/HIV-
  - 3 / 4 distant uptake related to inflammatory nodes

Beware of inflammatory nodal disease in HIV+ patients

FDG-PET/CT Limits : false negative

PET is unable to detect micrometastasis

But does it really matter ?

Considering that a 30 Gy dose could be enough to sterilize micrometastasis

- Locally advanced Tumors (T2> 4cm, T3 or N+): prophylactic treatment of all lymphatic area
- Small T1 or T2 lesions : what is the risk of positive nodes (especially inguinal nodes) ?

Strahlentherapie
und Onkologie

Original Article

Can the Radiation Dose to CT-Enlarged but FDG-PET-Negative Inguinal Lymph Nodes in Anal Cancer Be Reduced?

Sabine Kathrin Mai[1], Grit Welzel[1], Brigitte Hermann[1], Frederik Wenz[1], Uwe Haberkorn[2], Dietmar Jörg Dinter[3]

FDG-PET/CT for delineation

Author, year	Patients (Total)	Upstaging	Downstaging	Invariate	Change RT planes
Trautmann, 2005	21	10%	n.r.	90%	n.r.
Cotter, 2006	41	17%	n.r.	83%	n.r.
Piperkova, 2006	1	100%	0	0	n.r.
Anderson, 2007	3	33.3%	n.r.	66.6%	33.3%
Joon, 2007*	48	17%	6%	77%	19%
Schwarz, 2008	53	n.r.	n.r.	n.r.	n.r.
Nguyen, 2008*	48	17%	6%	77%	19%
Iagaru, 2009	8	n.r.	n.r.	n.r.	n.r.
de Winton, 2009	61	15%	8%	77%	13%
Forrest, 2009	39	n.r.	n.r.	n.r.	n.r.
Renaud, 2009	20	15%	n.r.	85%	n.r.
Kidd, 2010	77	n.r.	n.r.	n.r.	n.r.
Krengli, 2010	27	18.5%	0%	81.5%	3.7%
Bannas, 2010	22	9%	18%	73%	23%
Engledow, 2010	40	n.r.	n.r.	n.r.	12.5%
Vercellino, 2011	22	n.r.	n.r.	n.r.	20%
Sveistrup, 2012	91	14%	n.r.	86%	17%
Mistrangelo, 2012	53	37.5%	25%	37.5%	12.6%
Wells, 2012	30	17%	19%	65%	29%
Bhuva, 2012	43	30.2%	11.6%	58.2%	n.r.

Coregistration with radiotherapy planning CT:

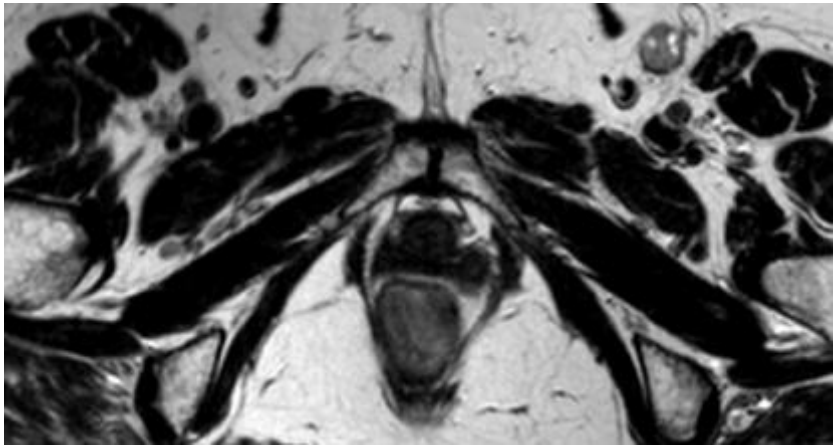
- Nodal delineation
- But not for tumor ?

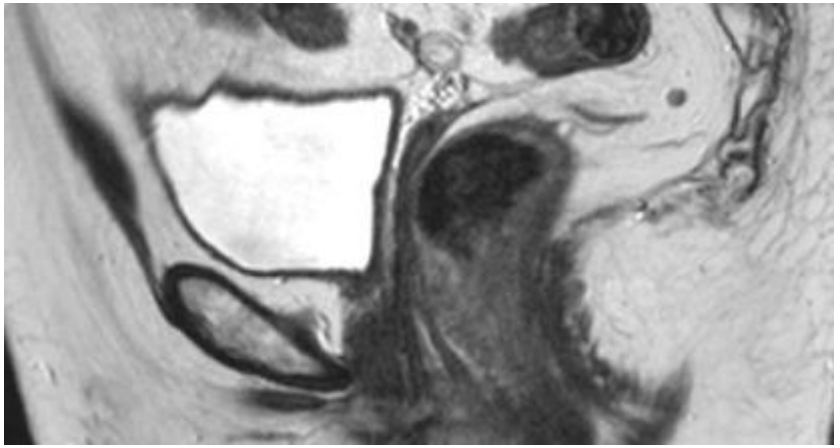
MRI for tumor delineation

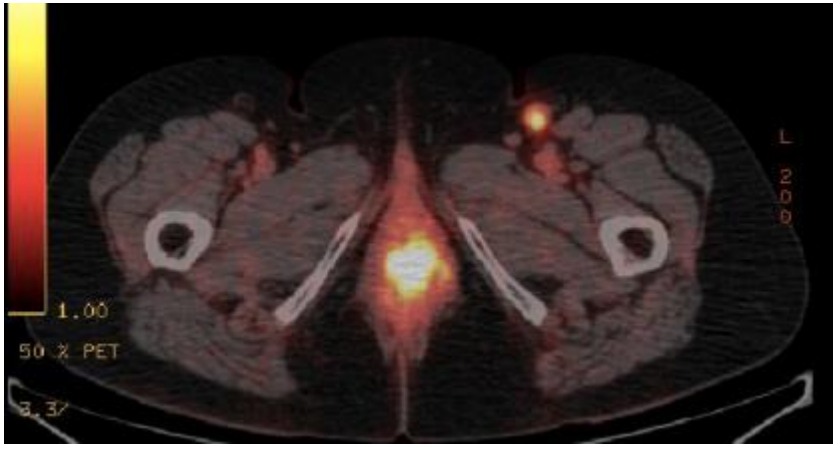
- Internal or external sphincter invasion
- Levatori muscle invasion
- Vaginal invasion

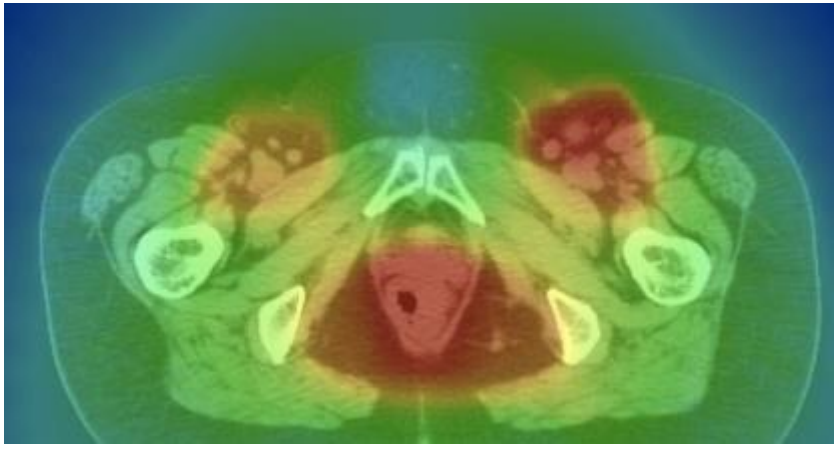
Mistrangelo M, Lesc A. PET-CT in anal cancer: indications and limits. 2013:

Concordance MRI/PET/dosimetry









Baseline FDG-PET/CT as prognostic factor ?

Radiotherapy and Oncology 95 (2010) 288–291

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Anal cancer PET

Anal cancer maximum F-18 fluorodeoxyglucose uptake on positron emission tomography is correlated with prognosis

Elizabeth A. Kidd [a], Farrokh Dehdashti [b,d], Barry A. Siegel [b,d], Perry W. Grigsby [a,b,c,d,*]

[a] Department of Radiation Oncology; [b] Mallinckrodt Institute of Radiology, Division of Nuclear Medicine; [c] Department of Obstetrics and Gynecology; and [d] Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA

Retrospective study- 77 patients

Higher Max SUV (>5.6) associated with
- N+ status,
- worse DFS
- worse treatment response

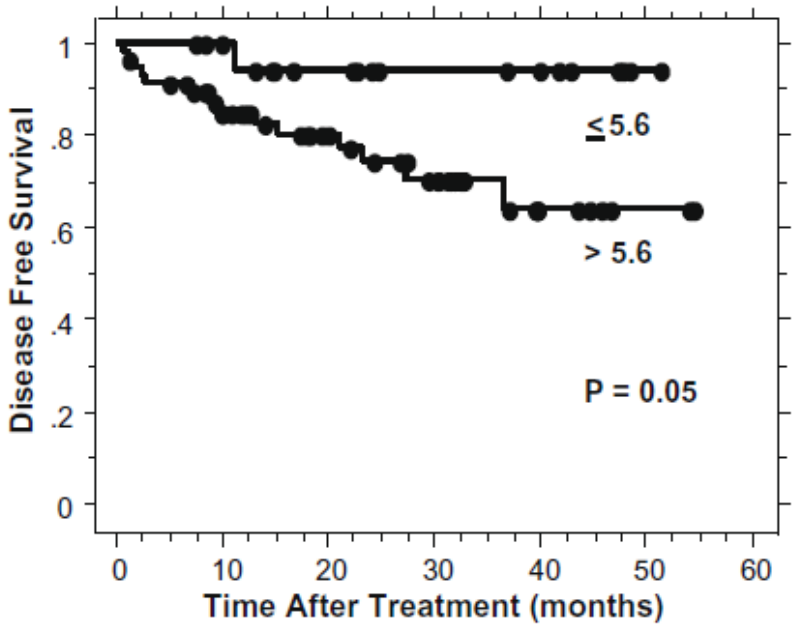


Fig. 3. Kaplan–Meier disease-free survival for high- and low-SUV_{max} subgroups.

Kidd EA et al. Radiother Oncol. 2010

Do we need higher dose on high SUV area ?

Baseline FDG-PET/CT as prognostic factor ? Conflicting results

Radiol med (2016) 121:54–59
DOI 10.1007/s11547-015-0562-9

ONCOLOGY IMAGING

Anal cancer FDG-PET standard uptake value: correlation with tumor characteristics, treatment response and survival

Letizia Deantonio[1,5] · Maria Elisa Milia[1] · Tiziana Cena[2,5] · Gianmauro Sacchetti[3] · Carola Perotti[1] · Marco Brambilla[4] · Lucia Turri[1] · Marco Krengli[1,5]

Retrospective study : 55 patients

Correlation between SUVmax and T stage and histology

No association between median SUVmax and PFS nor response

Table 2 Analysis of SUV with clinical parameters

	SUVmax median	SUVmax *Q1–Q3*	*p* value
Tumor stage			0.01
T1–T2	11.47	7.10–17.14	
T3–T4	15.54	12.22–22.37	
Nodal stage			0.89
N0	14.44	9.51–19.04	
N+	14.70	8.60–15.17	
Clinical stage			0.46
I–II	14.41	8.28–16.71	
III	14.70	8.60–22.37	
Histology			0.03
Squamous cell	14.98	10.47–21.09	
Others	7.67	6.80–15.71	
Grading			0.38
G1–G2	14.53	7.8–19.04	
G3	14.95	9.56–24.30	
Clinical response			0.17
CR	12.26	7.60–19.04	
PR	15.24	13.02–19.56	

Q1–Q3 first quartile and third quartile, *CR* complete response, *PR* partial response

Is SUVmax a pertinent parameter ?
Mean SUV ?
MTV ? *(Shali S et al. l. Eur J Radiol. 2016)*

Deantonio L et al. Radiol Med. 2016

Post-treatment follow-up

Goal : To assess the response and to diagnose recurrence when still resecable

- Standard Follow-up:
  - Clinical exam
    - Every 4-6 months during 5 years
  - CT / year
- Which place for new imaging modalities ?
  - MRI ?
  - FDG-PET/CT ?

Response assessment can be challenging

- frequent post-treatment modifications (edema, residual fibrosis or scar tissue) can mimic persistent or recurrent disease
- Systematic biopsies should be avoided because of radionecrosis risk

Post treatment FDG-PET/CT as prognostic factor ?

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 1, pp. 180–186, 2008

0360-3016/08/$-see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.09.005

CLINICAL INVESTIGATION — Anal Canal

TUMOR RESPONSE AND SURVIVAL PREDICTED BY POST-THERAPY FDG-PET/CT IN ANAL CANCER

Julie K. Schwarz, M.D., Ph.D.,* Barry A. Siegel, M.D.,†‡ Farrokh Dehdashti, M.D.,†‡
Robert J. Myerson, M.D., Ph.D.,*‡ James W. Fleshman, M.D.,†§ and Perry W. Grigsby, M.D.*†‖¶

MOLECULAR IMAGING AND BIOLOGY

Published Online: 19 July 2005

Mol Imaging Biol (2005) 7:309-313
DOI: 10.1007/s11307-005-0003-6

RESEARCH ARTICLE

Positron Emission Tomography for Pretreatment Staging and Posttreatment Evaluati

British Journal of Cancer (2011) 105, 498 – 504

www.bjcancer.com

Thomas G. Tra

[1]Southeast Radiation O
[2]Department of Radiolo

FDG-PET metabolic response predicts outcomes in anal cancer managed with chemoradiotherapy

FL Day[1], E Link[2], S Ngan[3], T Leong[3], K Moodie[4], C Lynch[5], M Michael[1], E de Winton[3], A Hogg[4], RJ Hicks[4] and A Heriot[*,5]

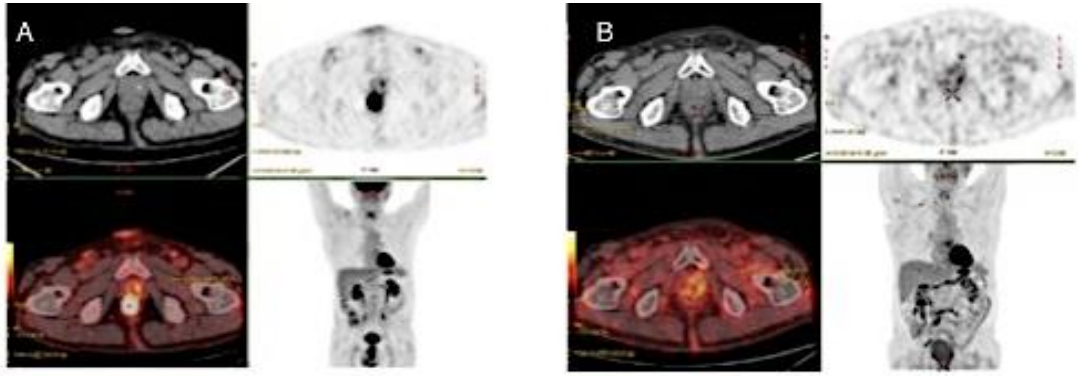
[1]Department of Haematology and Medical Oncology, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street, Melbourne, 8006, Victoria, Australia; [2]Centre for Biostatistics and Clinical Trials, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street, Melbourne, 8006, Victoria, Australia; [3]Department of Radiation Oncology, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street, Melbourne, 8006, Victoria, Australia; [4]Centre for Molecular Imaging, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street, Melbourne, 8006, Victoria, Australia; [5]Department of Surgical Oncology, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett Street, Melbourne, 8006, Victoria, Australia

Only retrospective studies
Small number of patients

Similar results :
CMR is predictive of good outcomes

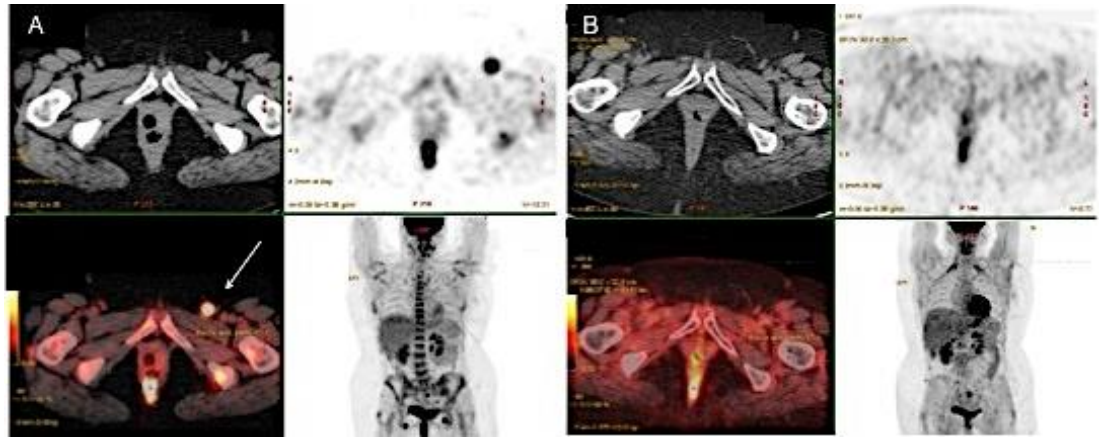
FDG-PET/CT in response assessment

High sensitivity (92%) and high negative predictive value (96.4%)



Pre-treatment FDG-PET/CT shows the anal tumor on axial slices (A). Corresponding images, obtained on post-treatment FDG-PET/CT performed 3 months after chemoradiotherapy (B), show low FDG uptake (complete metabolic response). At the end of follow-up the patient was alive and without evidence of recurrence.

Example of Complete Metabolic Response

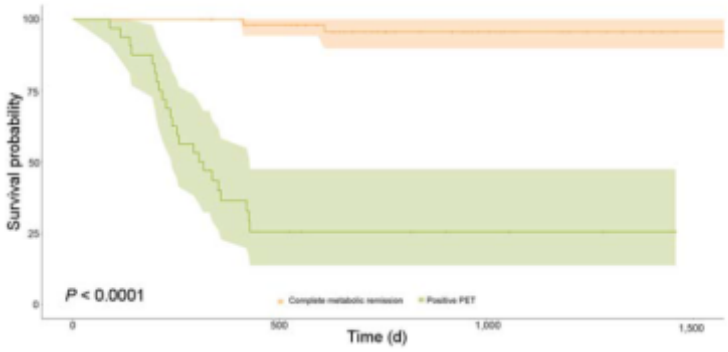


Pre-treatment FDG-PET/CT shows the anal tumor on axial slices and shows a left inguinal node (white arrow) (A). Corresponding images, obtained on post-treatment FDG-PET/CT show persistent increased FDG uptake in anal canal (considered as non complete response), but complete regression of inguinal node uptake. Persistent disease was proven by biopsyed 4 months after chemoradiotherapy (B),

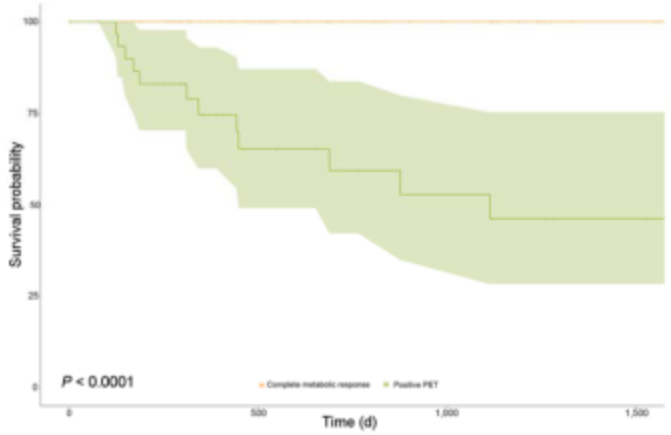
Example of partial metabolic response

Houard et al. JNM 2017

FDG-PET/CT in response assessment



PFS



CSS

the 2-year PFS rate was 96% for patients with CMR, and 28% for non-CMR patients (p<0.0001). The 2-year CSS rate was 100% for patients with CMR and 59% for non-CMR patients (p<0.0001).

Very high negative predictive value may prevent unnecessary biopsies or surgery

Different schedules/different results

Practical Radiation Oncology (2016) xx, xxx–xxx

Original Article

Posttreatment FDG-PET-CT response is predictive of tumor progression and survival in anal carcinoma

Kelly E. Goldman MD [a,†], Evan C. White MD [a,*,†], Aroor R. Rao MD [b], John S. Kaptein PhD [c], Winston W. Lien MD [b]

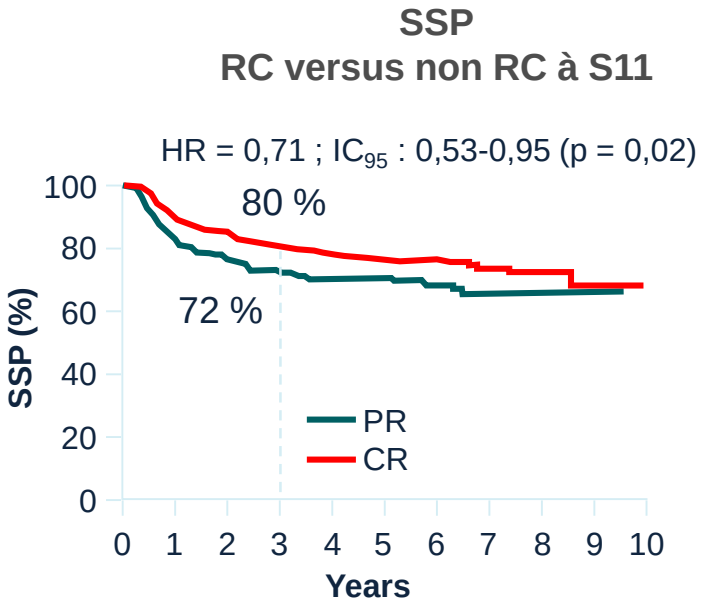
[a] *Department of Radiation Oncology, Kaiser Permanente Los Angeles Medical Center, Los Angeles, California*
[b] *Department of Radiation Oncology, Southern California Permanente Medical Group, Los Angeles, California*
[c] *Research Laboratory, Southern California Permanente Medical Group, Los Angeles, California*

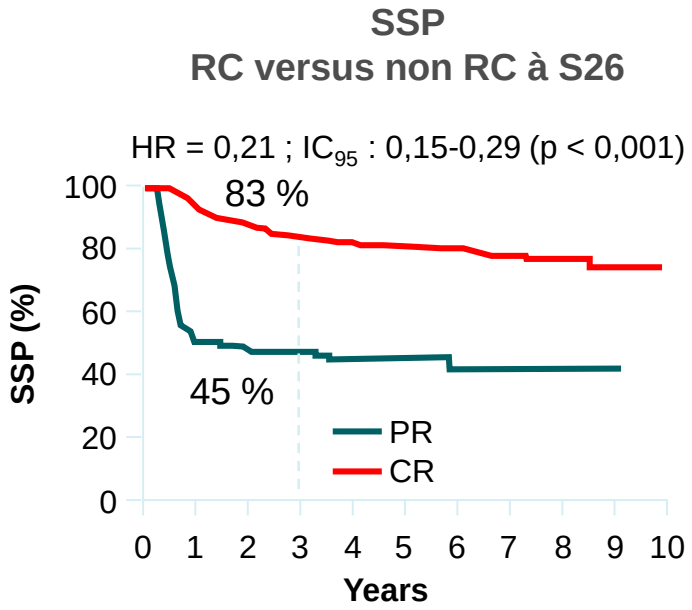
Received 17 September 2015; revised 4 January 2016; accepted 8 January 2016

Better predictive value of FDG-PET/CT performed after 12 weeks

Highly predictive of PFS and OS

Optimal time for response assessment ?





Response assessment at W11 seemed too early : 60 % of patients considered with partial response at S11 were in complete remission at W26

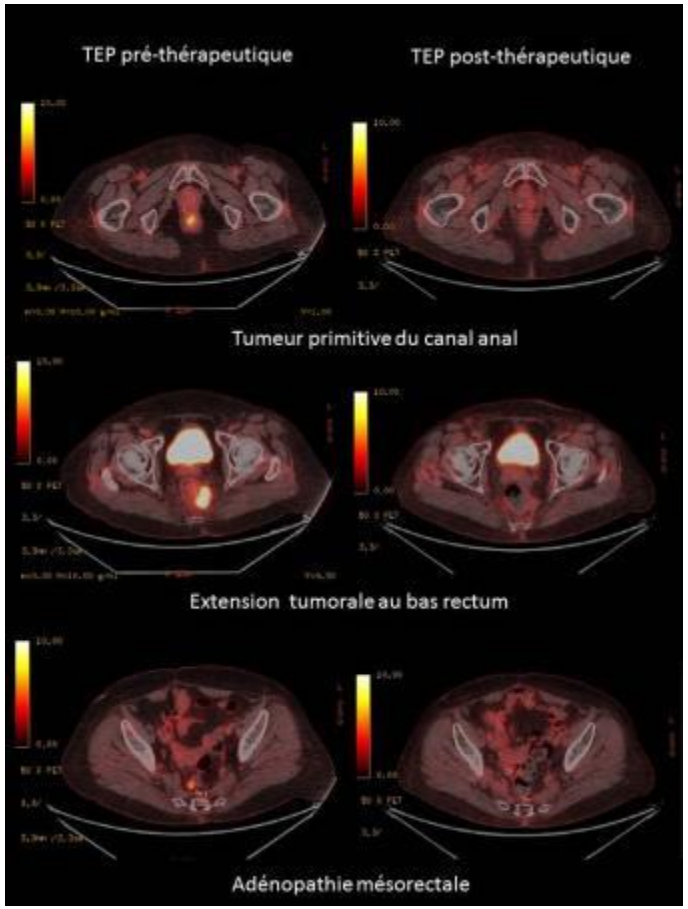
ASCO® 2012 - D'après Glynne-Jones R et al., abstr. 4004 actualisé

Except in the case of progression, it is necessary to wait until 4-6 months after the end of radiochemotherapy, before discussing a salvage surgery in case of residual tumor

FDG-PET/CT in response assessment

Take Home Message

- FDG-PET/CT : optional 4-6 months after the end of treatment
- High VPN>90 % to assess complete response
- Highly predictive of long-term outcomes



What's next ?

We need prospective studies to confirm the place of FDG-PET/CT in response assessment and prognostic

Use the PET to build our future clinical trials :

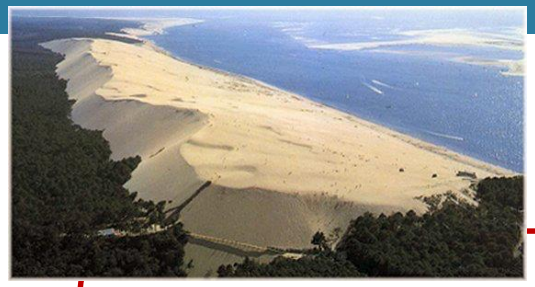
- End of « One dose fits all »
- De-escalation for small tumors / intensification for locally advanced tumors
- individualize radiotherapy planning with SUV dependant dose painting ?

And what about FDG-PET/MRI ?

Thanks for your attention

Bordeaux à l'aube, janvier 2017


Fashion in France
beret
red scarf
stripes
« baguette » bread
Cliché!
France seen from abroad



DON’T MISS : Climb the Dune of Pilat (biggest Dune in Europe), go down to the sea, and have a drink at « La Corniche » to see a beautiful sunset

Taste a Cannelé (typical cake specialty from Bordeaux)
By Baillardran
Or La Toque Cuivrée

Discover the very new « city of wine » (just opened in June)
http://www.laciteduvin.com/en
Enjoy a 360° view of Bordeaux and discover wines from across the world
Tram B, stop « la cité du vin »

DON’T MISS !Ride your bike on the docks, go to the right river through Chaban-Delmas bridge, discover Darwin area and go back through Peter Bridge: stop at the miroir d’eau (water mirror)

Drink Lillet for the aperitif

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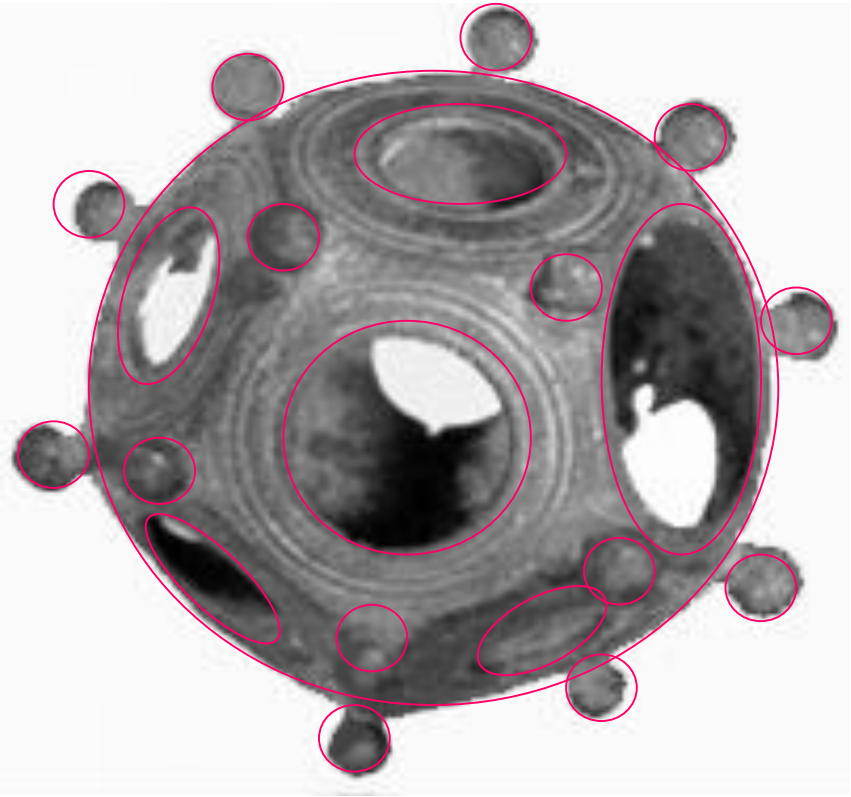
ESNM

WWW.ESTRO.ORG/SCHOOL

GTV delineation using molecular imaging

Ursula Nestle

Topographic imaging information



diagnostic imaging:

What is that?

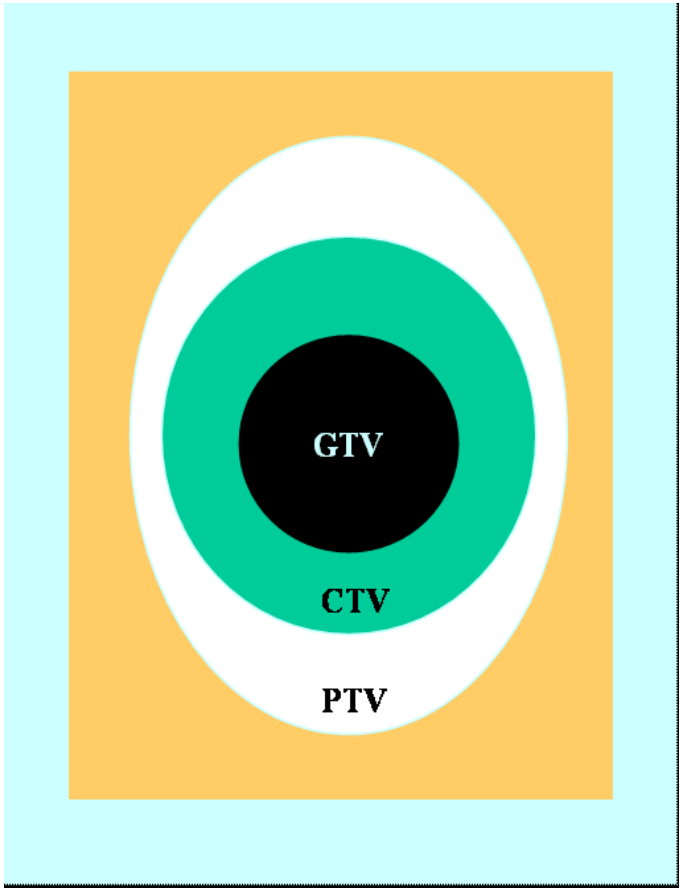
RT treatment planning:

Where is that?

GTV-delineation:
sources for assessment of tumor extension

clinical information
- Inspection, Palpation
- Endoscopy
- Histo-/cytology
…

Imaging
- CT
- PET
- MRI
…



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Even if there is a PET-scan:

- Consult radiologist / NM specialist for clear identification of pathologic findings
- Include all available clinical information
- For optimal contrast/less reflection:
  - darkened room
  - screen on 90 angle°
- Use optimal image zooming: 1:1 image/screen

Doctor`s hands are **not** stable instruments

Twice the zoom makes your fingers seem twice as steady!

Caution: overzooming = tunnelvision

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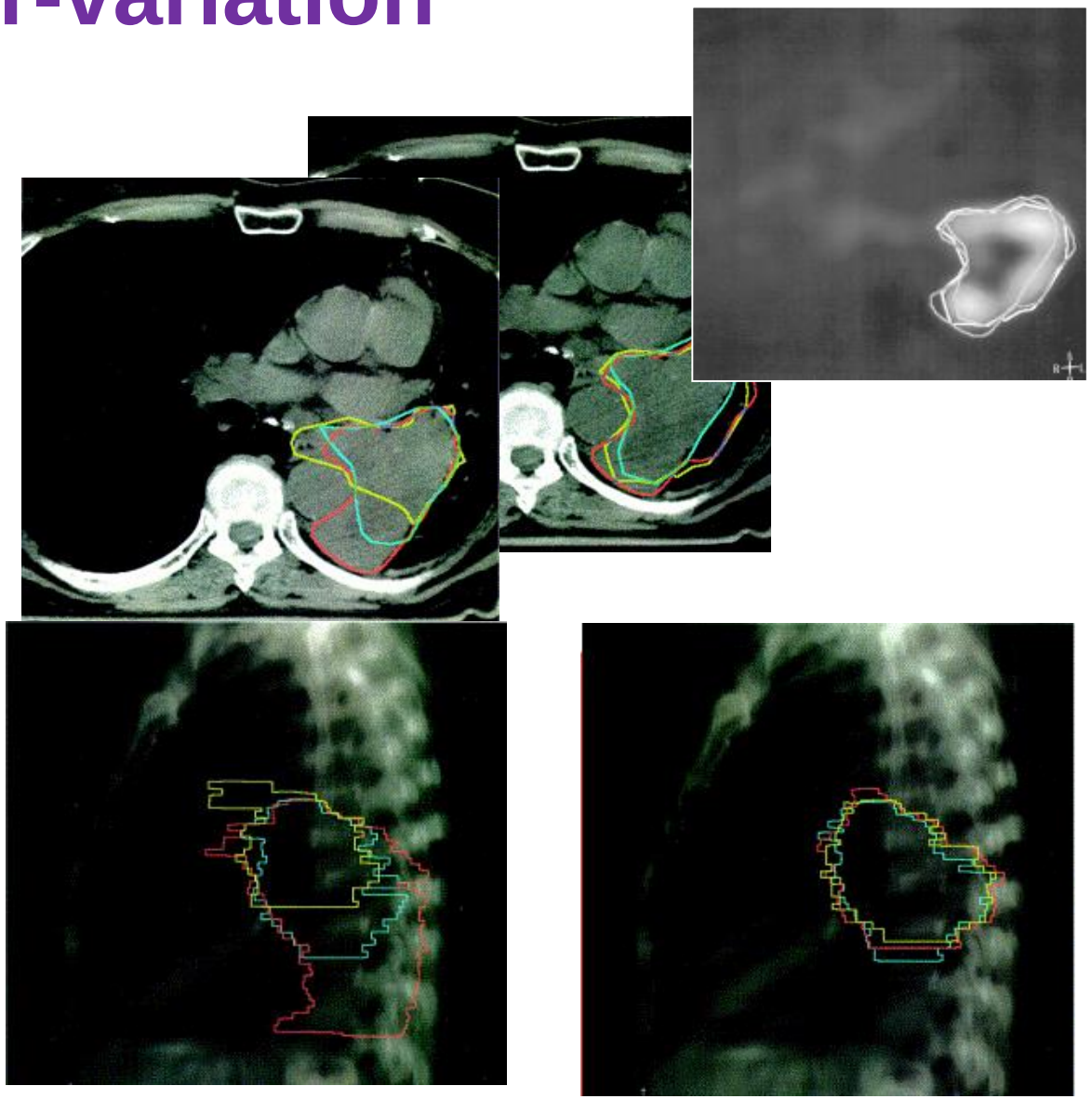
PET: Inter-observer-variation

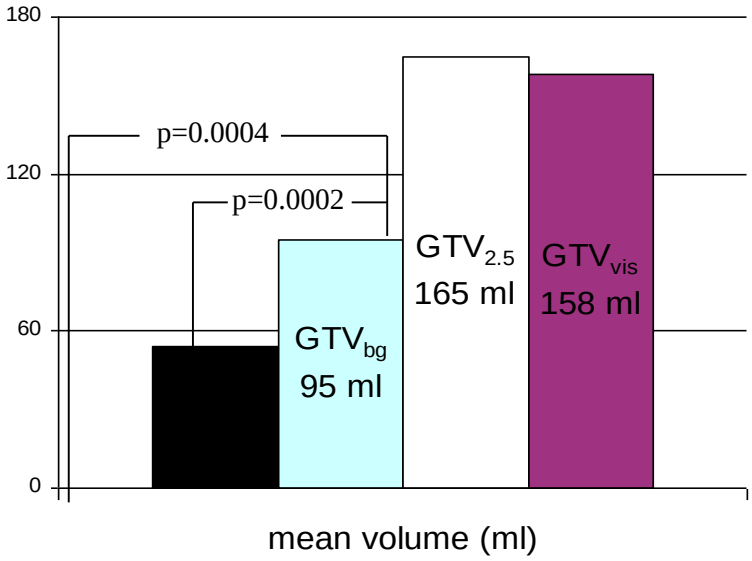
GTV-Definition by 3 RO

large interindividual differences in GTV-definition

addition of PET:
less variation

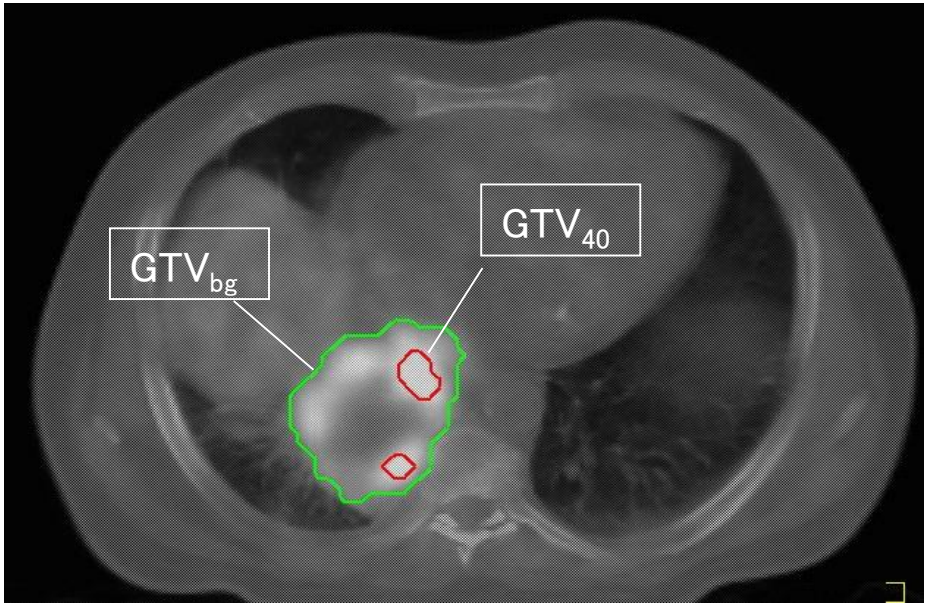


However: the contouring method matters!



25 primary NSCLC tumors,
4 contouring methods:
1 visual, 3 thresholding

correlation of differences with
- SUV_{max}
- size of lesion
- FDG-Inhomogeneity



Nestle JNM 2005

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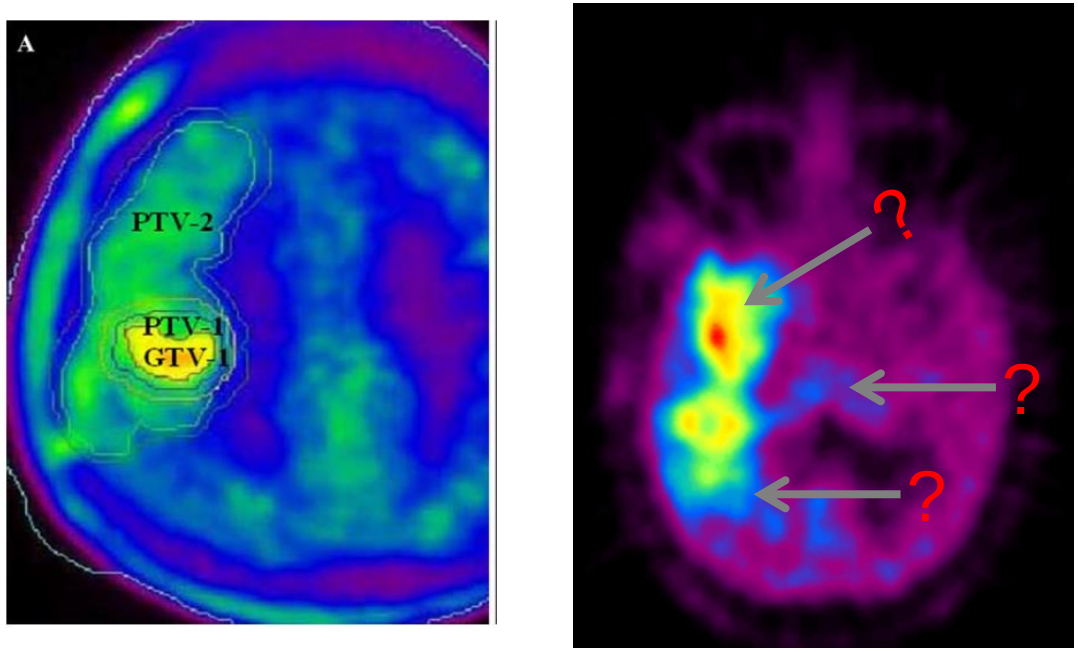
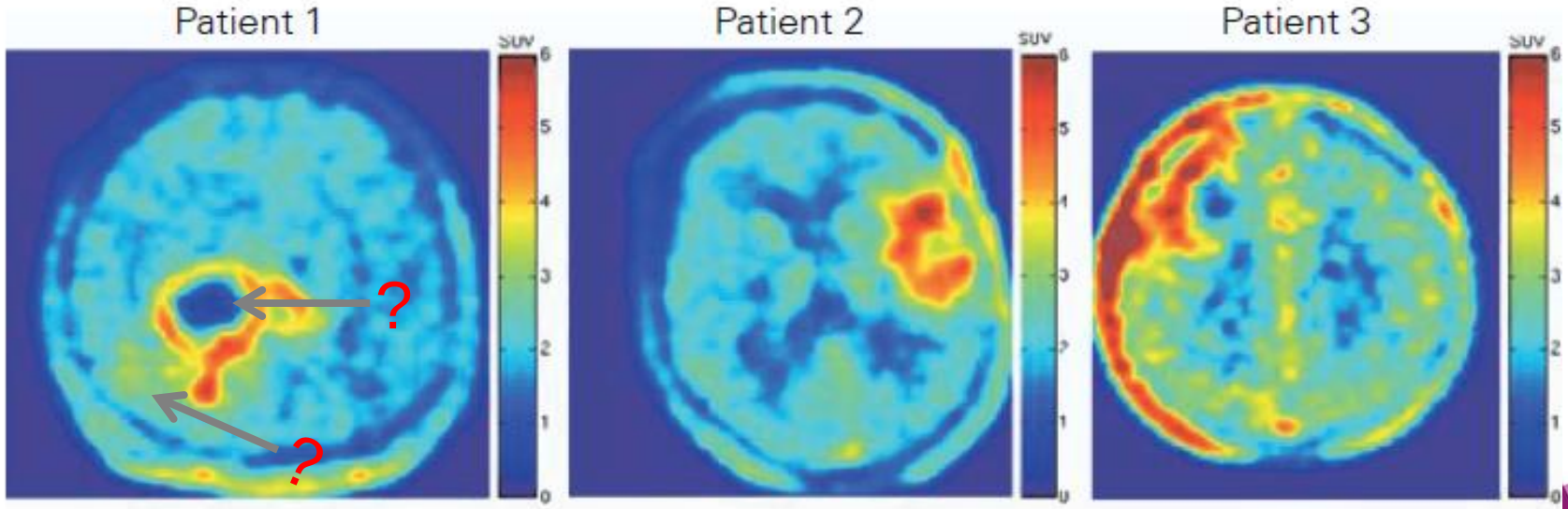
Problem: what the hell is the GTV?





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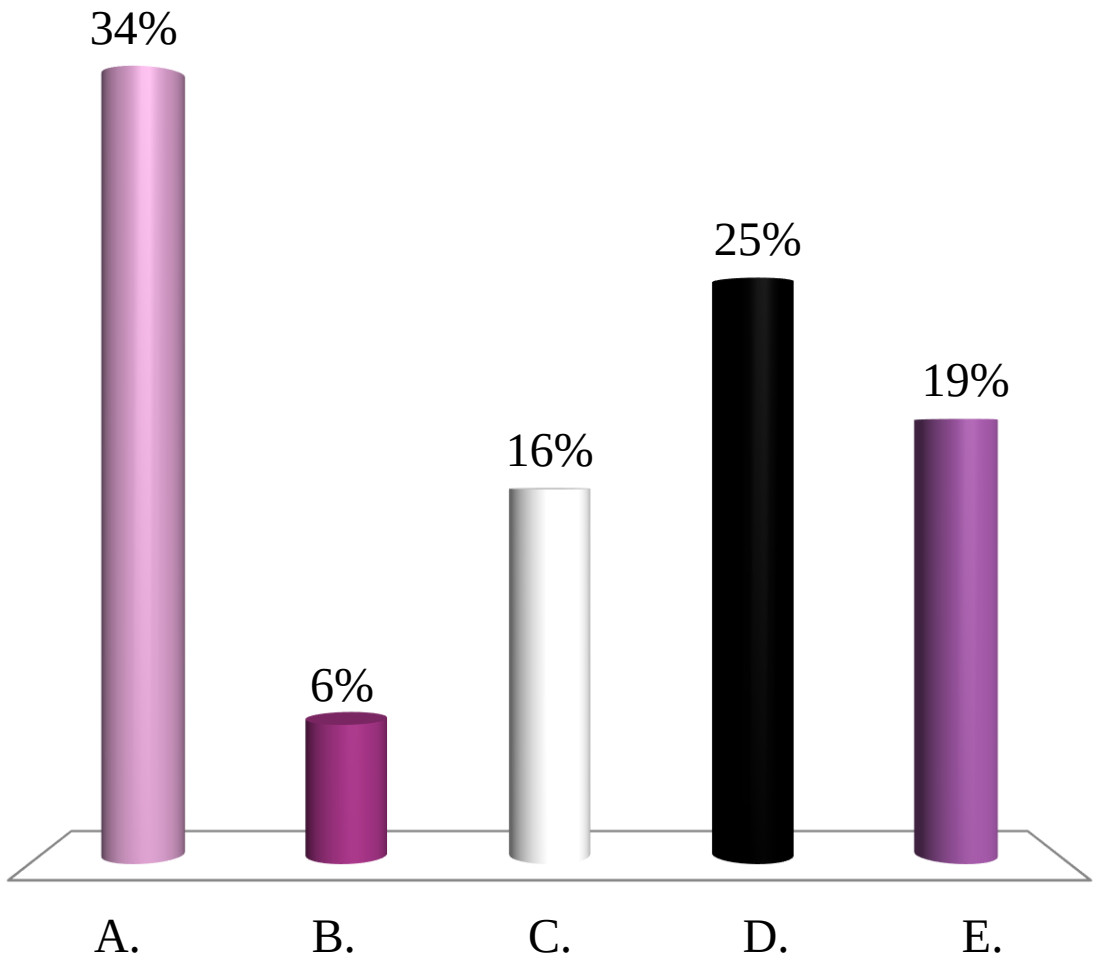
In your routine work, how do you contour PET positive lesions?

A. Visually
B. Using a percentage of the maximum uptake
C. Using the method provided by my contouring system
D. Using the contour provided by the nuclear medicine physician
E. Using the CT



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Visual delineation

visual judgement important part in GTV delineation:

- selection of patient, selection of target
- correction for incorrect inclusion of benign uptake

Visual GTV-delineation

- Advantage:
  includes brain of observer
  - engrams of diagnostic and clinical experience
  - visualizing of image context and anatomy

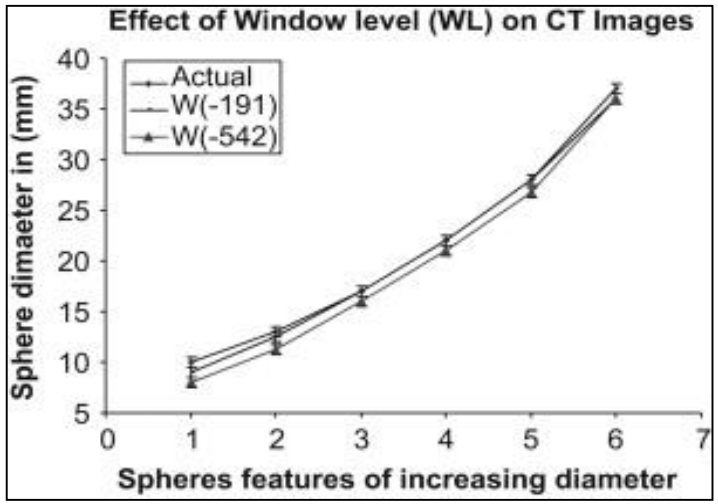
- Disadvantage
  - time consuming
  - standardisation difficult …

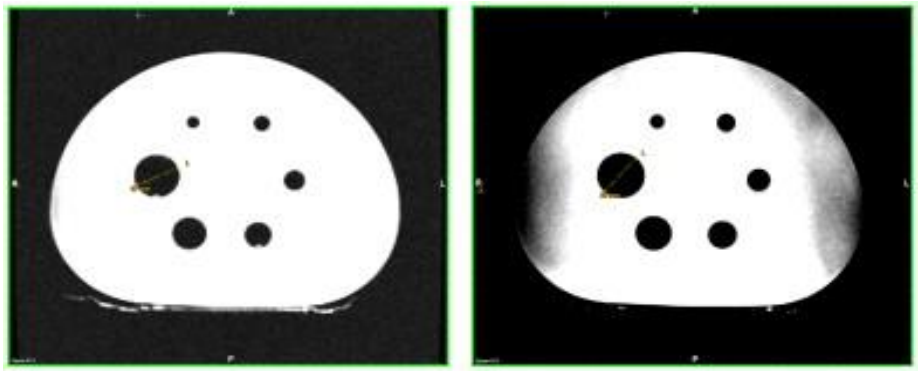
Standardisation of visual delineation

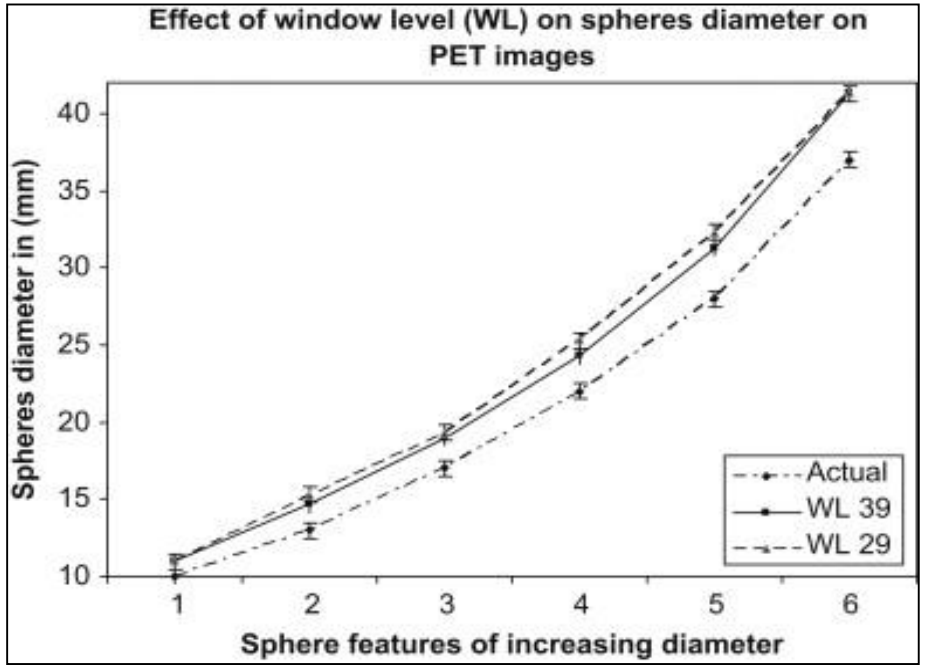
Methods

- department-specific protocols (Bayne 2010)
- courses …
- inclusion of NM-viewer in RT-contouring proces
- experience

Impact of window level







Phantom study CT/ MRI/ PET
- up to 2 mm difference in size
- PET: + PVE in big spheres

Dalah et al, Appl Radiat Iso 2010

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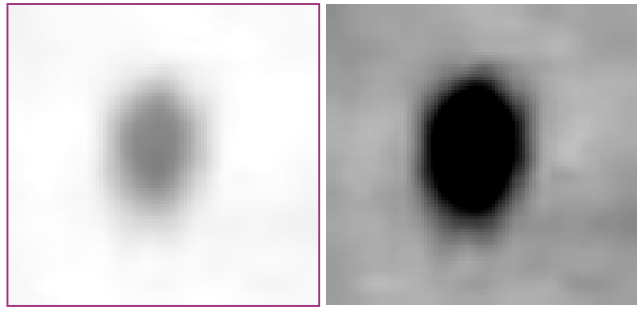
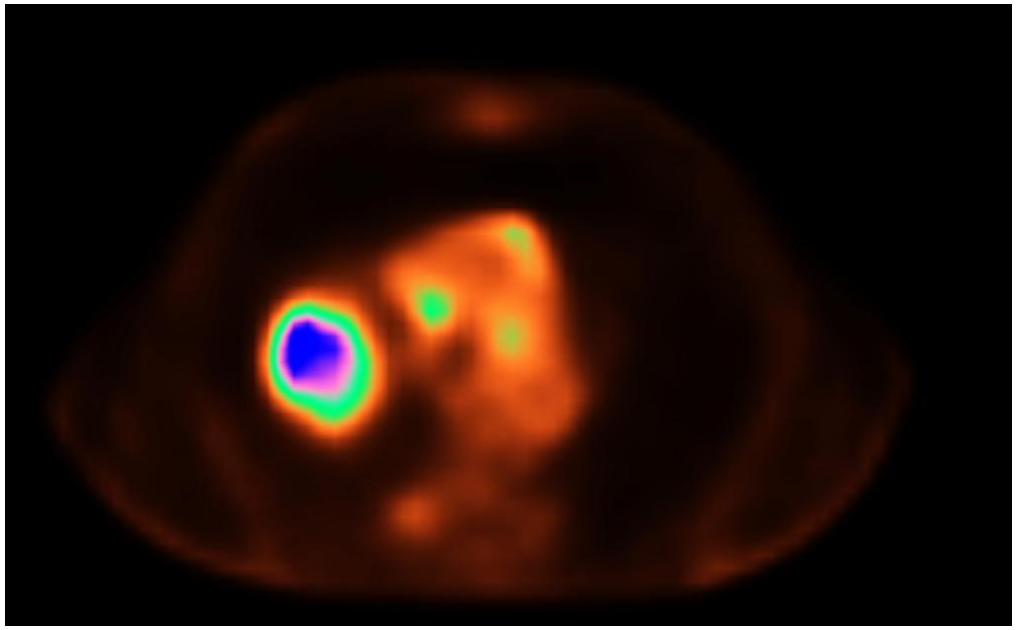
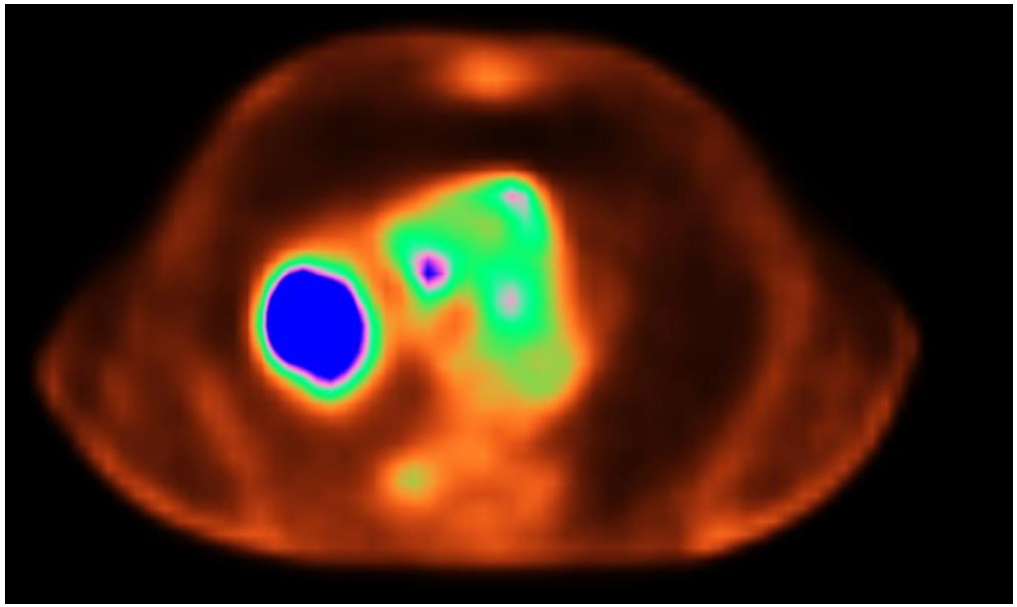
PET: window setting



- Window-level setting:
  - standardized diagnostic setting necessary
  - Do not use colour scale for visual contouring
    lines of changing colour may mimic inexistent tumor borders





Same tumor, different settings

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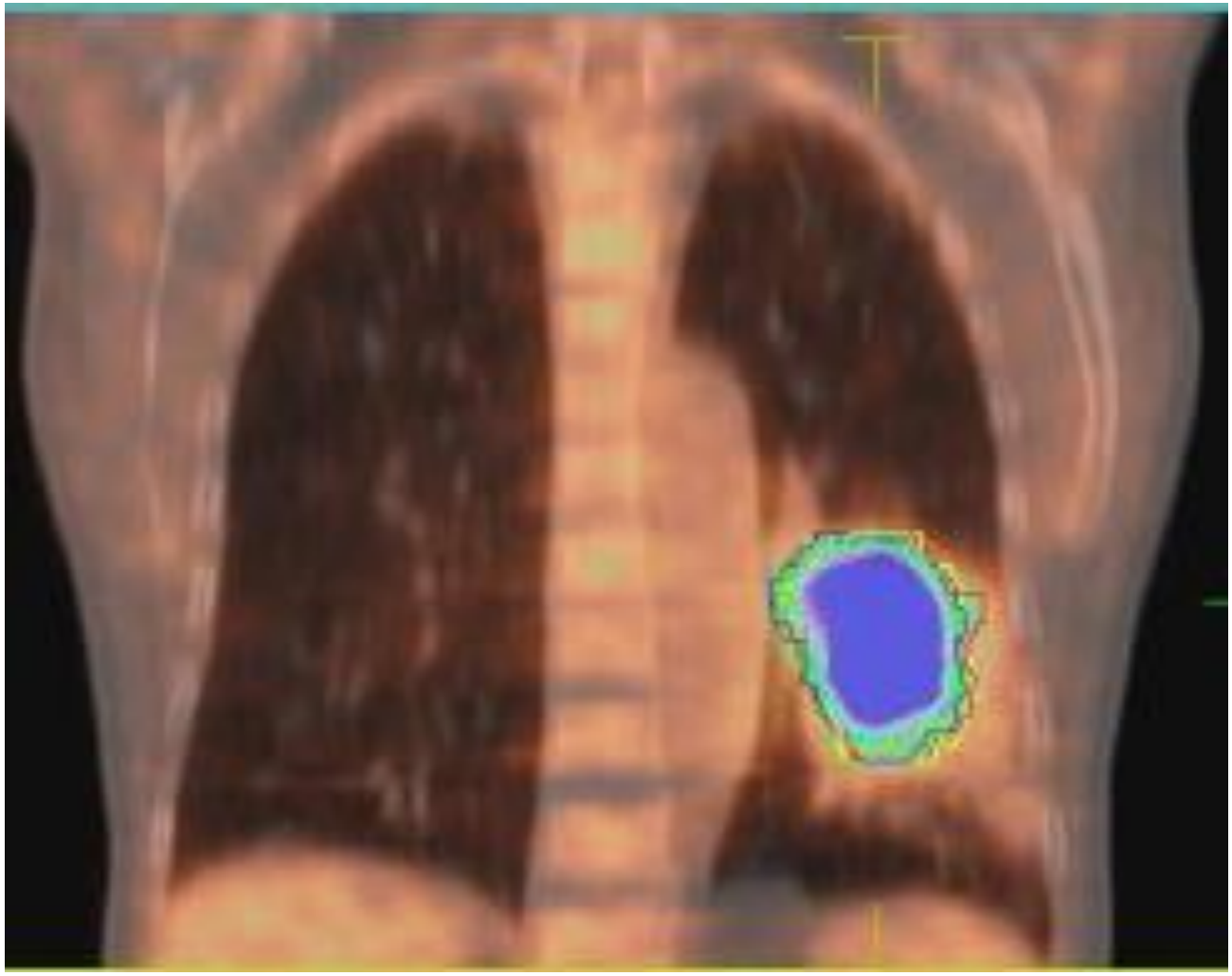
“intelligent” visual contouring



Bayne 2010

standardized clinical protocol leads to acceptable IOV

Conclusions: Observer variation contributed little to total variation in the GTV and axial distances. A visual contouring protocol gave reproducible results for contouring GTV in NSCLC.

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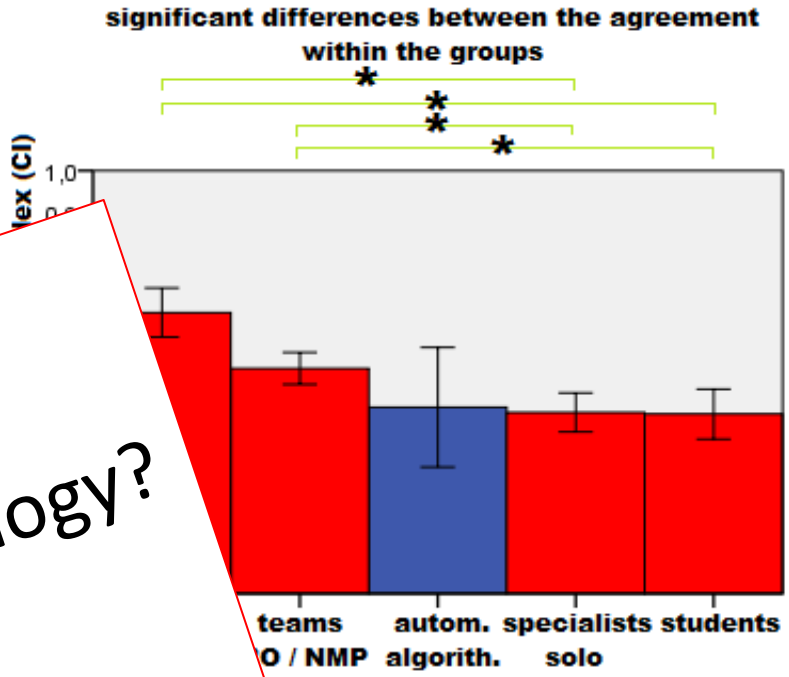
Observer variability vs. method variability

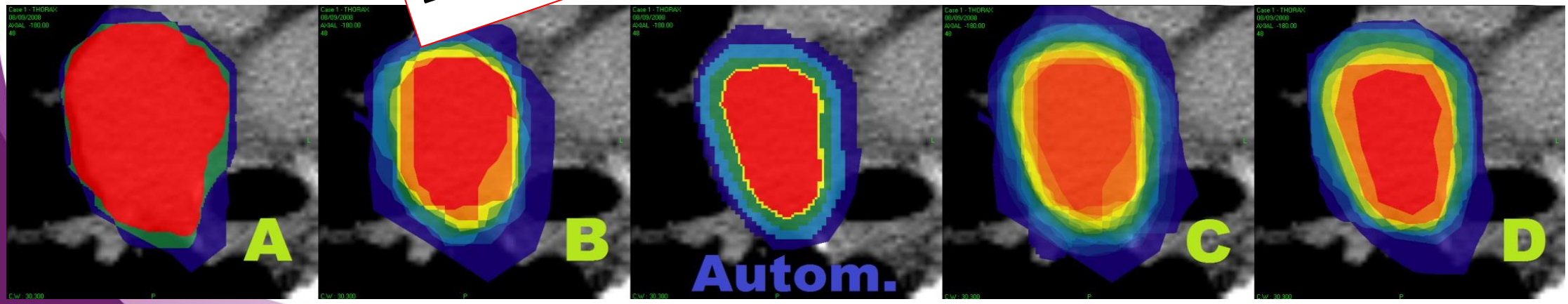
- 1 case, 40 contours
- Experts(**A**) and teams RO & NM (**B**)
  → Significantly higher IOV (
- IOV Specialis
- „PET-years“ n
- IMV of automat

C. Doll et al. 2012



What is the gold standard:
- size of tumor in CT?
- size of tumor by pathology?
- ITV?
- expert delineation?

	B	C	D
	0,67	0,53	0,44	0,43	0,42
Kappa Index	0,80	0,69	0,59	0,57	0,57



Problem: Ground truth

- To calibrate a correct contouring method, the knowldedge on the correct tumor borders is essential, e.g. from:

- Phantom-measurements
  Problem: usually homogenous spheres, glass wall, homogenous background
  = not representative for tumors
- simulated images
  Problem: extremely harmful to produce, proximity to reality depends on assumptions
- image data with histopathology correlation
  not many datasets available, all have shortcomings: shrinking, distortion, problem of coregistration, diffuse infiltration
- tumor size known from other imaging
  Problem: reason for second imaging? other problems in size determination

•possible surrogates:

- comparison with expert contours, ideally consistent in multiple observers
- visual or mathematical consensus-contour of different methods

Automatic delineation

YAPETISM

(yet another PET image segmentation method …)

- Thresholding
  - Fixed threshold (e.g. predefined SUV or % of maximal SUV)
  - Adaptive thresholding („contrast oriented“, „source-to-background“)
- Region growing (variant of contrast)
- watershed (variant of contrast)
- pipeline (multi-step)
- gradient based (edge finding)
- hybrid (including CT information)

Zaidi EJNMMI 2010
Shepherd, 2011, submitted
Lee R&O 2010

Delineation

Table 1 Summary of main pros/cons of the various categories of PET image segmentation techniques

Category	Characteristics	Limitations
Manual techniques	Visual interpretation and manual delineation of contours. Very simple to use. Tools to transfer RT objects to treatment planning systems available from most vendors	Time consuming. Susceptibility to window level settings. Suffer from intra- observer variability. Consensus reading by physician and radiation onc in busy clinical departments
Thresholding techniques	Most frequently used due to their simple implementation and high efficiency	aking. Too sensitive to PVE, tumour geneity and motion artefacts. Some methods focus on volume, others focus on intensity differences. Combination of both seems to provide best results [95]
Variational approaches	Subpixel accuracy, bound atively efficient. They are developed and allow for i such as shape	Sensitive to image noise. As a PDE, stability and convergence could be subject to numerical fluctuations, especially if the parameters are not properly selected
Learning methods	Utilize patter ion power. Two main types: supervised (classification) and unsupervised (clustering)	Computational complexity especially in supervised methods, which require time-consuming training. Feature selection besides commonly used intensity is a flexibility but can also be a challenge
Stochastic models	Exploit statistical differences between tumour uptake and surrounding tissues. Most natural to deal with the noisy nature of PET	Effect of initialization and convergence to local optimal solutions are concerns, especially when compromises are made to improve efficiency

Calibration of system necessary !

Zaidi EJNMMI 2010

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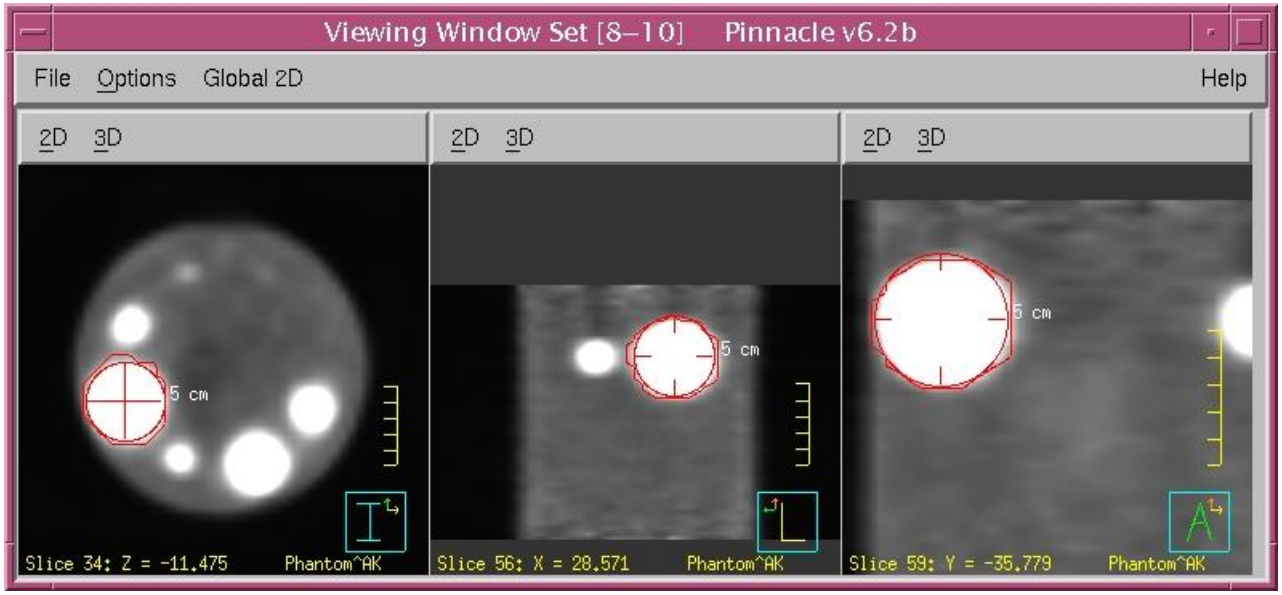
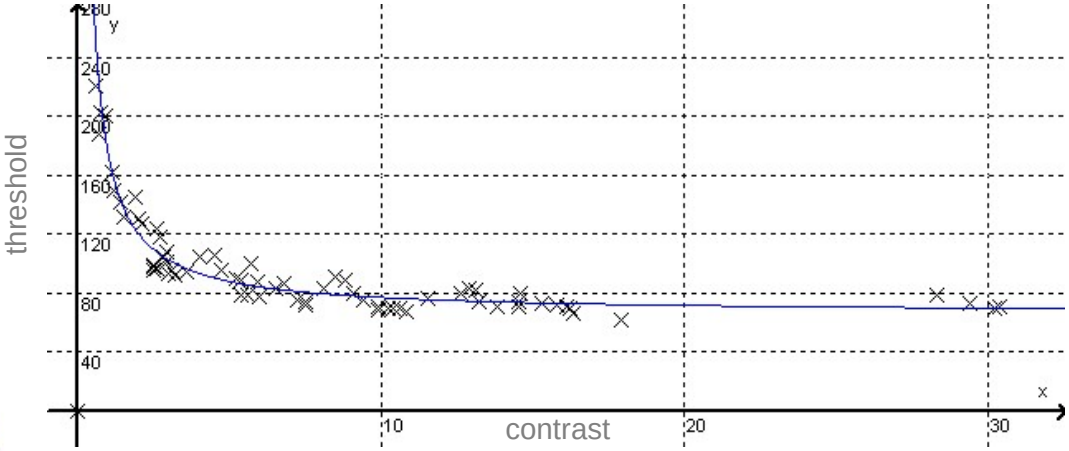
Adaptive thresholding e.g. Homburg algorithm





source / background – algorithm:

$I_{threshold} = (x * I_{lesion}) + (y * I_{background})$

Schaefer EJNM 2008

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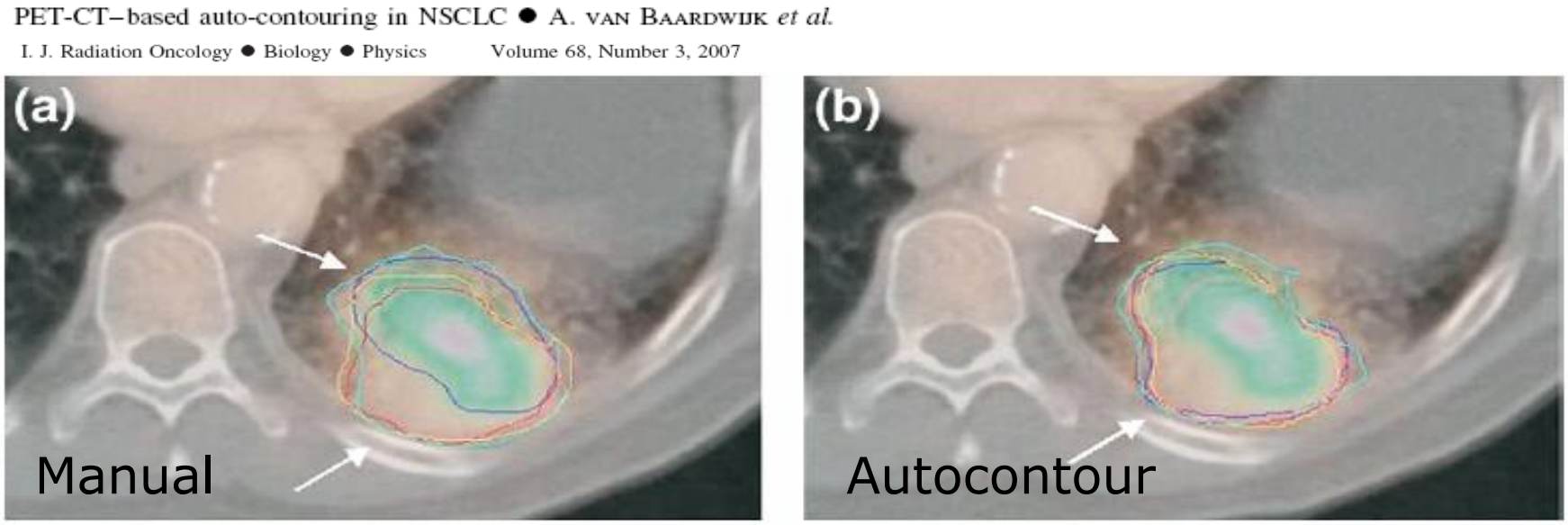
Requirements of PET(-CT) data for use in RT

Auto-contouring vs manual contouring of primary tumour



- Multi-observer study
- Autodelineation reduces Gross Tumor Volume significantly
- Reduces interobserver variability
- Overall: autocontouring improves delineation of target volumes

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The„Turku contouring challenge“

label	team	type	median rank	
			phant.	patient
A	01	PL	17	19
B	02	WS	1.5	1.5
C	03	PL	24	31.5
D			23.5	27
E			10.5	12.5
F		T2	4	7
G	04	MD	28.5	23
H		T4	6	9
I			18.5	15.5
J			17.5	20.5
K_1	05	MD	13.5	25.5
K_2			20.5	31.5
L		RG	14.5	17
M	06	HB	n/a	12
N	07	WS	8.5	26
O	08	T1	3	23
P			28.5	11
Q		T2	13.5	14
R			11.5	16.5

label	team	type	median rank	
			phant.	patient
S_1	09	RG	31	7
S_2			31.5	8
T_1			20	20.5
T_2			25	22.5
U	10	PL	20	12
V			27.5	14
W	11	GR	25	23
X	12	MD	28.5	32.5
Y		T1	3	3.5
Z		T3	10.5	2
Γ			4.5	3.5
Λ		T2	7	7.5
Ω			18.5	26
Φ	13	PL	8.5	29.5

”accuracy metrics”
combines DSC
with Hausdorff distance

„**Winner**“:
visually adapted
thresholding method

label	algorithm type	description
MD	manual delineation	slice-by-slice outlining of PET VOIs using a computer mouse
RG	region growing	variants of the classical algorithm
WS	watershed	variants of the classical algorithm
PL	pipeline	multi-step algorithms that combine established image processing methods
GR	gradient-based	novel edge-finding method
HB	hybrid	novel segmentation algorithm for multi- spectral images, adapted for PET/CT

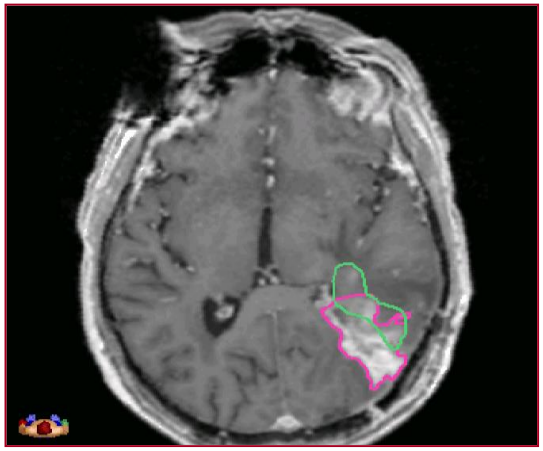
Shepherd, T. et al. 2013 IEEE

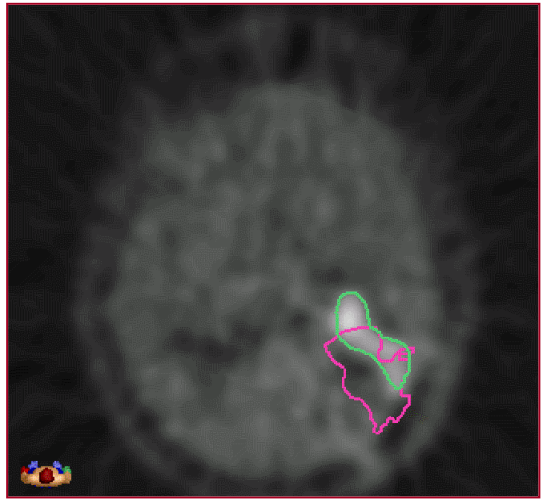
Report of AAPM TG211: Classification and evaluation strategies of auto-segmentation approaches for PET

M. Hatt[1], J. Lee[2], C. Caldwell[3], I. El Naqa[4], C.R. Schmidtlein[5], E. De Bernardi[6], W. Lu[7], U. Nestle[8], D. Visvikis[1], T. Shepherd[9], S. Das[10], O. Mawlawi[11], V. Gregoire[2], H. Schöder[5], R. Jeraj[12], A. Pugachev, E. Spezi, M. MacManus[13], X. Geets[2], H. Zaidi[14], A.S. Kirov[5*]

Conclusions: Based on the large number of published PET-AS algorithms and their relative lack of validation, selecting and implementing one algorithm among those available is challenging. **There is however accumulating evidence in available comparison studies that PET-AS algorithms relying on advanced image paradigms perform better than simple threshold-based approaches.** The second conclusion of this report is that a standard test (i.e. a benchmark) dedicated to evaluation of both existing and future PET-AS algorithms needs to be designed. The first steps in designing this standard are presented in the second half of the report. The primary intention of this benchmark is to aid clinicians in evaluating and selecting PET-AS algorithms for use in clinical practice.

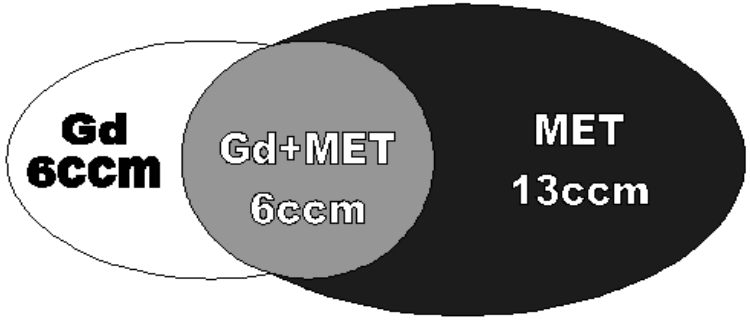
MET-PET / T1Gd-MRI image fusion. Volumetrical evaluation
(Grosu IJROBP 2005)





MET uptake corresponds to Gd enhancement	5/39 Patients (13%)
MET uptake located outside of Gd enhancement	29/39 Patients (74%)
Gd enhancement located outside of MET enhancement	27/39 Patients (69%)

MET uptake corresponds to hyperintensity on T2	0/18 Patients (0%)
MET uptake located outside of hyperintensity on T2	9/18 Patients (50%)
hyperintensity on T2 located outside of MET uptake	18/18 Patients (100%)



manual delineation, tumor/normal tissue index of 1.7 was considered

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 2, pp. 479–485, 2009
Published by Elsevier Inc.
Printed in the USA.
0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2008.04.050

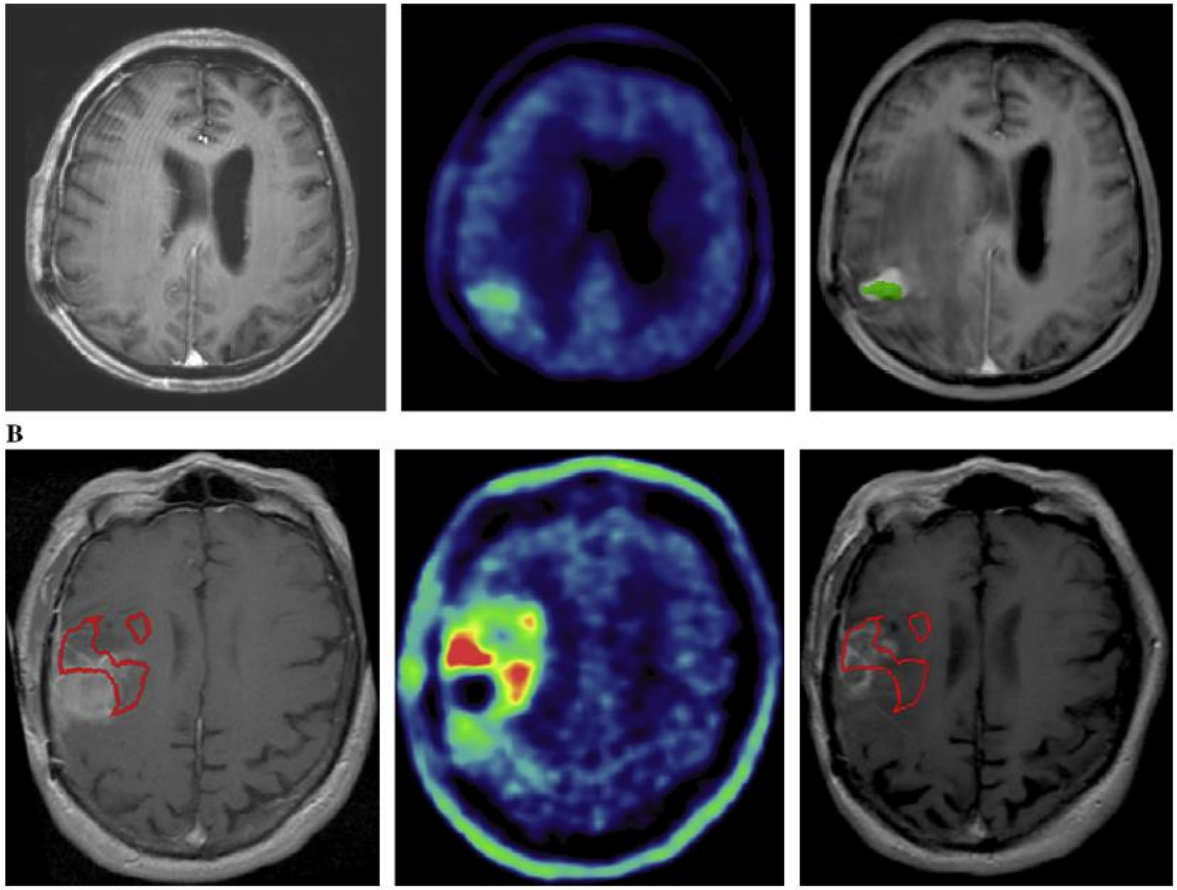
CLINICAL INVESTIGATION **Brain**

ASSOCIATION OF ^{11}C-METHIONINE PET UPTAKE WITH SITE OF FAILURE AFTER CONCURRENT TEMOZOLOMIDE AND RADIATION FOR PRIMARY GLIOBLASTOMA MULTIFORME

IRWIN H. LEE, M.D., PH.D.,* MORAND PIERT, M.D.,† DIANA GOMEZ-HASSAN, M.D., PH.D.,‡ LARRY JUNCK, M.D.,§ LISA ROGERS, M.D.,§ JAMES HAYMAN, M.D.,* RANDALL K. TEN HAKEN, PH.D.,* THEODORE S. LAWRENCE, M.D., PH.D.,* YUE CAO, PH.D.,* AND CHRISTINA TSIEN, M.D.*

Departments of *Radiation Oncology, †Nuclear Medicine, ‡Radiology, and §Neurology, University of Michigan, Ann Arbor, MI

In five patients, the PET-GTV was not fully encompassed by the 95% IDS, and all of these patients recurred with noncentral failures. In comparison, only 2 of 14 patients whose PET-GTV was fully encompassed by the 95% IDS had noncentral failures. This included 3 patients who have not yet failed with more than 12 months of follow-up. Using the Fisher exact test, this apparent association between suboptimal coverage of the PET-GTV and subsequent noncentral failure was statistically significant ($p < 0.01$).



1.5/ mean cerebellar uptake, uptake in normal tissues excluded manually

A Biologically Adapted Dose-Escalation Approach, Demonstrated for ^{18}F-FET-PET in Brain Tumors

Mark Rickhey[1], Oliver Koelbl[1], Christoph Eilles[2], Ludwig Bogner[1]

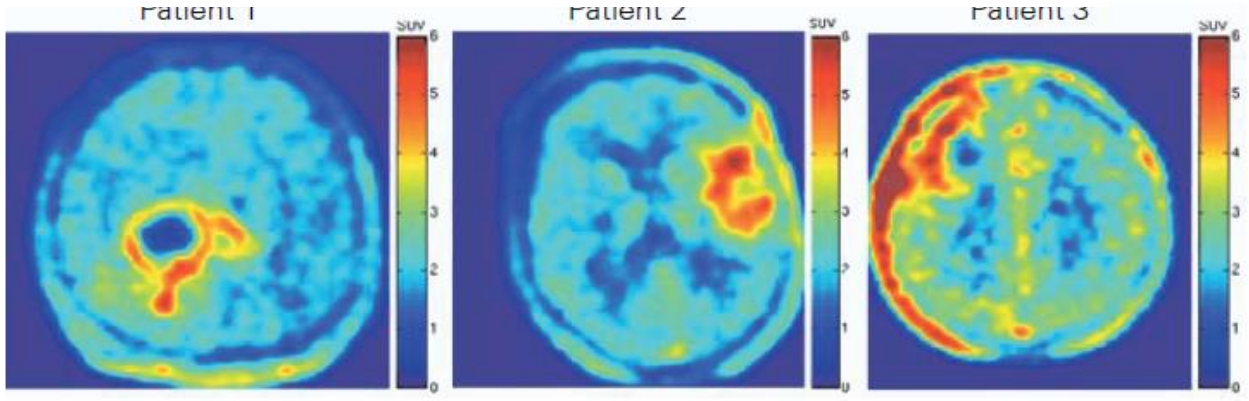


Figure 1. PET images of all patients in a representative transverse slice. An SUV > 3 was regarded as tumor. In patient 3, the target volume was reduced after consulting additional MRI. The accumulation in the cranial bone was not related to the tumor.

Strahlenther Onkol 2008;184:536–42
DOI 10.1007/s00066-008-1883-6

SUV > 3

^{18}F-FET-PET-Based Dose Painting by Numbers with Protons

Mark Rickhey[1], Zdenek Morávek[1], Christoph Eilles[2], Oliver Koelbl[1], Ludwig Bogner[1]

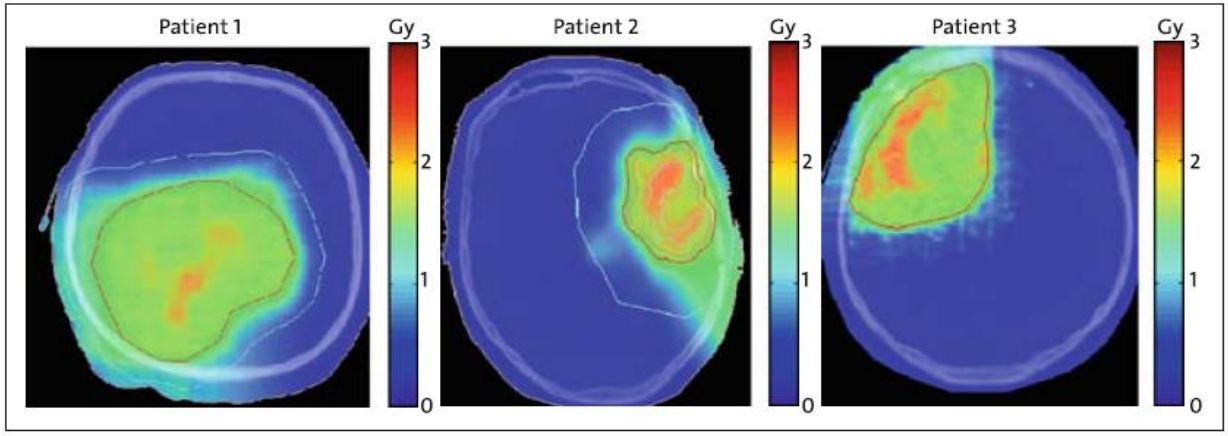


Figure 3. DPBN dose distributions obtained with spot-scanning protons (IMPT) in a transverse slice. As for the associated ^{18}F-FET-PET images the authors refer to [27]. The limits of the linear model were set to D_{min} = 1.8 Gy and D_{max} = 2.7 Gy.

Strahlenther Onkol 2010;186:320–6
DOI 10.1007/s00066-010-2014-8

ESTRO School

J Neurooncol (2008) 87:333–339
DOI 10.1007/s11060-008-9519-3

CLINICAL-PATIENT STUDIES

Simultaneous integrated boost technique by helical tomotherapy for the treatment of glioblastoma multiforme with ^{11}C-methionine PET: report of three cases

Kazuhiro Miwa · Masayuki Matsuo · Jun Shinoda · Naoki Oka · Takayuki Kato · Ayumi Okumura · Tatsuya Ueda · Kazutoshi Yokoyama · Jitsuhiro Yamada · Hirohito Yano · Shinichi Yoshimura · Toru Iwama

uptake. The tumor margin, on intensive MET, was considered to be that area demonstrating a threshold of 2.0 for the standardized uptake value (SUV) of the tumor, compared to that of the contralateral normal brain index. An index of 1.3 was considered the tumor margin based on moderate MET uptake. GTV-2 was defined as the area of

PTV1: t/b 2.0
PTV2: t/b 1.3

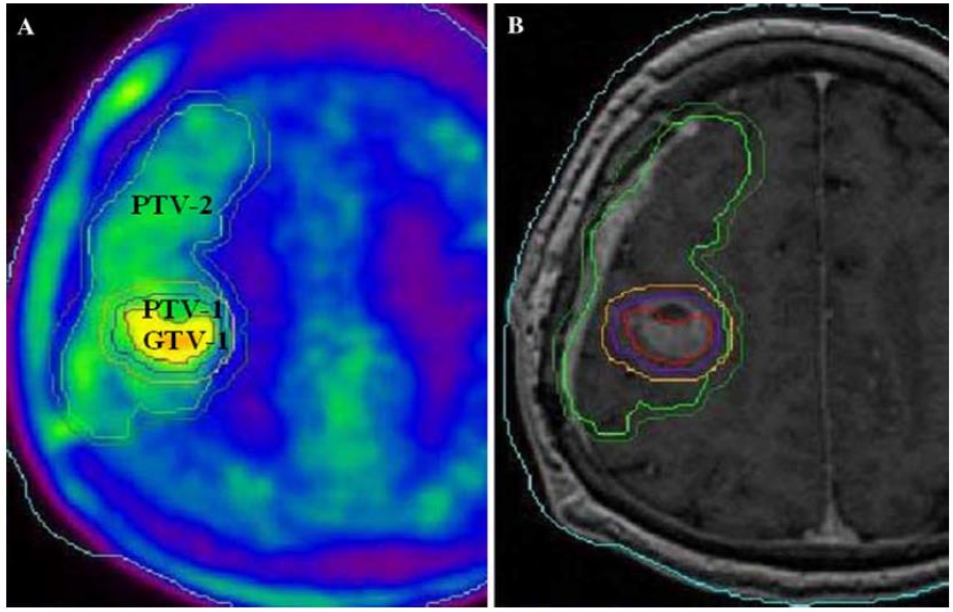


Fig. 1 Dose maps of case 1. (a) Gross tumor volume (GTV)-1 was defined as the area of intensive ^{11}C-methionine (MET) uptake. GTV-2 was defined as the area of moderate MET uptake. Planning target volume (PTV)-1 encompassed the GTV-1 plus a 5-mm PTV-2 encompassed the GTV-2 plus a 2-mm margin. (moderate MET uptake (PTV-2) could not be detected

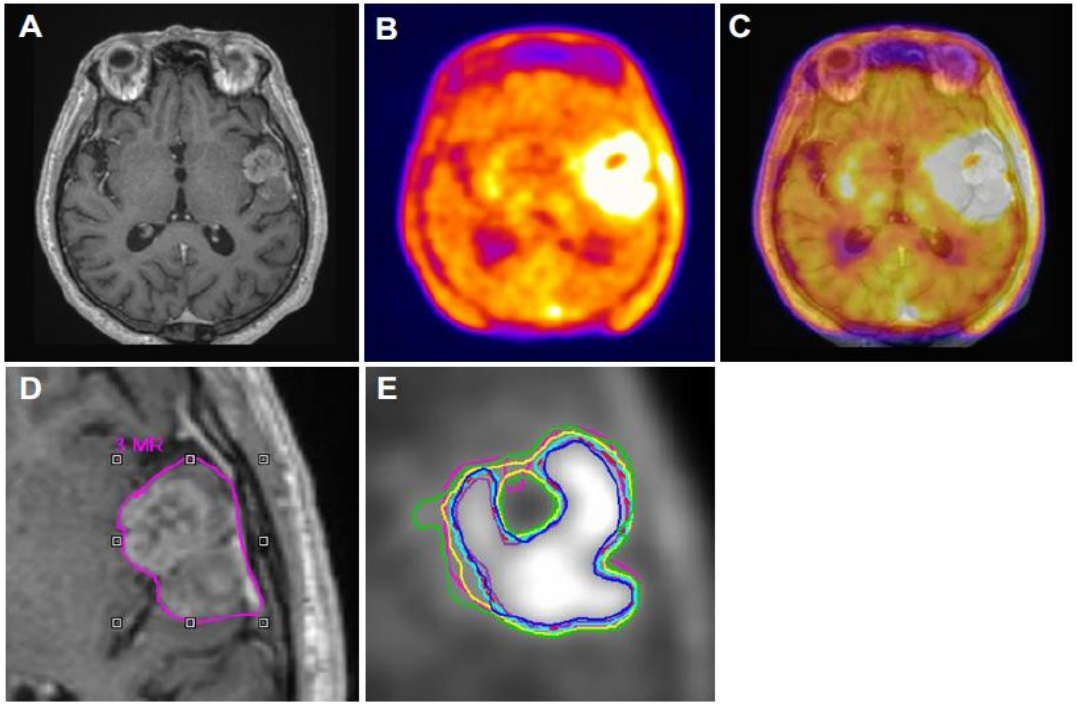


Fig. 4 (A) Gadolinium enhanced T1-weighted MRI, (B) corresponding ^{18}F-FET PET, and fused PET/MR (C) transaxial slices of a clinical study with a glioblastoma showing differences in target-volume definition. Indicated are (D) the gross tumor volume (GTV) delineated on MRI (GTV_{MRI}), and (E) enhanced details of PET-based GTVs obtained by manual delineation of contours (GTV_{man}; *magenta*), an isocontour of a standardized uptake value (SUV) of 2.5 ($GTV_{2.5}$; *purple*), a fixed threshold of 40% ($GTV_{40\%}$; *green*) and 50% ($GTV_{50\%}$; *cyan*) of the maximum signal intensity, signal-to-background ratio (SBR)-based adaptive thresholding (GTV_{SBR}; *yellow*), gradient find (GTV_{GF}; *blue*), and region growing (GTV_{RG}; *red*) segmentation algorithms. Note that GTV_{MRI} overestimates the tumor extension relative to GTV_{man}

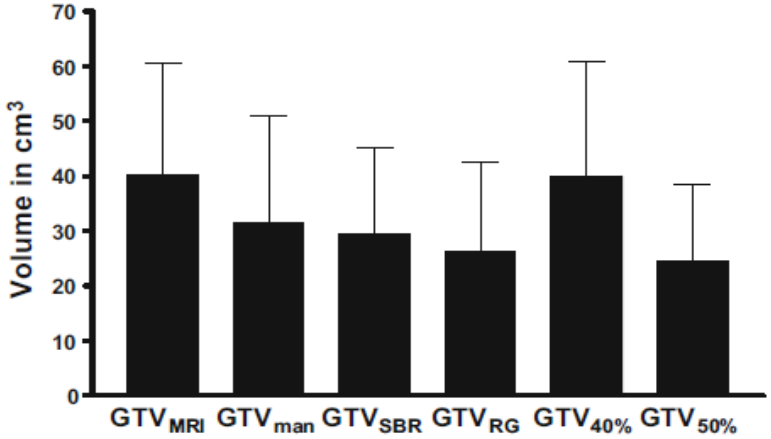


Fig. 6 Comparison of mean tumor volumes for 18 patients and in only 19 lesions where MRI, manual delineation, thresholding using 40% and 50% of the maximum intensity, as well as RG and SBR techniques were able to adequately delineate the tumor volume. *Error bars* indicate SD on the mean. Results are shown for the gross tumor volume (GTV) delineated on MRI (GTV_{MRI}) and PET-based GTVs obtained by manual delineation of contours (GTV_{man}), an isocontour obtained using a fixed threshold of 40% ($GTV_{40\%}$) and 50% ($GTV_{50\%}$) of the maximum signal intensity, signal-to-background ratio (SBR)-based adaptive thresholding (GTV_{SBR}), and region growing (GTV_{RG}) segmentation algorithms

Vees,… Zaidi
EJNMMI 2009

Conclusions The selection of the most appropriate ^{18}F-FET PET-based segmentation algorithm is crucial, since it impacts both the volume and shape of the resulting GTV. The 2.5 SUV isocontour and GF segmentation techniques performed poorly and should not be used for GTV delineation. With adequate setting, the SBR-based PET technique may add considerably to conventional MRI-guided GTV delineation.

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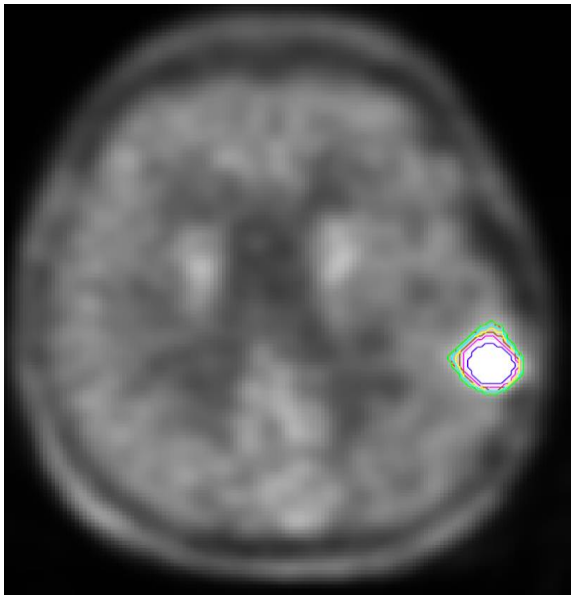
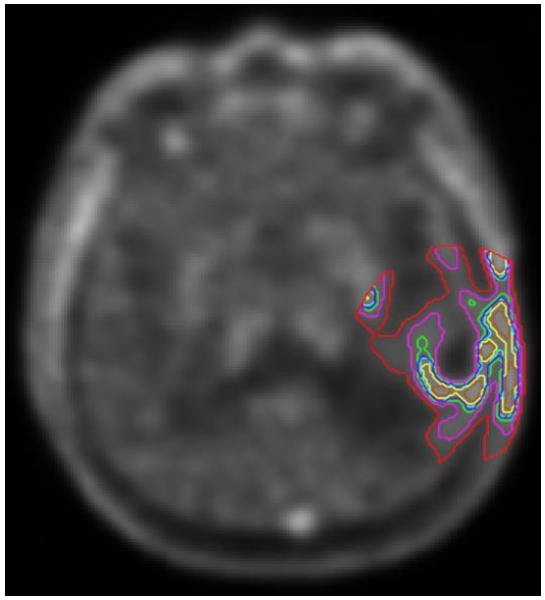
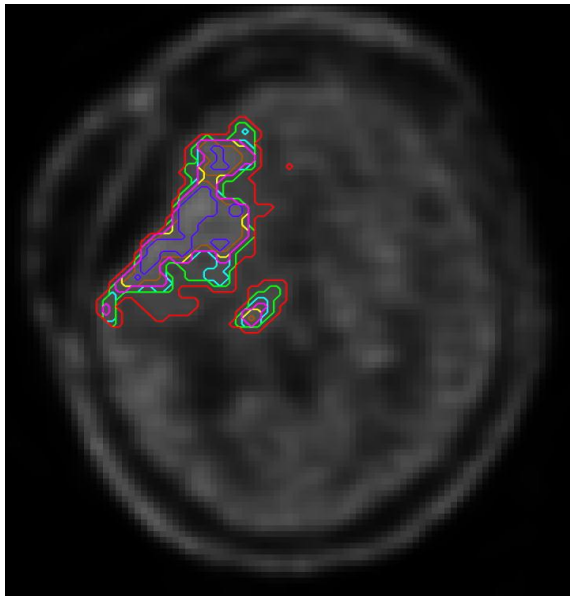
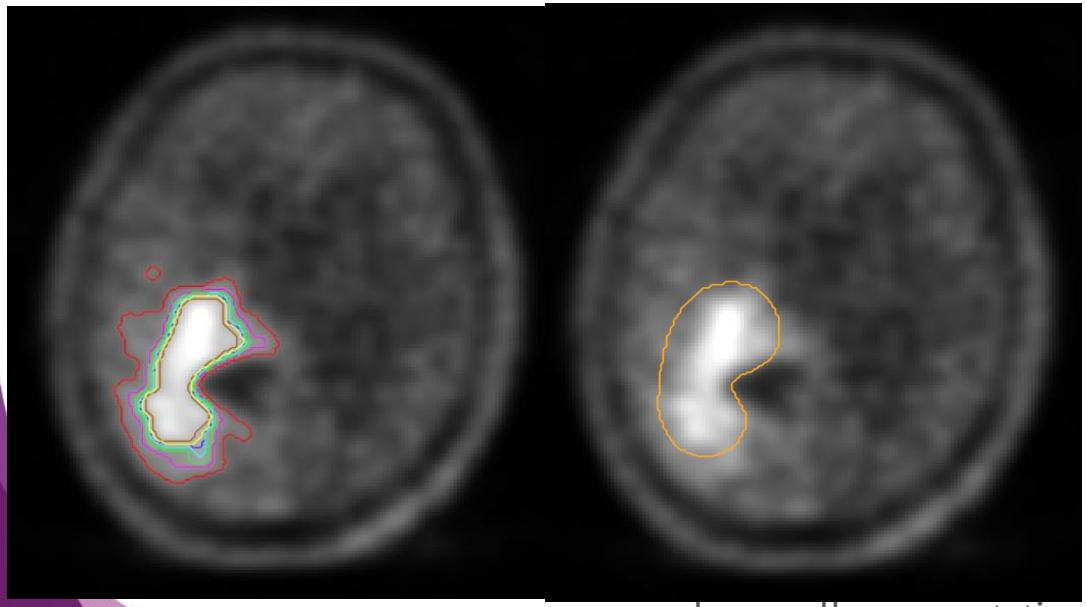
Usability of contouring-methods, Random walk



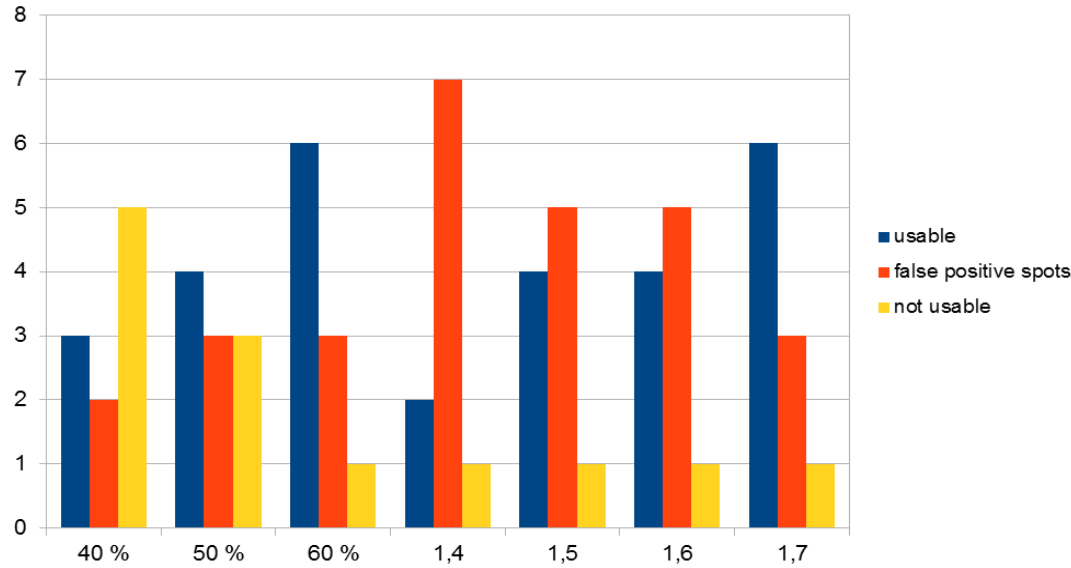




40% red
50% pink
60% blue
1,4 green
1,5 turkis
1,6 yellow
1,7 brown



random walk segmentation



Requirements of PET(-CT) data for use in RT

Auto-contouring vs manual contouring: pitfalls

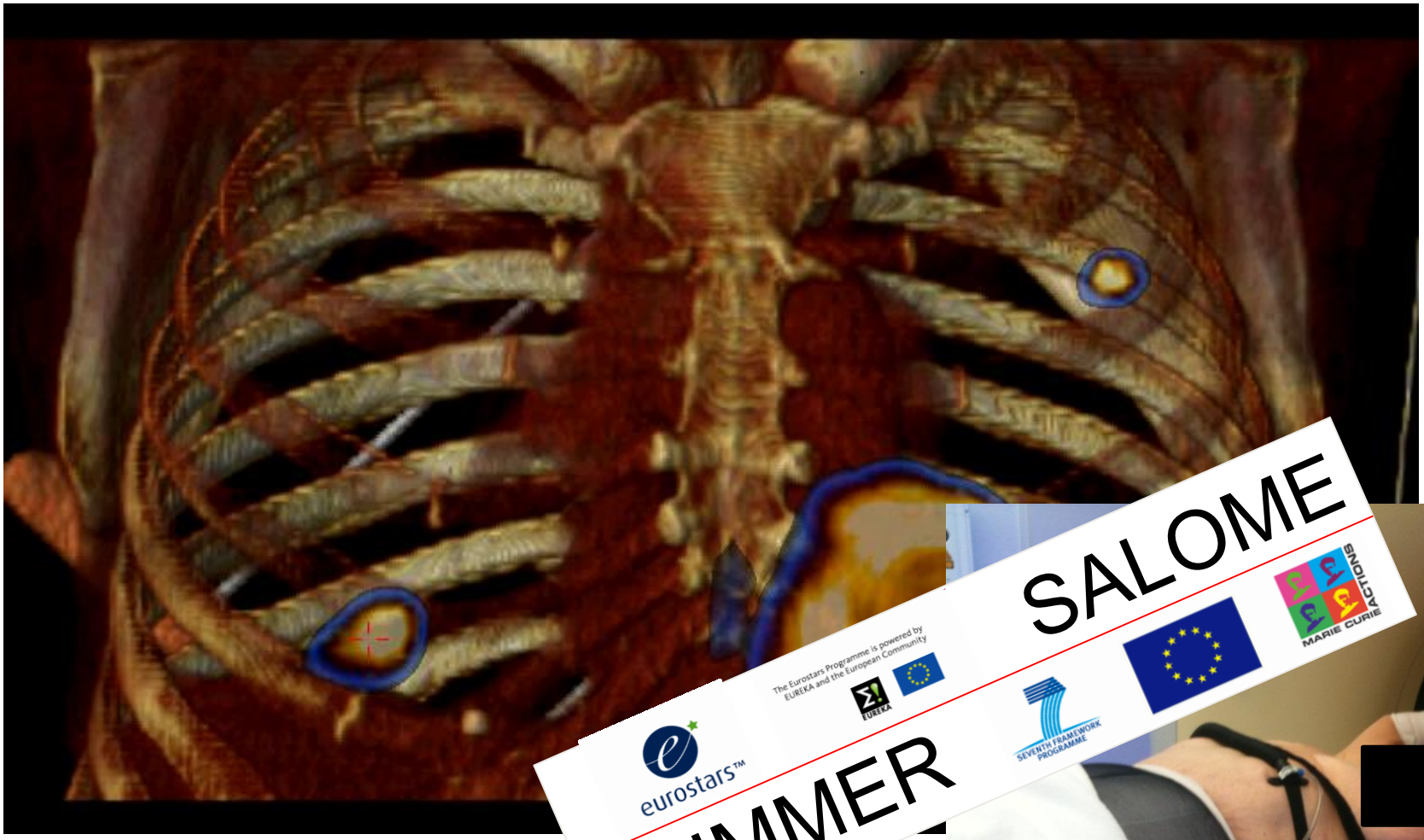
- Autocontouring is a very helpful tool but the physician should always check whether the SUV contour needs adaptation (which is often the case)
- Stated differently….

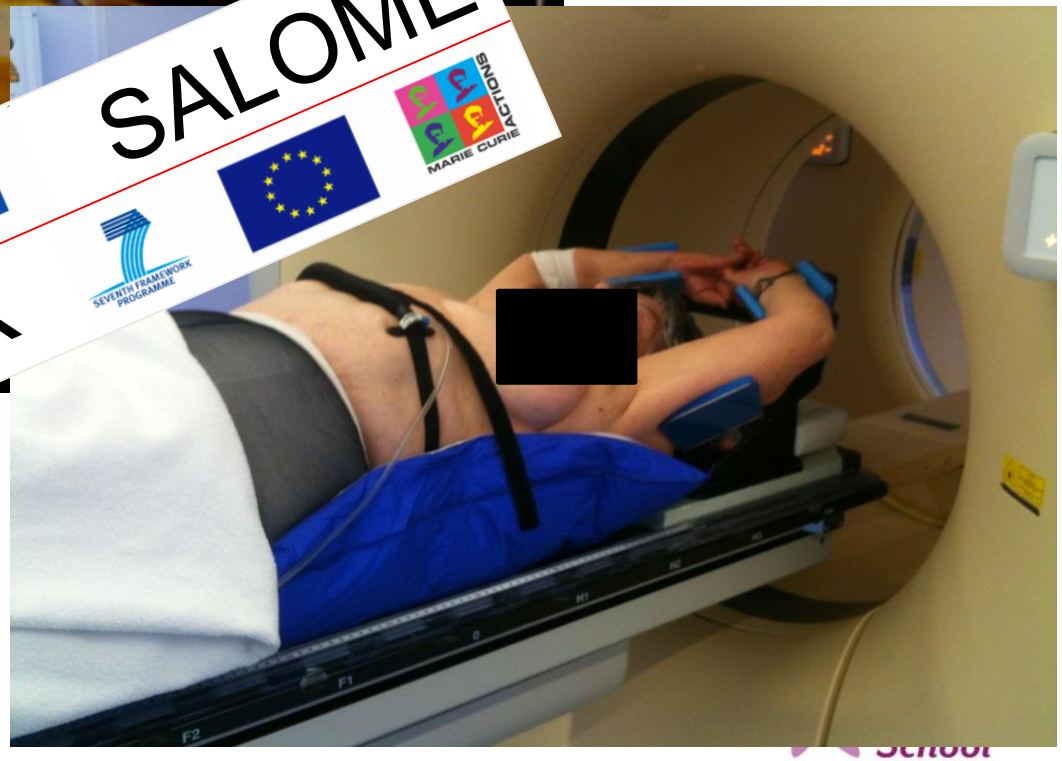
protocol is followed diligently (10). Automated contouring should certainly continue to be explored, but as a tool to assist human judgment, not a substitute for it. When using automated contouring in clinical practice, we must be aware of its limitations and be prepared to edit the results. In clinical trials in which PET-assisted treatment planning is included, the target volumes should not simply be defined by the SUV. Sufficient flexibility should be included to allow for the incorporation of other information. Fully automated contouring can sometimes be 100% reproducible but 100% wrong.

Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 1, pp. 2–4, 2008 M. MacManus, R. Hicks

ESTRO School

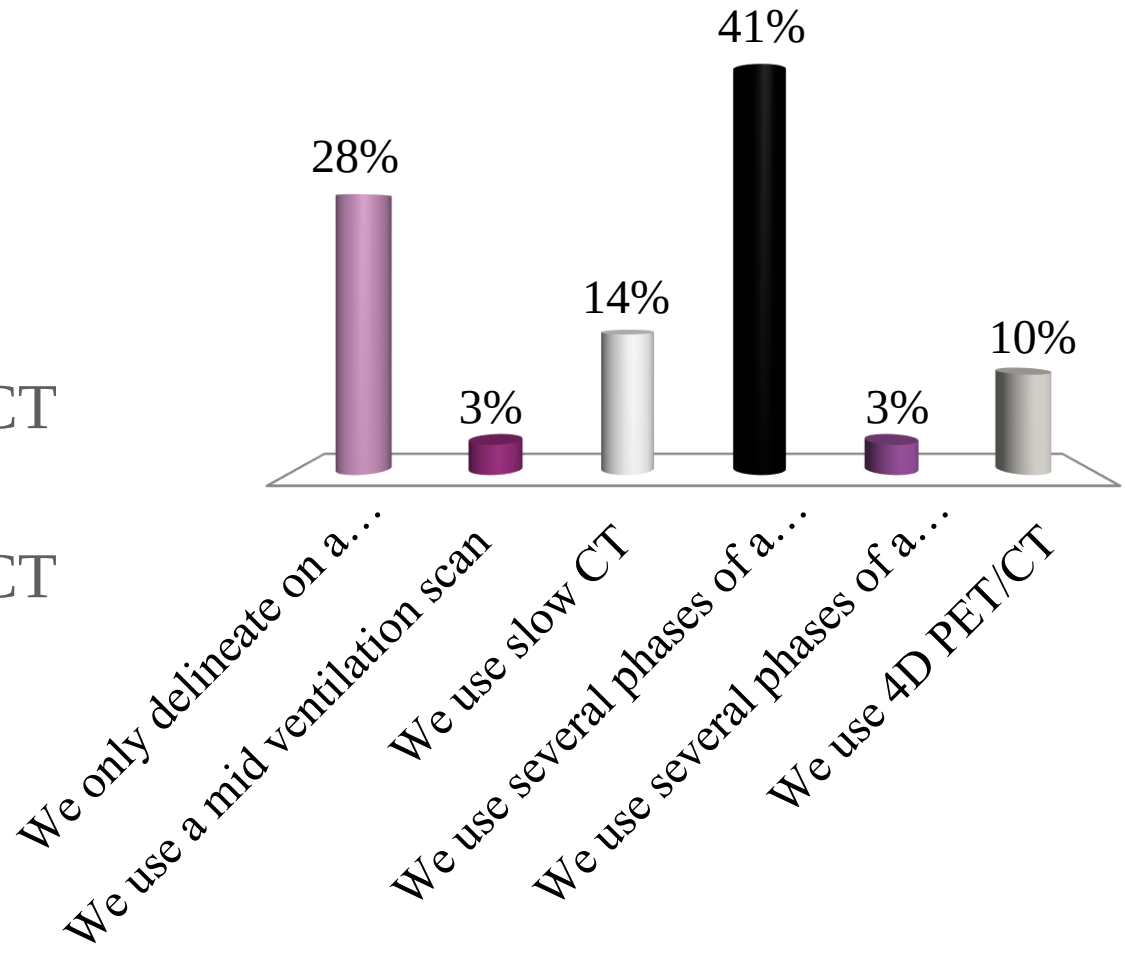
4D PET/CT for GTV-Definition in SBRT?





In your daily work, how do you cope with movements in lung cancer patients

A. We only delineate on a random planning CT
B. We use a mid ventilation scan
C. We use slow CT
D. We use several phases of a 4D-CT and delineate an ITV
E. We use several phases of a 4D-CT and use the van Herk formula
F. We use 4D PET/CT



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Movement concepts for SBRT using 4D-CT

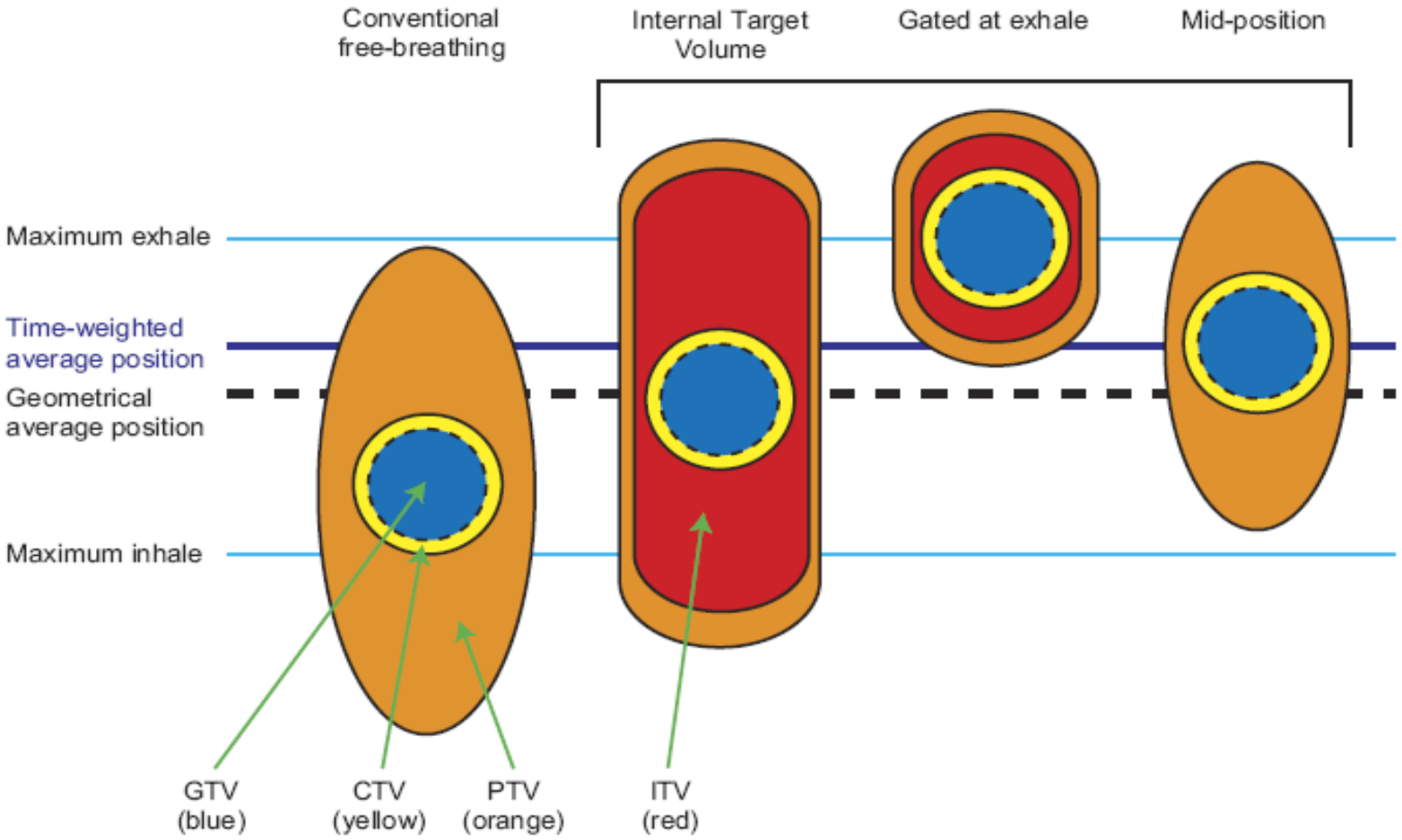


Fig. 1. Schematic overview of different treatment-planning concepts: conventional free-breathing, internal target volume (ITV), gating (at exhale), and mid-position. GTV = gross tumor volume; CTV = clinical target volume; PTV = planning target volume.

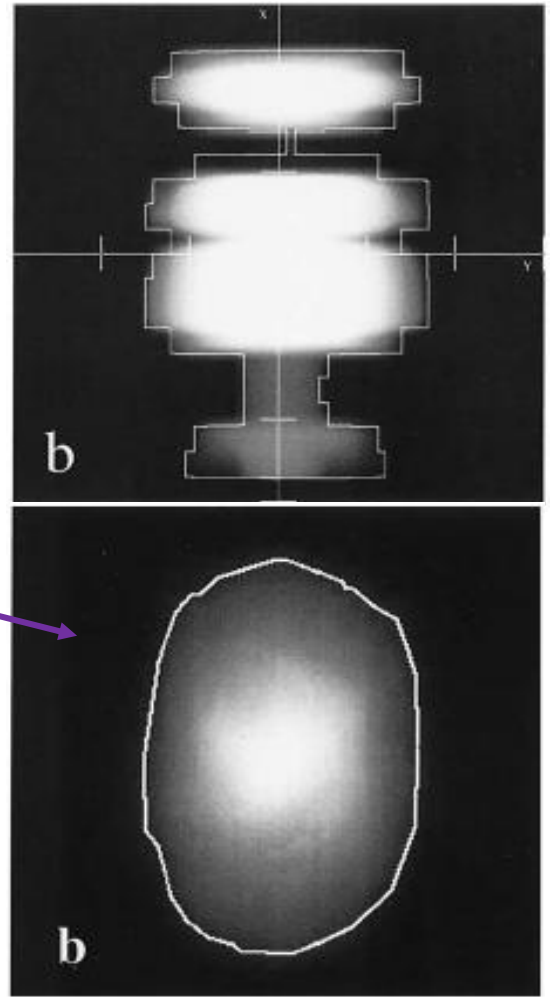
Wolthaus *et al.* (IJROBP 2008)

ITV: PET and breathing movements

Phantom measurements with moving spheres
in ungated PET and CT

CT: significant distortion

PET: image similar to ideal capsular shape
depicting sphere + motion



→ Possibility of exact imaging of 4-D-tumor volume

→ Reduction of risk for topographical miss
from „snapshot“-CT

Caldwell IJROBP 2003 55; 1381-1393

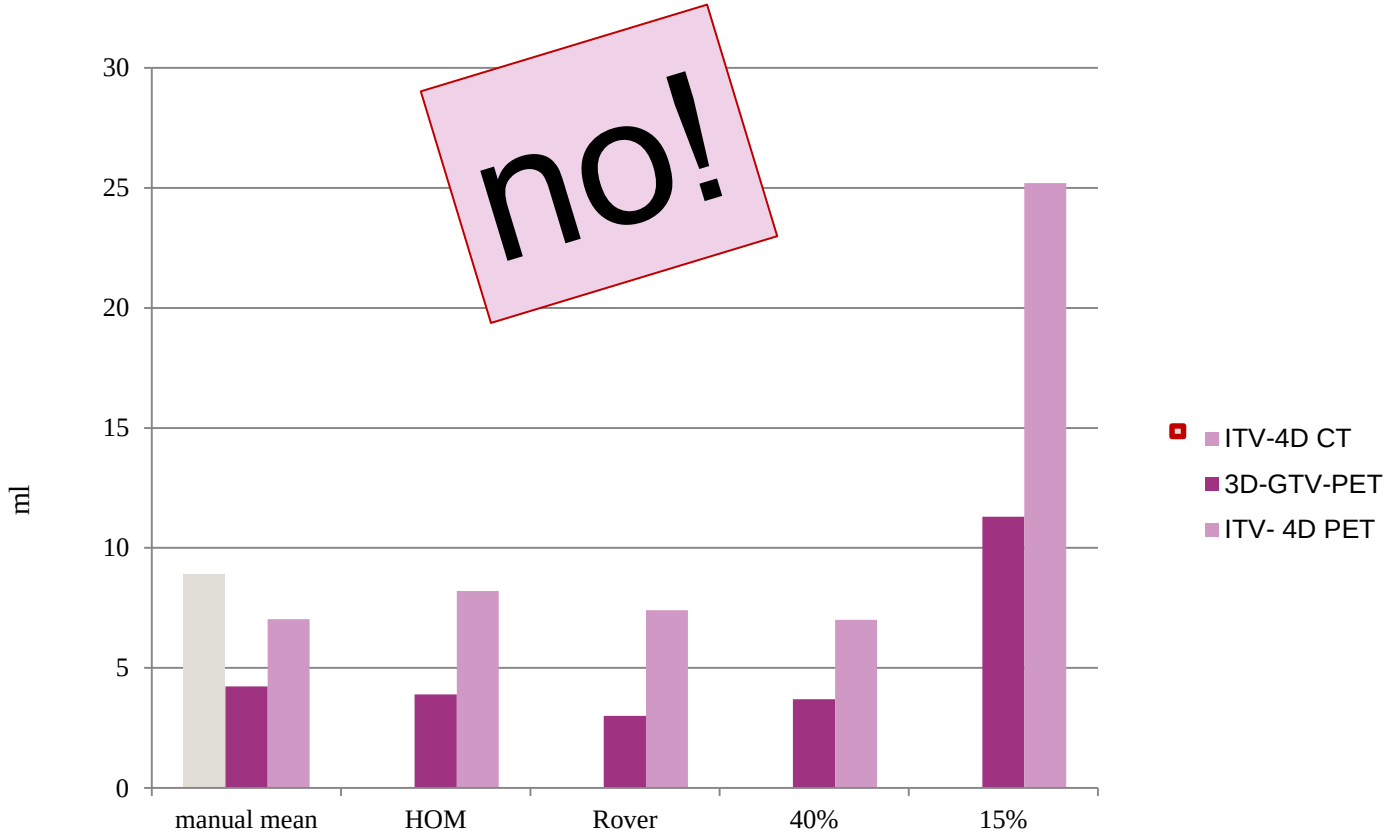
Can we derive an internal target volume from 3D PET?

- 12 NSCLC scheduled for SBRT; 4D PET/CTs, 4 observers:

- 1. ITV in 4D CT „gold standard“

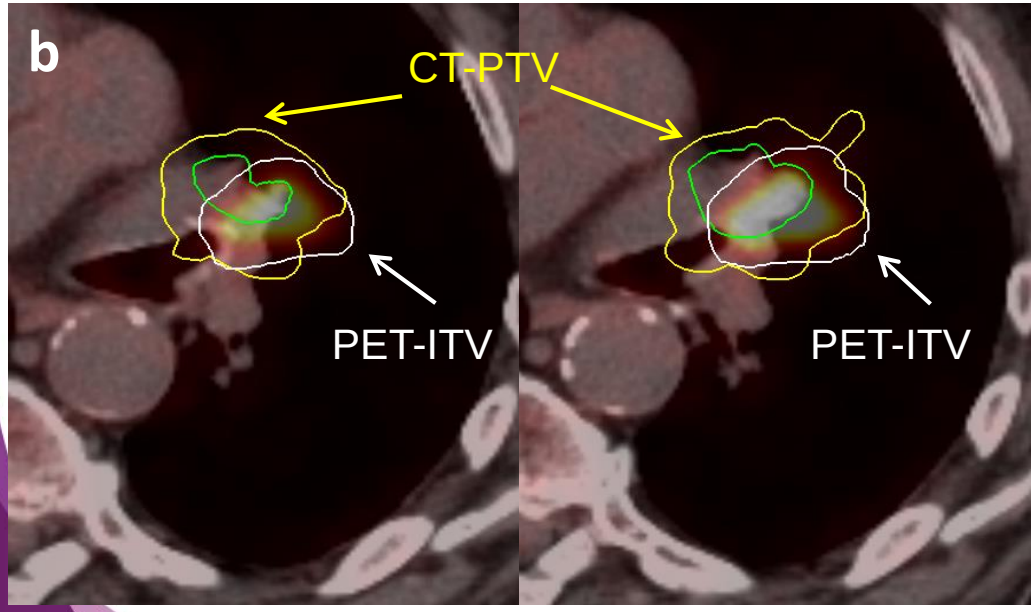
- 2. „GTVs“ in 3D PET
- 3. ITVs from 4D PET

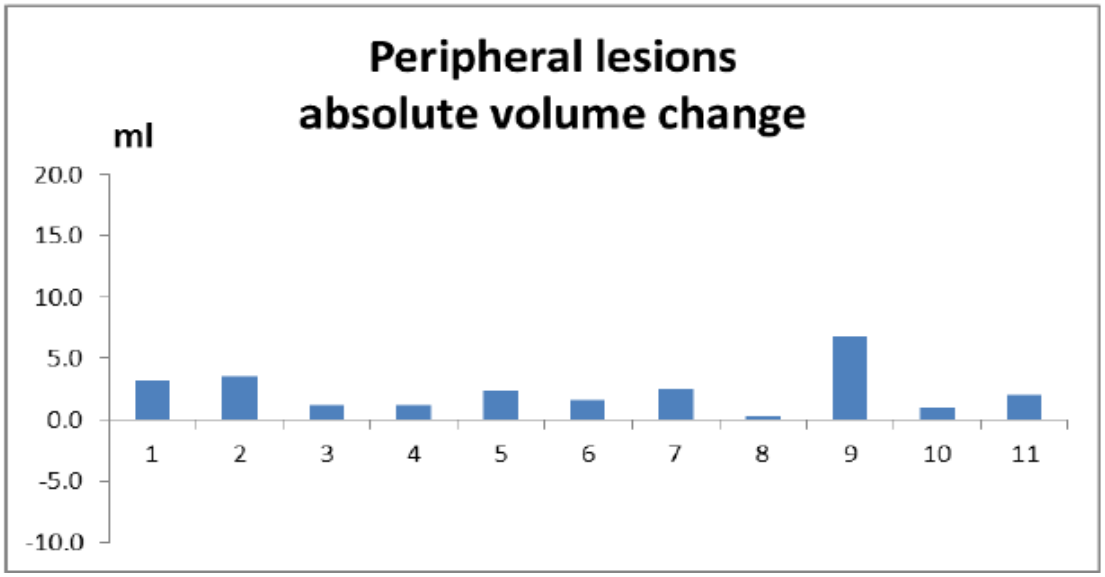
- manual
- Homburg algorithm
- Rover algorithm
- 40% SUVmax
- 15% SUVmax

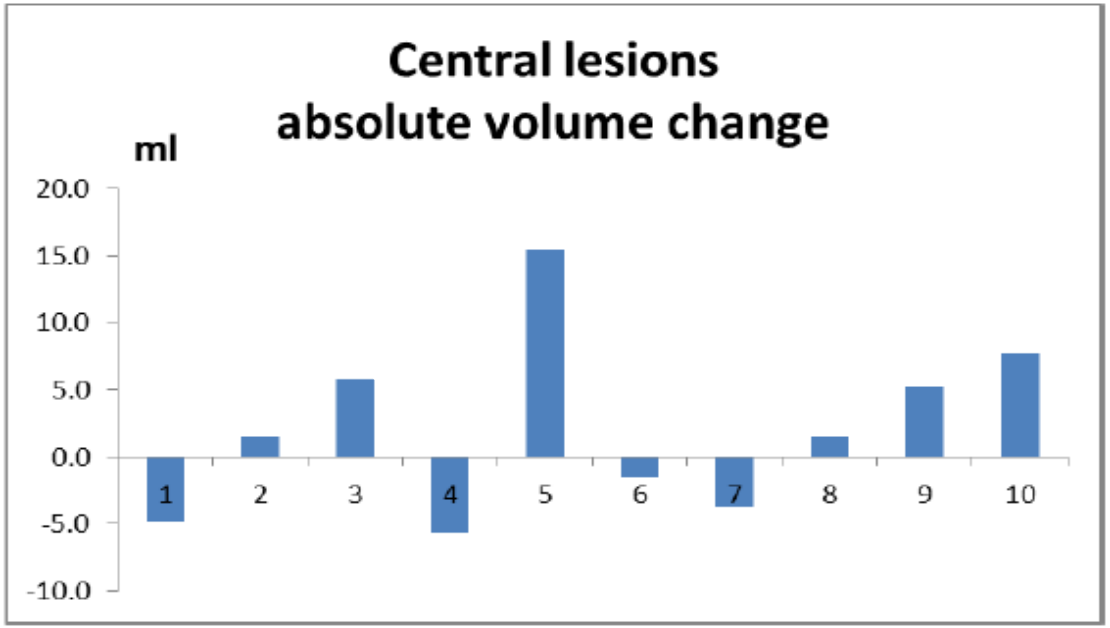


Impact of 4D PET-CT in SBRT-planning

- central (n = 10) vs. peripheral (n=11) NSCLC
- contouring ITV, 4 observers:
  - in 4D CT, PET-viewing side by side
  - in coregistered 4D PET/CT

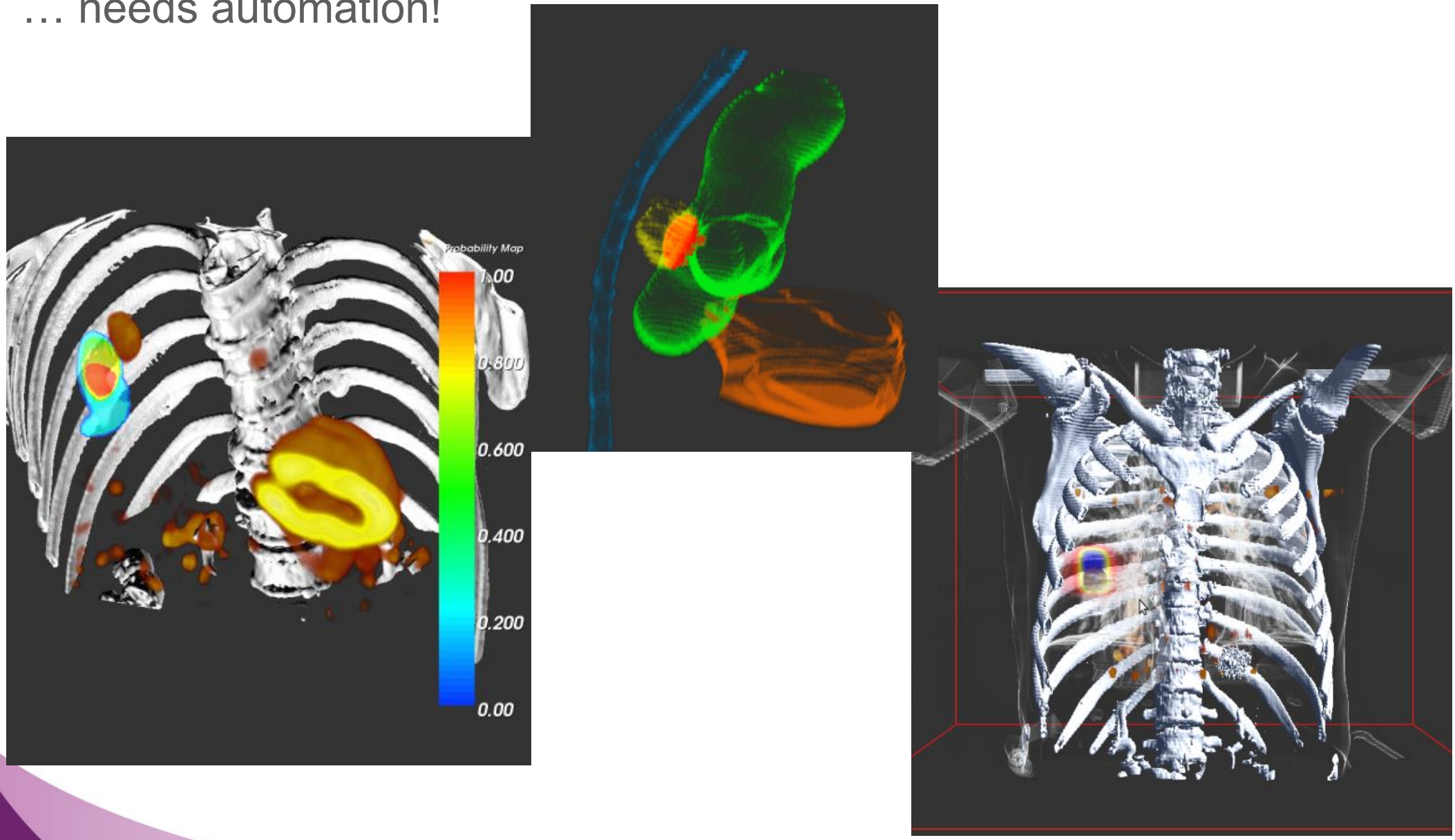






4D PET/CT Delineation…

… needs automation!



Take home messages

- PET based target volume contouring is a open field of research, where
- human brain and manual interaction is needed and desirable and
- consultation of NM specialist/radiologist improves contouring accuracy

- autocontouring methods
  - may reduce workload
  - may improve inter-observer-variability
  - may need calibration
  - do bear inter-method variability

- however, e.g. 4D-contouring will require automatic methods

- institutional standardisation of process of PET based contouring should be established

- CAVE uncritical use of autosegmentation tools provided by manufacturer of PET or PS !

ESTRO School

Image-based Segmentation of Target Volumes

ESTRO Teaching Course on Advanced Molecular Imaging

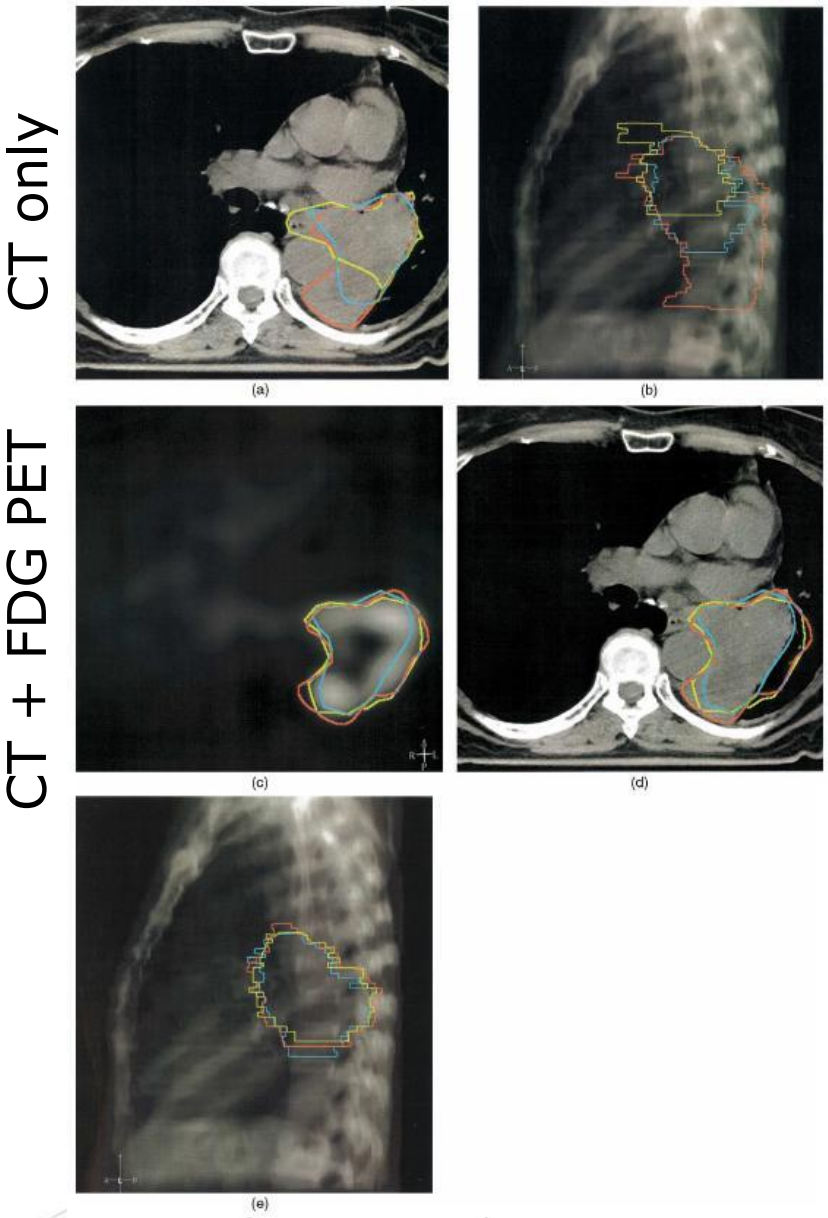
Bordeaux, April 9-13, 2017

Daniela Thorwarth, Section for Biomedical Physics, University Hospital for Radiation Oncology Tübingen, Germany

FDG PET/CT improves consistency of GTV delineation in NSCLC

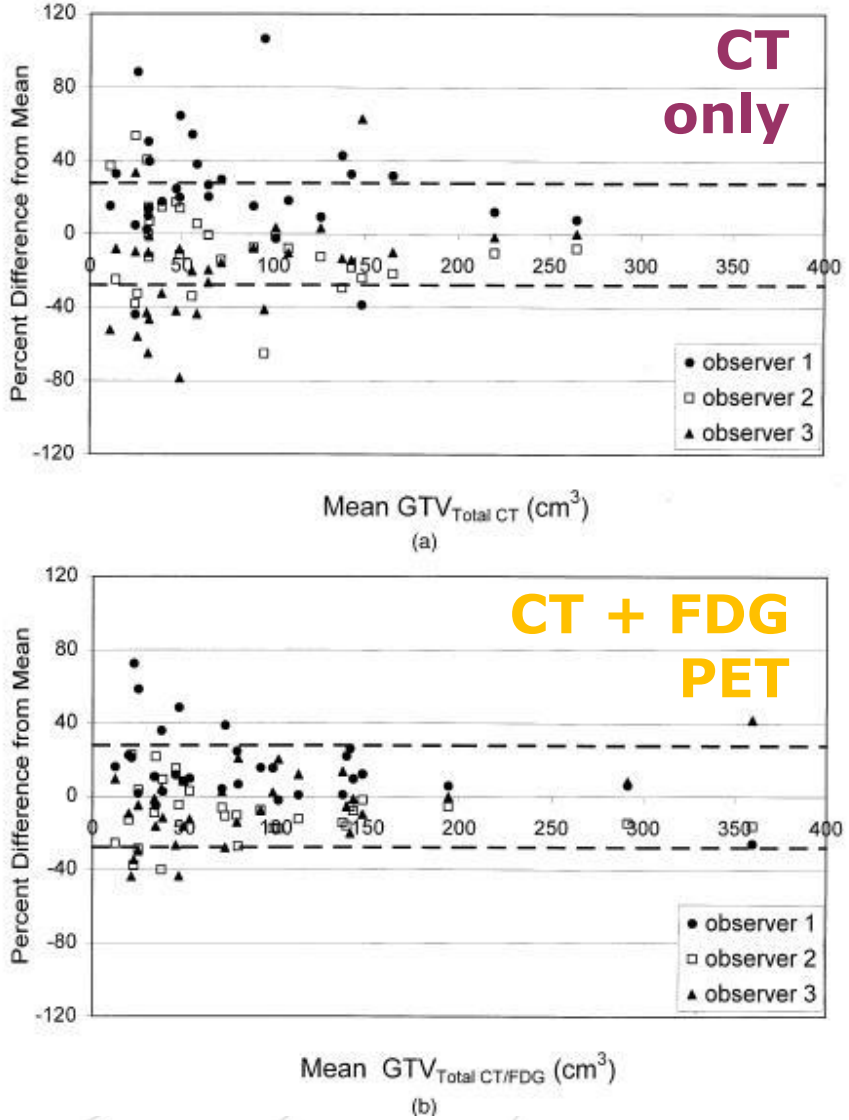
- N=30 NSCLC patients were contoured with and without fused PET/CT data.
- Mean variation of GTV with combined modalities was significantly lower than with CT alone.

Caldwell C et al. Int J Radiat Oncol Biol Phys 2001; 51: 923-31.



FDG PET/CT improves consistency of GTV delineation in NSCLC

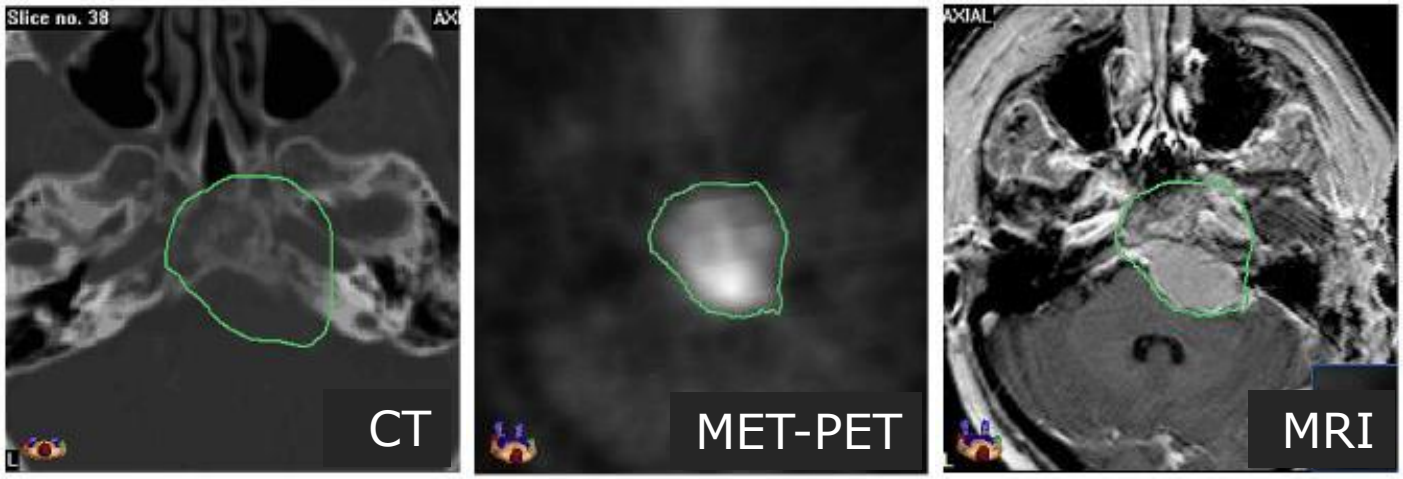
In **12/30**, respectively **23/30** patients all three observers‘ volumes were within the standard deviation.



Caldwell C et al. Int J Radiat Oncol Biol Phys 2001; 51: 923-31.

Improved accuracy in target volume delineation when using PET+MR

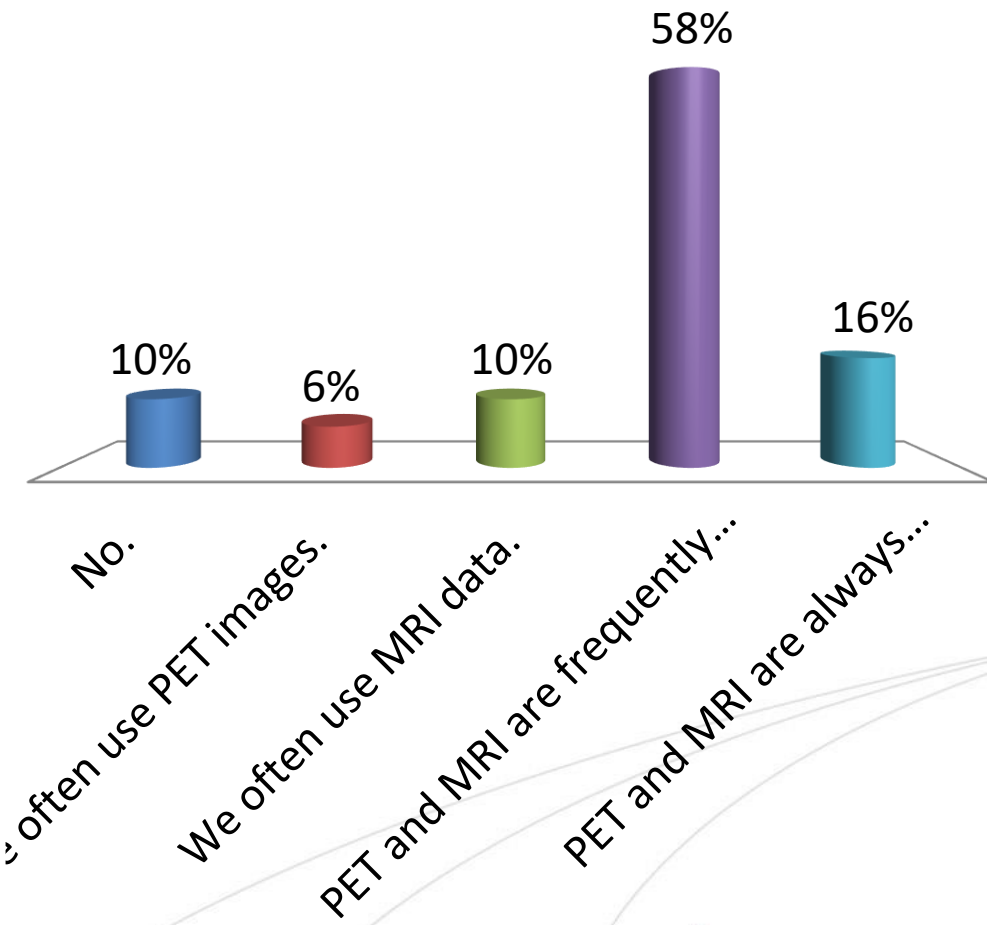
Astner S et al. Int J Radiother Oncol Biol Phys 2008; 72: 1161-7.



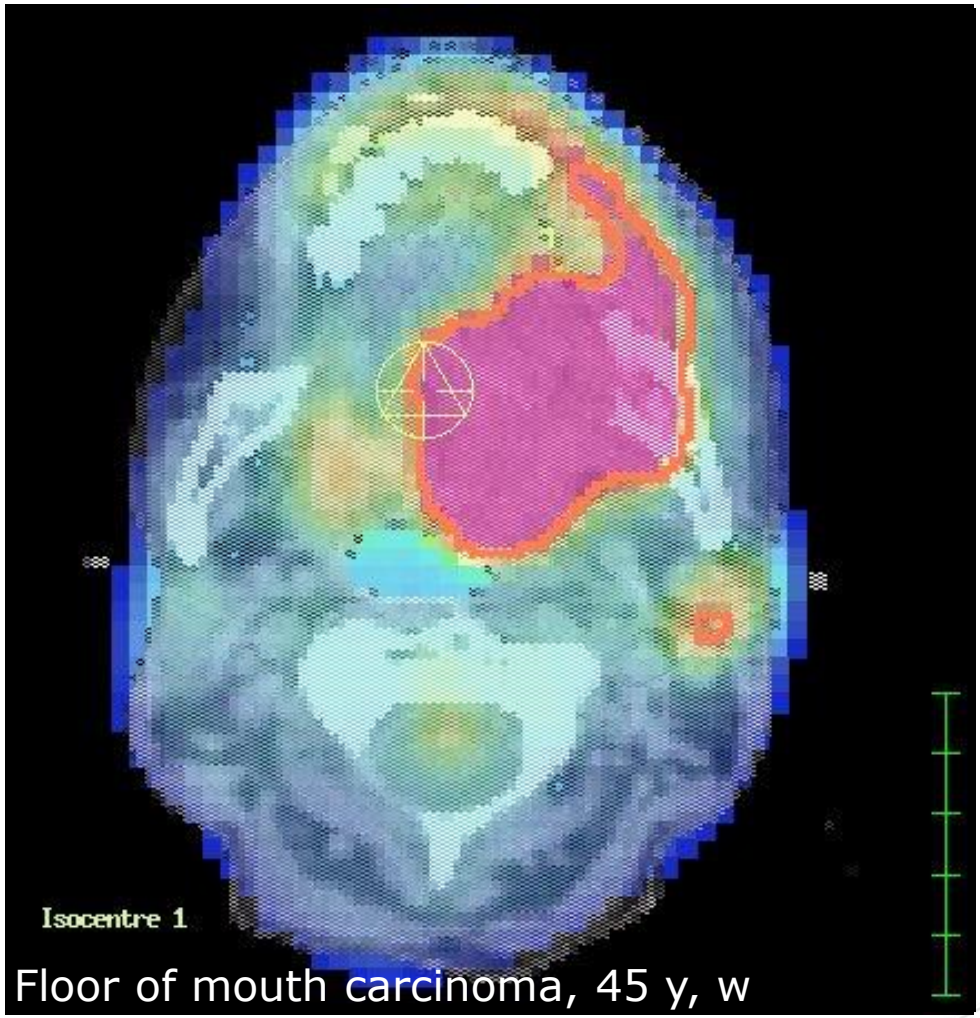
- Usage of PET+MRI beneficial for RT target volume delineation.
- Most patients showed differences between MRI- and PET-based volumes.

Do you use additional imaging for target volume delineation in your department?

A. No.
B. We often use PET images.
C. We often use MRI data.
D. PET and MRI are frequently available.
E. PET and MRI are always available.



Different Contouring Algorithms

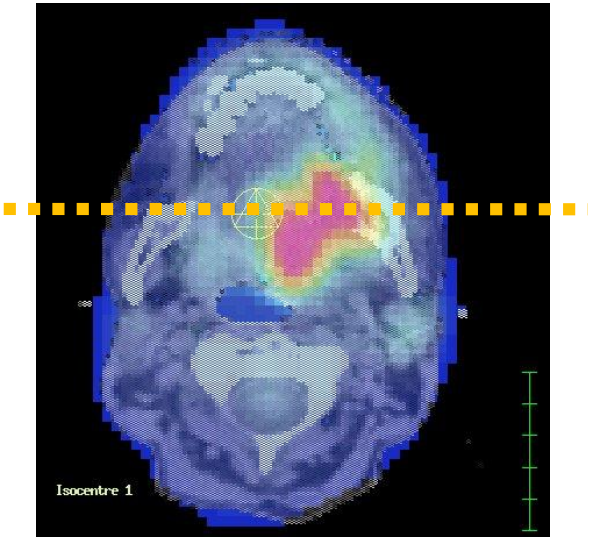


Floor of mouth carcinoma, 45 y, w

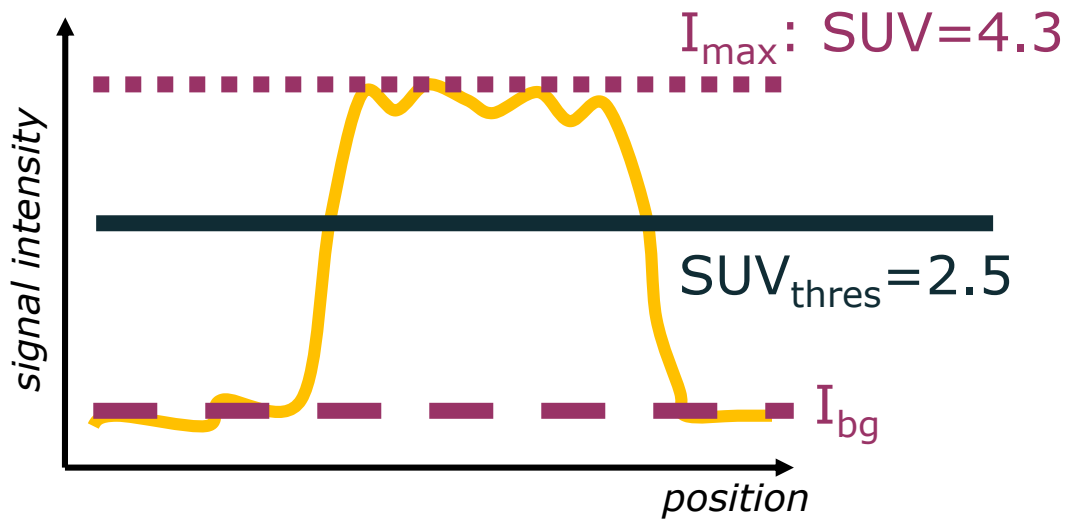
- Most commonly used for TVD: [^{18}F]FDG
- Image Registration / Patient Positioning very important issue
- **Which is the correct method to use?**

Absolute thresholding

PET image



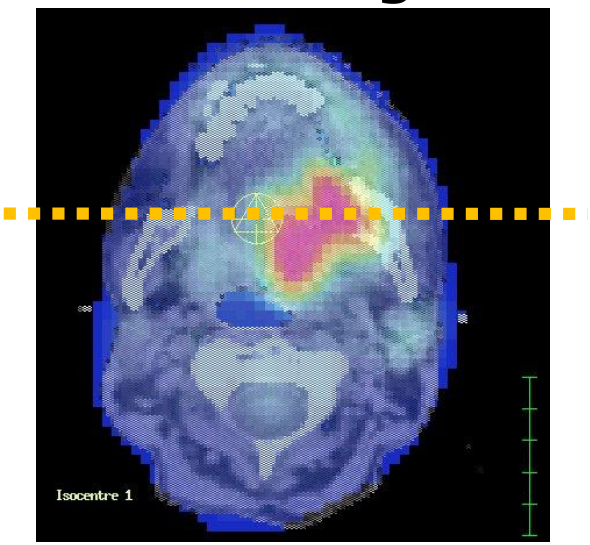
Line profile



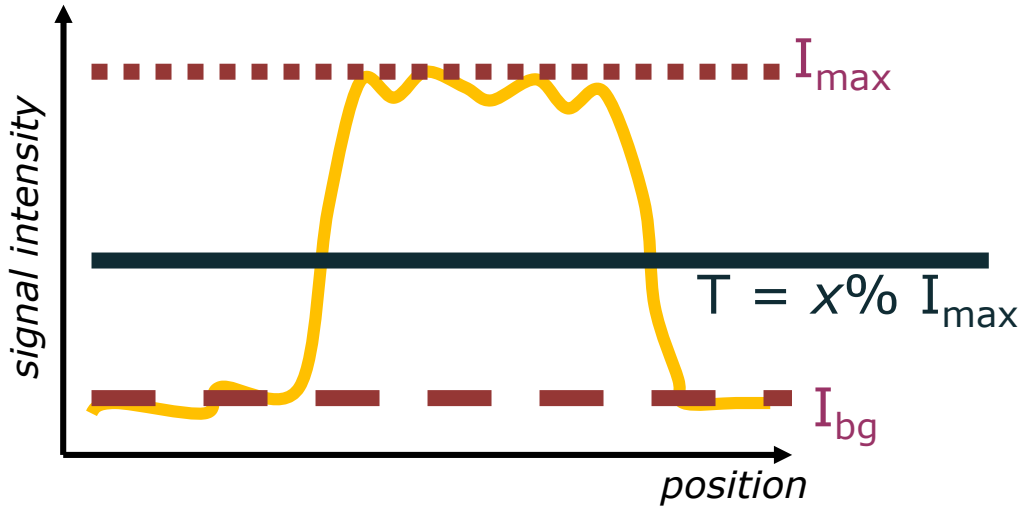
- Fix SUV-threshold of 2.0/2.5
- Easy to implement
- Often fails due to high physiologic background activity
- Absolute SUVs are strongly influenced by various technical factors

Relative Thresholding

PET image



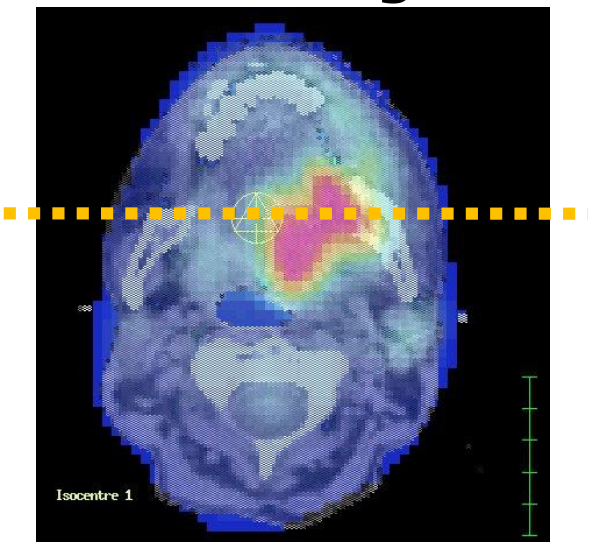
Line profile



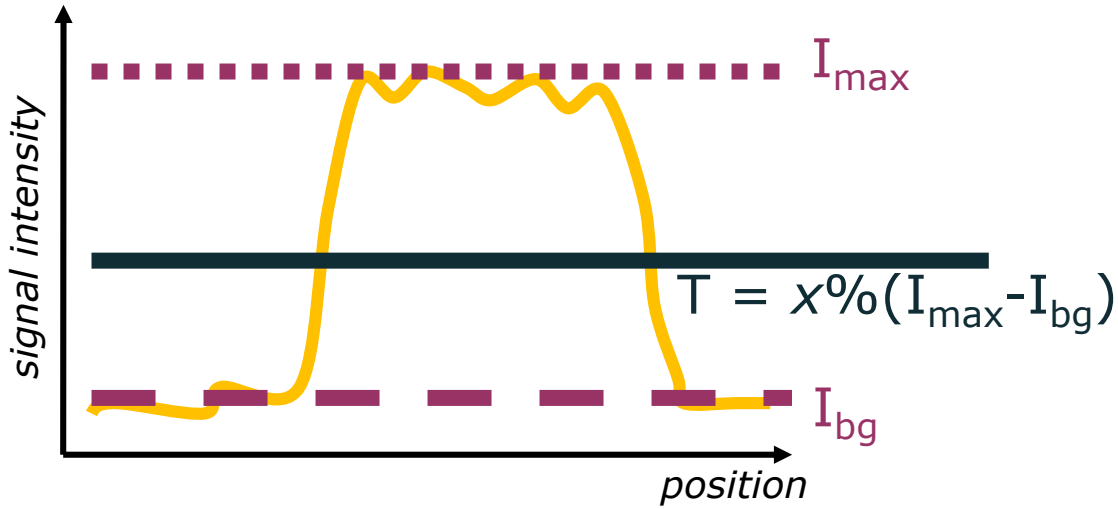
- Relative Threshold *T*, depending on the max. intensity
- Commonly used: *x*=42% (40-50%)
- Easy to implement
- Calibration with phantom measurements possible
- Frequently used in clinical routine

Iterative thresholding

PET image



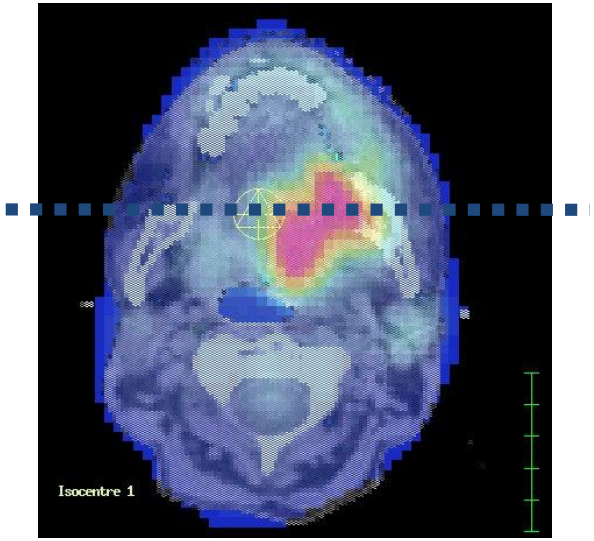
Line profile



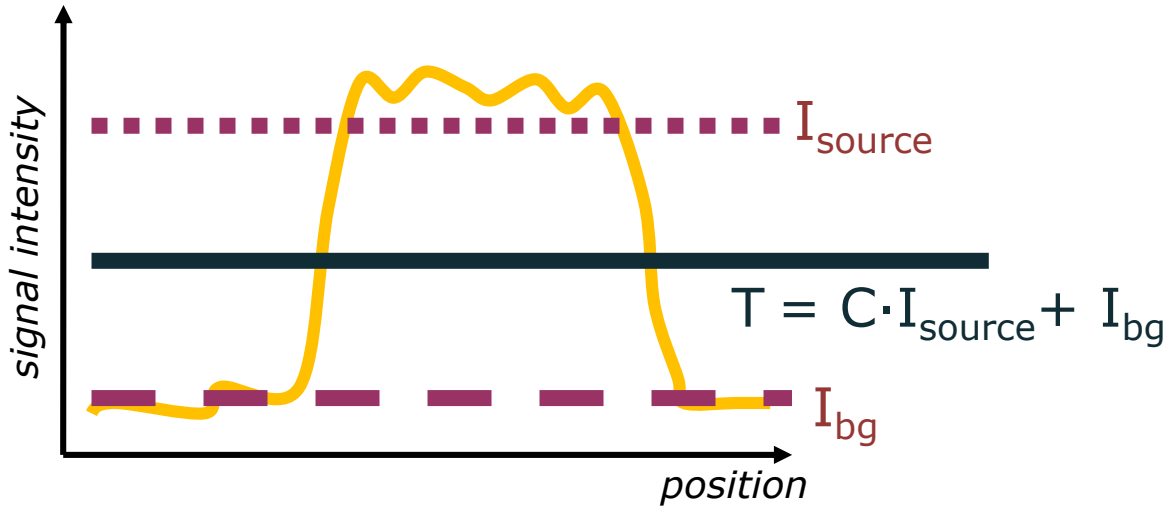
- Background-subtracted relative threshold level
- Adjustable threshold *x*
- Iterative approach based on phantom measurements

Source-to-background algorithms

PET image



Line profile



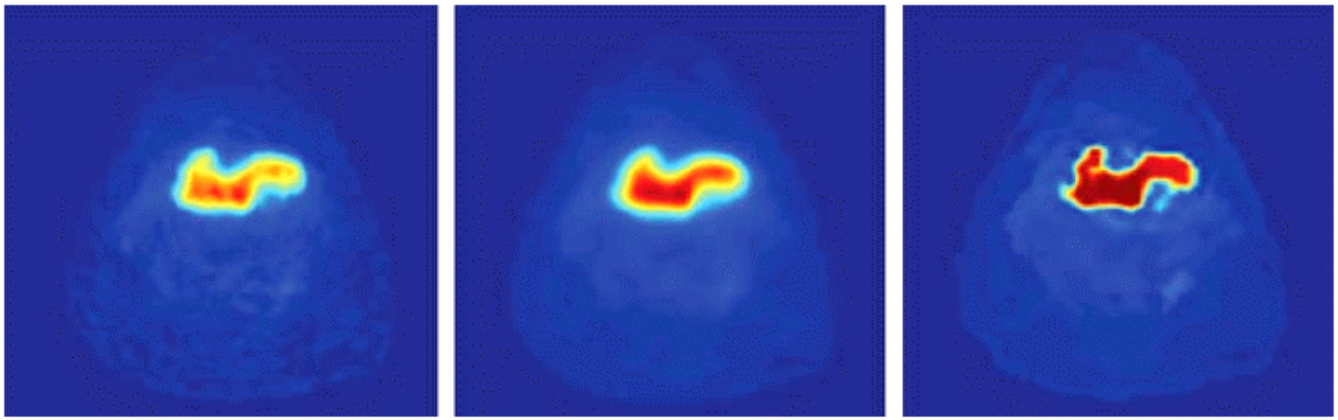
- Constant C determined from phantom measurements
- Works very well for quasi-spherical lesions
- *Value of C depending of different factors:*
  - *Lesion size and shape*
  - *Scanner type and calibration*
  - *Reconstruction protocol*
  - *Image analysis software*

Schaefer et al, EJNMMI 2008; 35(11): 1989-99.

Gradient-based auto-contouring

1. Image processing
   - **Denoising** by bilateral edge-preserving filter
   - **Deblurring** (edge enhancement) by iterative deconvolution

Fig. 2 Axial PET images from a patient with a hypopharyngeal tumour. On the *left panel*, the PET image corresponds to the raw image reconstructed with 3D OSEM algorithm. The application of the bilateral filter and the deconvolution algorithm restored the intensity gradient (*right panel*) in comparison with the classical 4-mm Gaussian filter (*middle panel*)



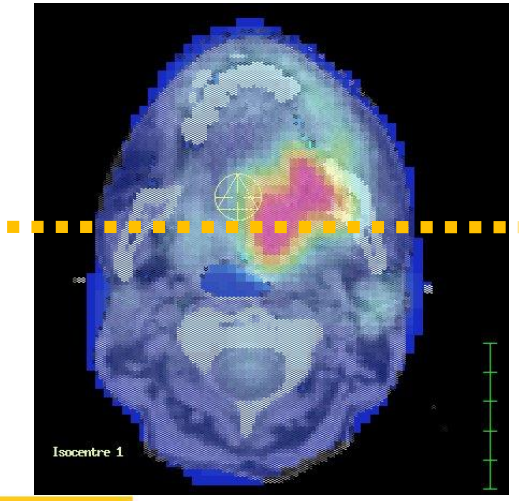
Geets et al, EJNMMI 2007; 34: 1427-1438.

Gradient-based auto-contouring

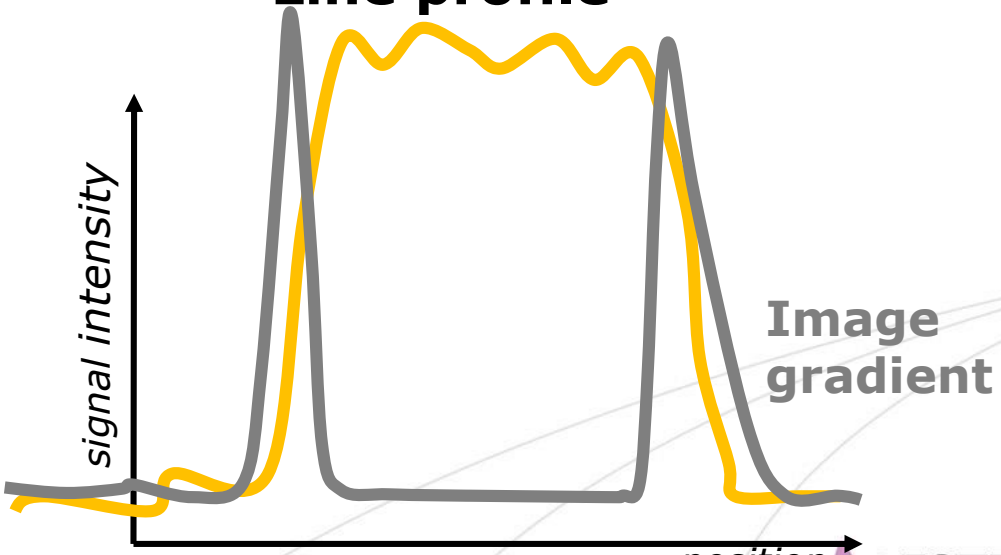
2. Gradient-based segmentation

- Derive a gradient-intensity image:
  Plains & Plateaus → Mountain chains & Valleys
- Crest detection by applying Watershed Transformation
- Cluster analysis

PET image

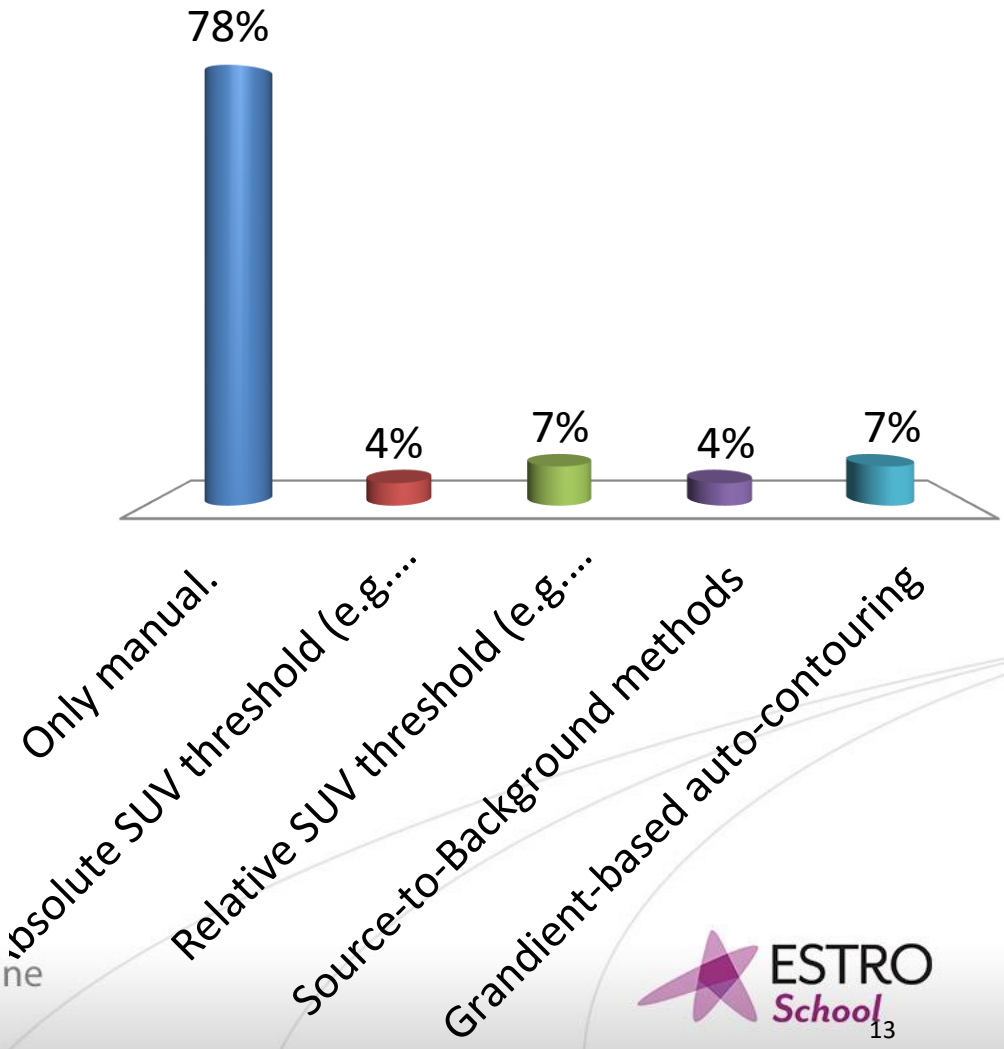


Line profile



Which (semi-)automatic method are you using for PET based target volume delineation?

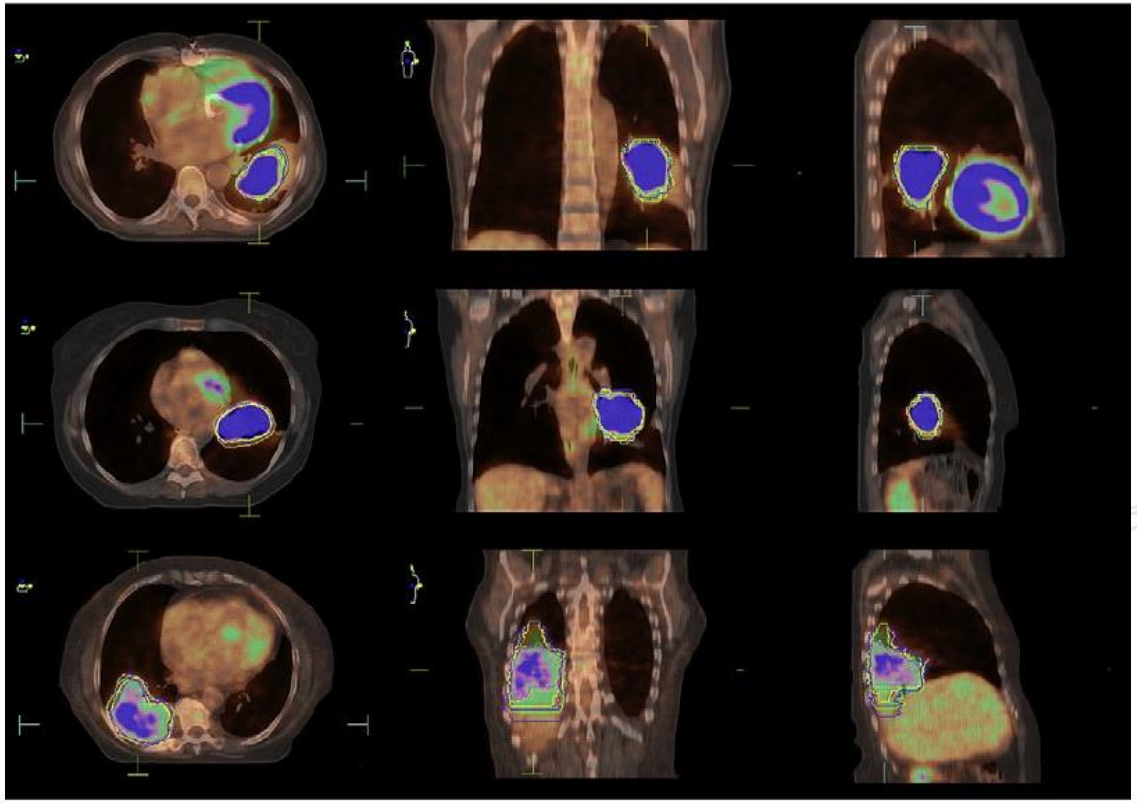
A. Only manual.
B. Absolute SUV threshold (e.g. SUV=2.5)
C. Relative SUV threshold (e.g. Th=50%SUV_{max})
D. Source-to-Background methods
E. Grandient-based auto-contouring



Comparison of automatic PET contouring methods to „intelligent“ manual delineation

- GTVs contoured by 6 experts using a **highly standardized protocol**
- Autocontouring with SUV=2.5, 3.5, 4.0, and 40% SUV_{max}
- Automatic delineations differed widely
- Visual contouring protocol gave reproducible results

Bayne M et al. Int J Radiother Oncol Biol Phys 2010; 77: 1151-7.



When there is no „contouring expert“ available – ask your colleague

Doll C et al. Strahlenther Onkol 2014; 190: 555-62.

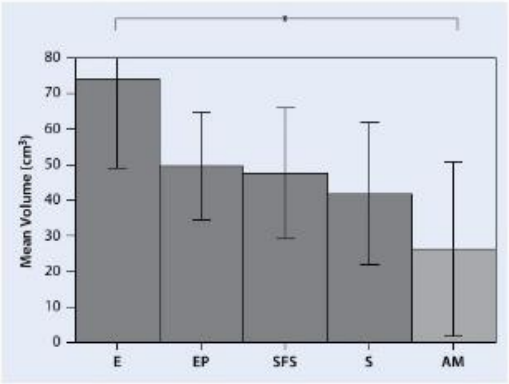


Fig. 2 ◀ Contour comparison between groups: Mean volume. Intervals represent confidence intervals, significant difference indicated by *line at the top*

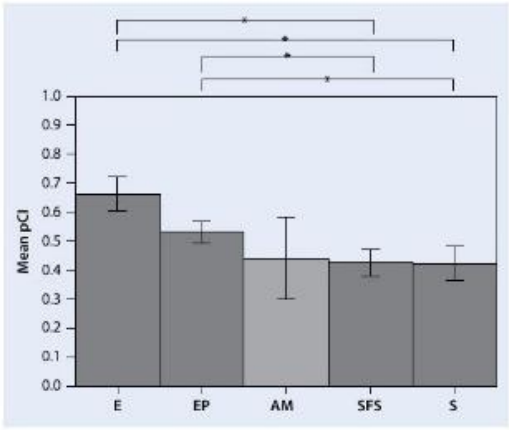
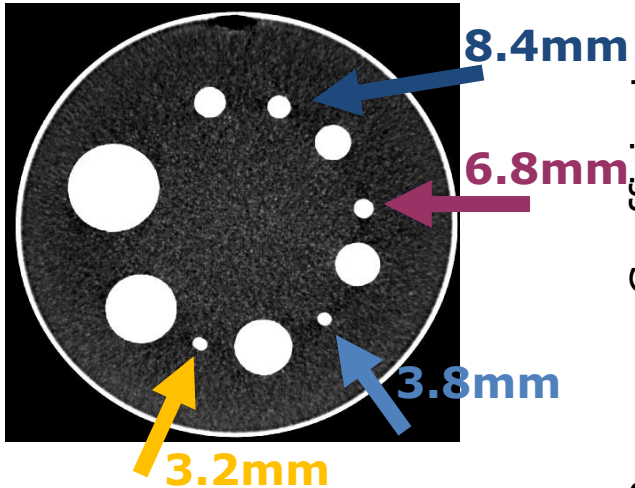


Fig. 3 ◀ Contour comparison between groups: Mean Pairwise Concordance Index (*pCI*). Intervals represent confidence intervals, significant differences indicated by lines at the top

- N=44 interdisciplinary oberservers contoured GTV on PET/CT
- Oberservers were **E**xperts (3), **E**xpierenced interdisciplinary **P**airs (9), **S**ingle **F**ield **S**pecialists (13), **S**tudents (10), **A**utomatic **M**ethods (5)
- E and EP showed sign. better agreement within groups
- Study suggests interdisciplinary cooperation

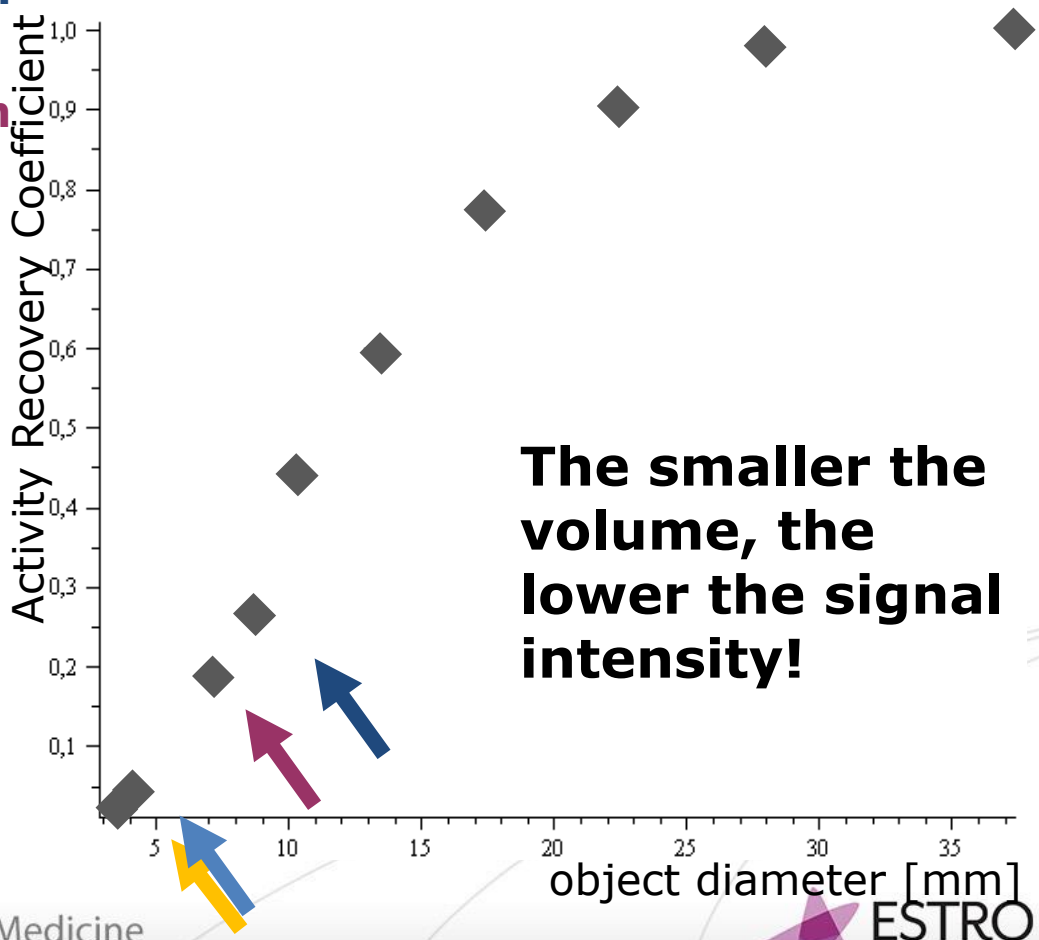
Activity Recovery and Partial Volume Effects

^{68}Ga Phantom measurements:



CT, with CA

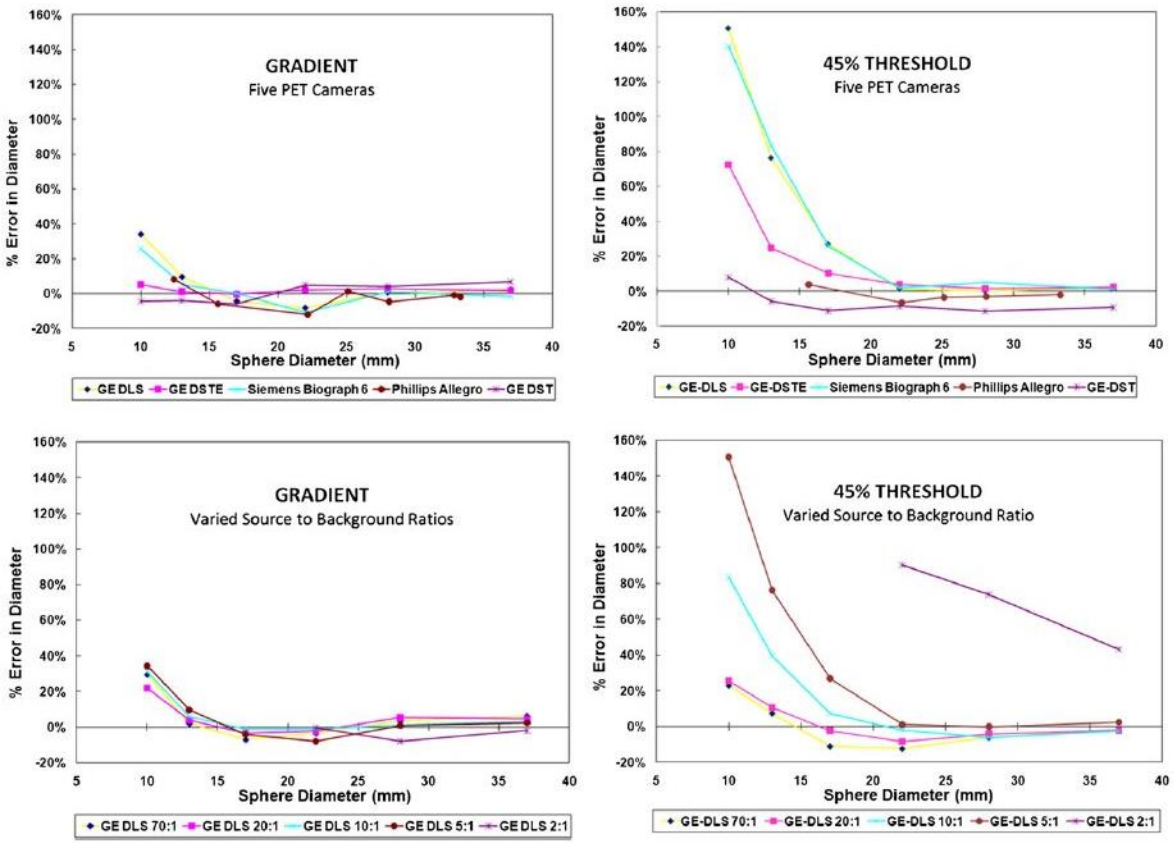
PET, contrast 1:0



The smaller the volume, the lower the signal intensity!

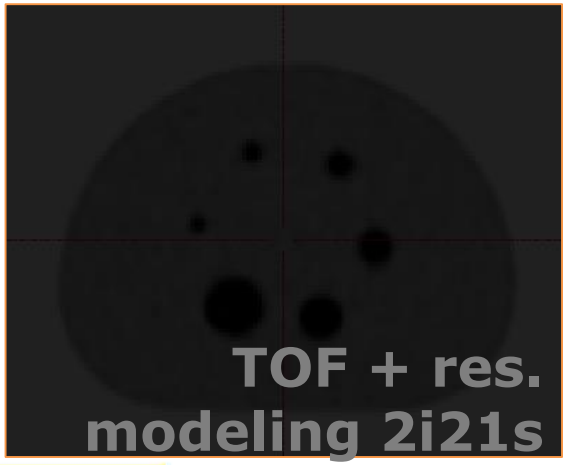
Small lesions are difficult to detect with PET

Werner-Wasik M et al. IJROBP 2012;82:1164-71.

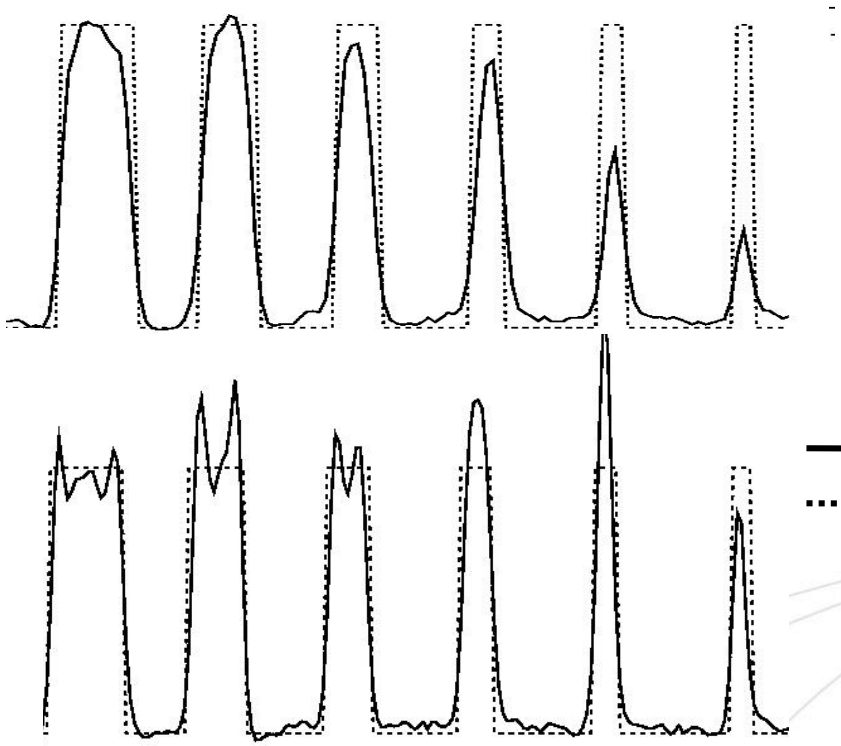


- Comparison of Gradient-based segmentation and thresholding methods
- Grad. is the most accurate method and the most robust under varying imaging conditions

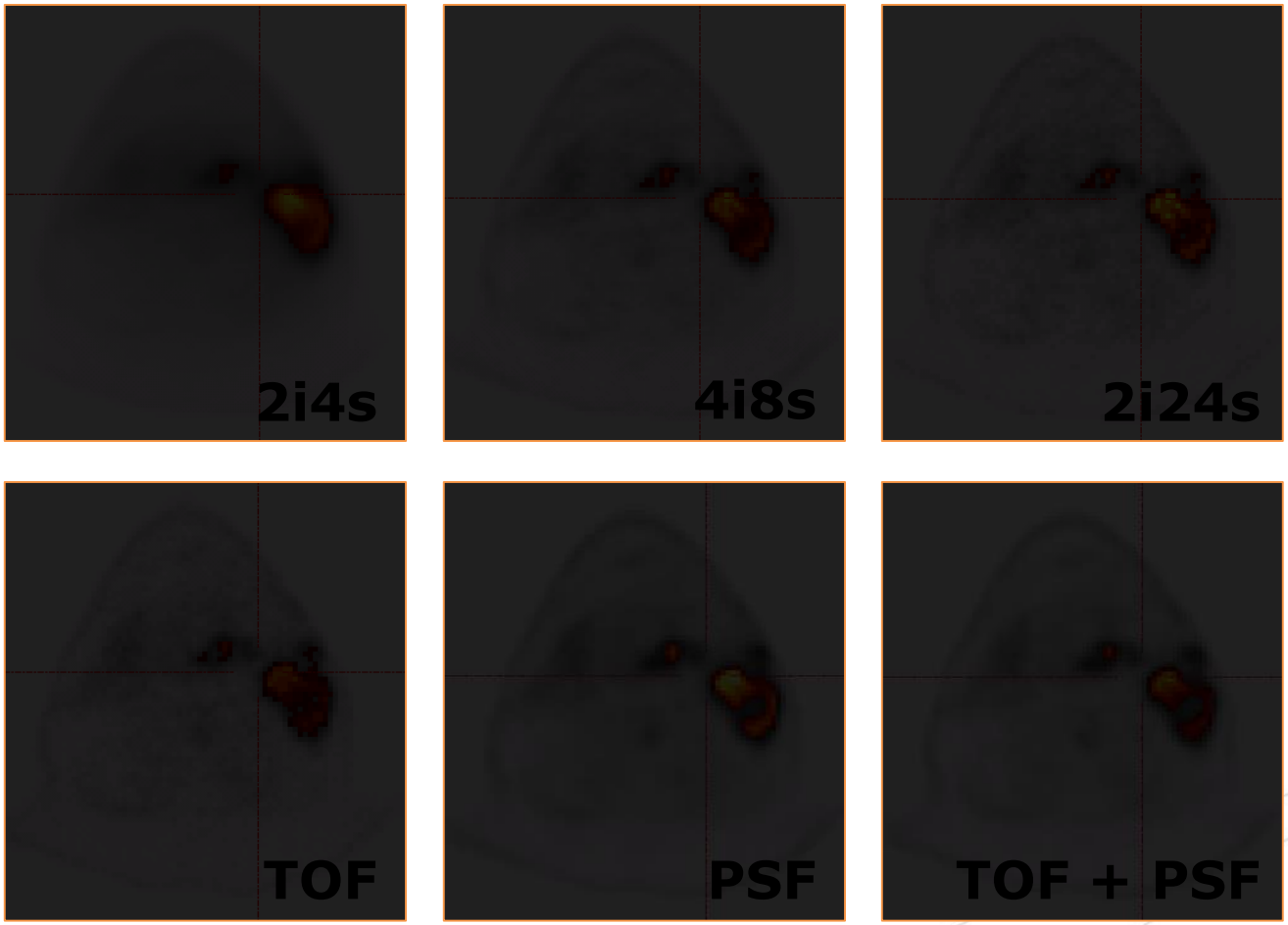
PET reconstruction has an influence on contouring



Contrast 6:1, constant concentration



Effect of PET reconstruction on auto-segmentation



Threshold:

40% SUV_{max}

Validation of segmentation algorithms is crucial

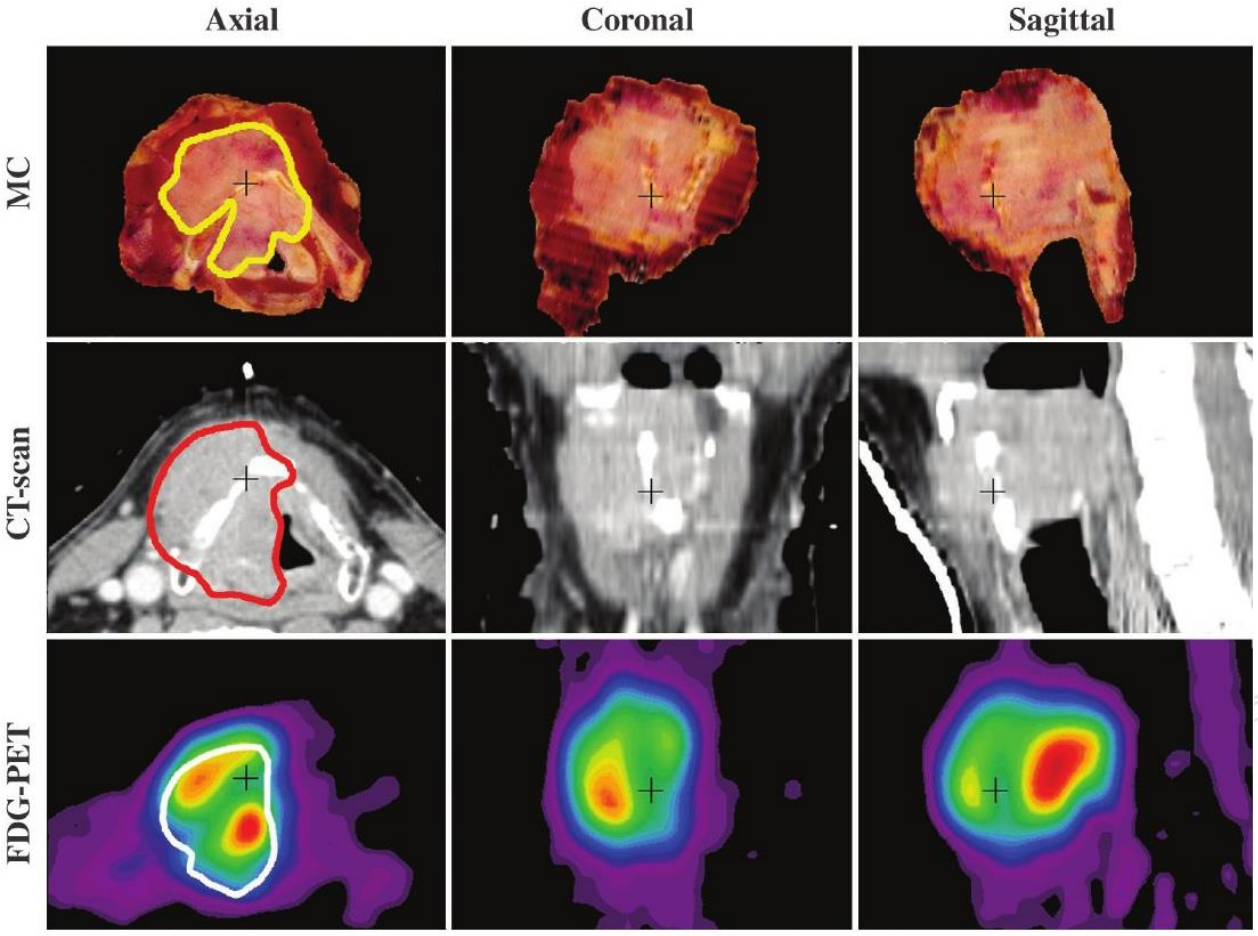
1. **Histopathology (gold standard)**
   - Difficult to assess.
   - Changes in volume and orientation may be challenging

2. **Validation with phantom measurements**
   - Necessary to have
   - Real tumours are often not spherical
   - Cannot substitue validation with pathology

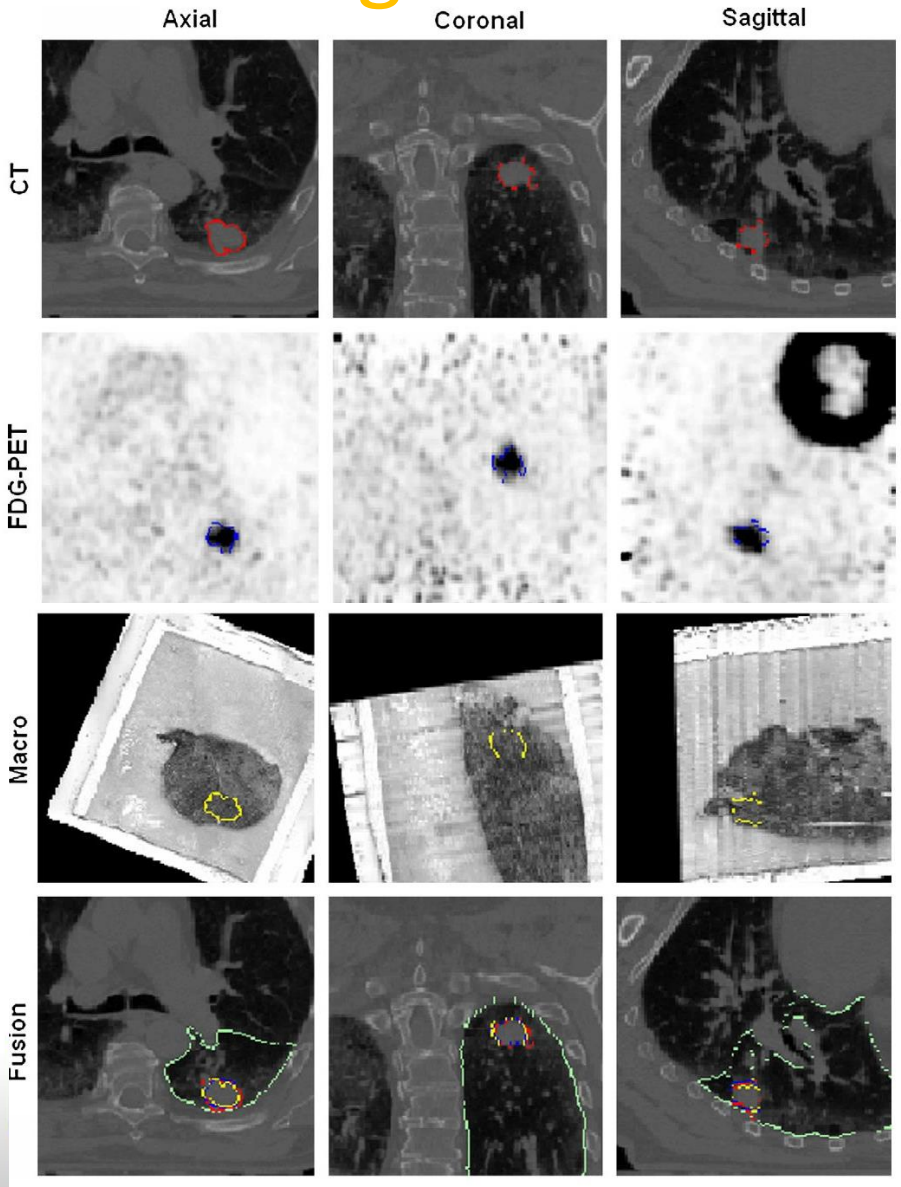
3. **Comparison to manual delineations**
   - Intra-observer variations
   - Regularized auto-segmentation method may always yield similar accuracy

Validation of image based-contouring methods with pathology

- Validation of image-based contouring with pathology
- N=9 HNC cases
- PET GTVs were smaller than from CT or MRI
- Volume of surgical specimen correlated best with FDG-PET



Gradient-based PET segmentation improves target volume definition in NSCLC



Wanet M et al. Radiother Oncol 2011;98:117-25.

- N=10 NSCLC patients
- GTV delineation on CT±PET
- Comparison with surgical specimen
- PET yields more robust delineation in poorly defined tumors
- Gradient based seg. outperformed threshold method in terms of accuracy and robustness

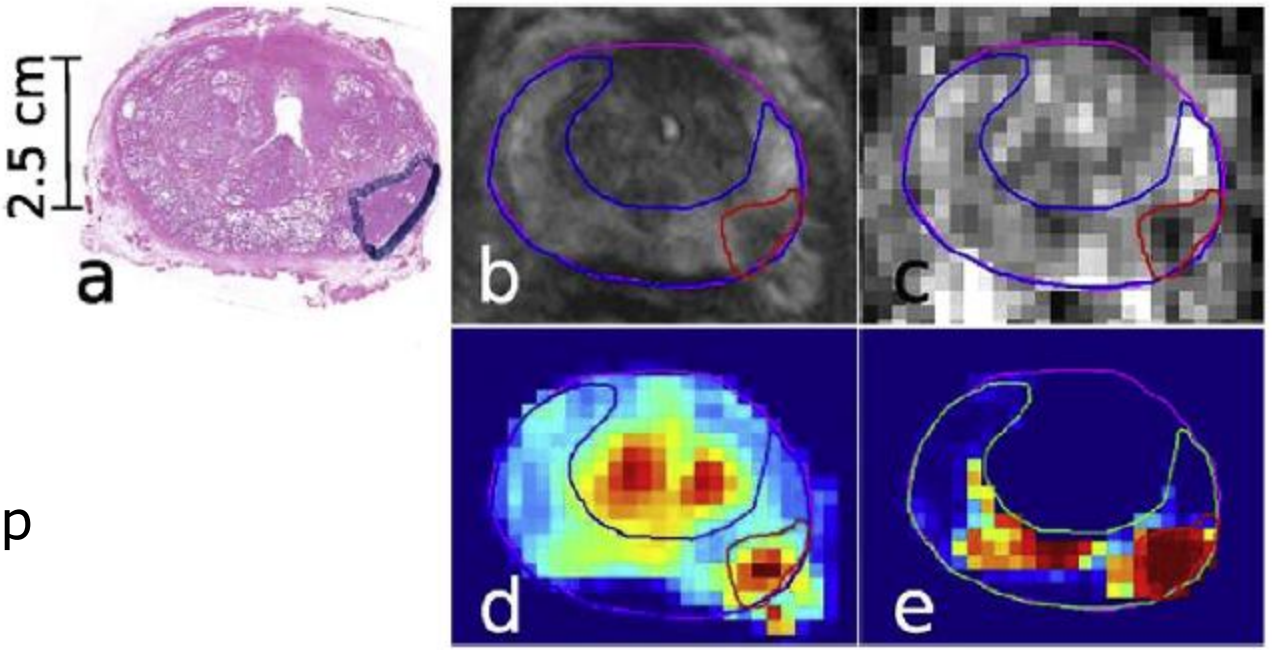
ESTRO School

Multi-parametric functional imaging for tumor volume segmentation

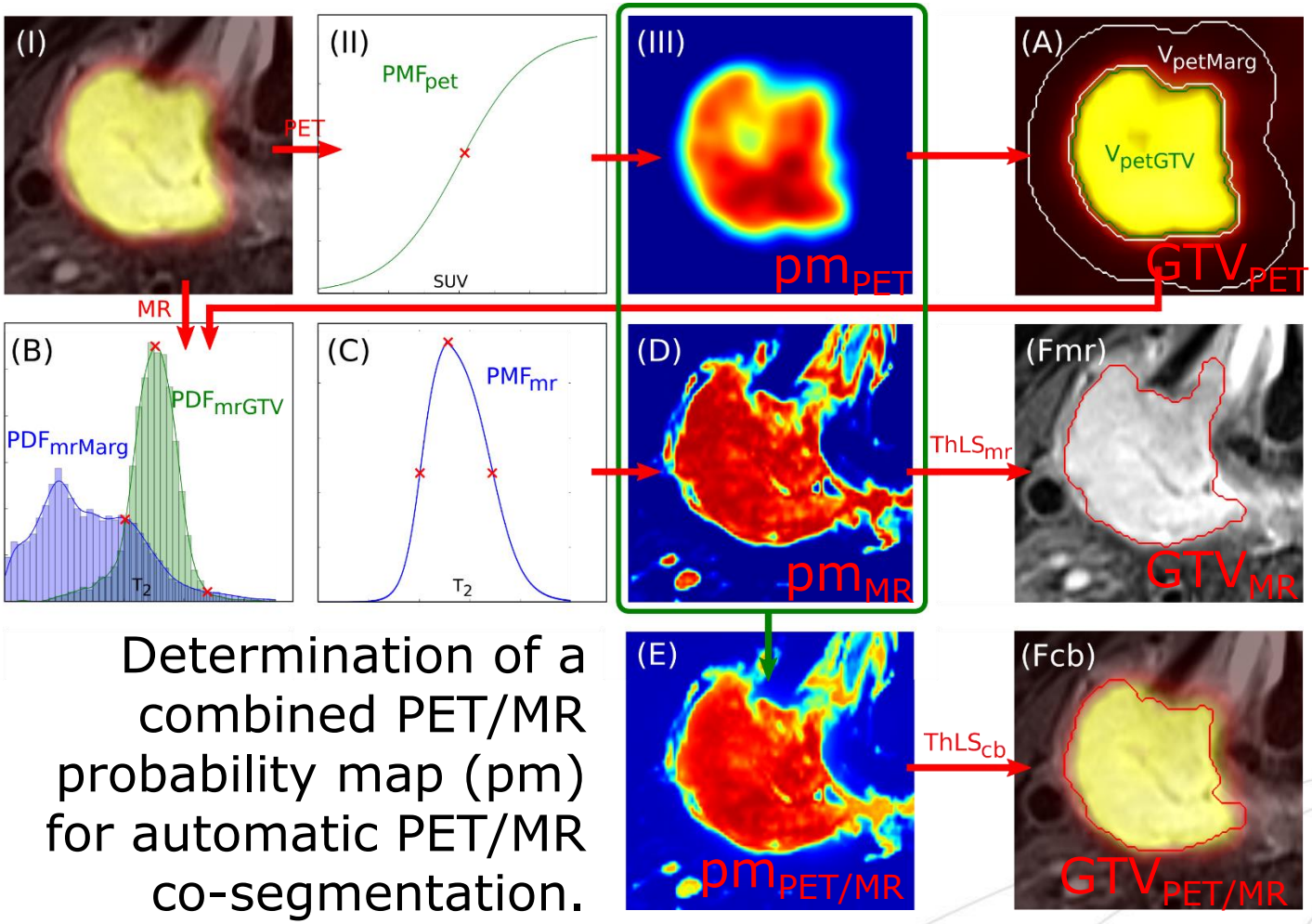
Groenendaal G, et al. IJROBP 2012; 82(3): e537-44.

- Statistical model predicts tumor presence on a voxel level based on DCE- and DW- MRI
- could serve as a basis for dose painting

a. Tumor section
b. T2-weighted image
c. ADC map
d. K_{trans} map
e. Probability map of tumor presence



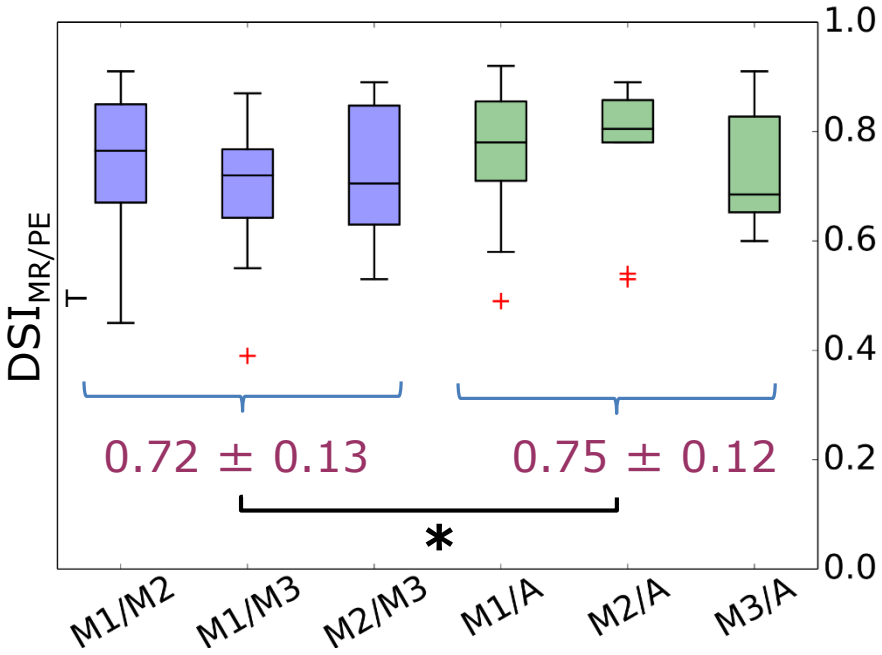
Combining information from PET and MRI: Automatic co-segmentation of FDG PET/MR for HNC

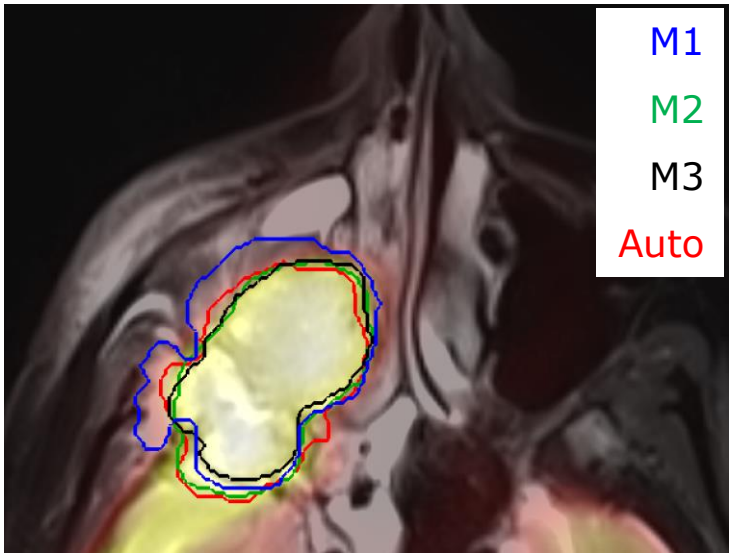


Determination of a combined PET/MR probability map (pm) for automatic PET/MR co-segmentation.

Automatic Co-Segmentation of tumor volumes based on combined PET/MR data

- Validation with n=10 FDG MR/PET data sets (HNC)
- Automatic contours robust and consistent with manual volumes





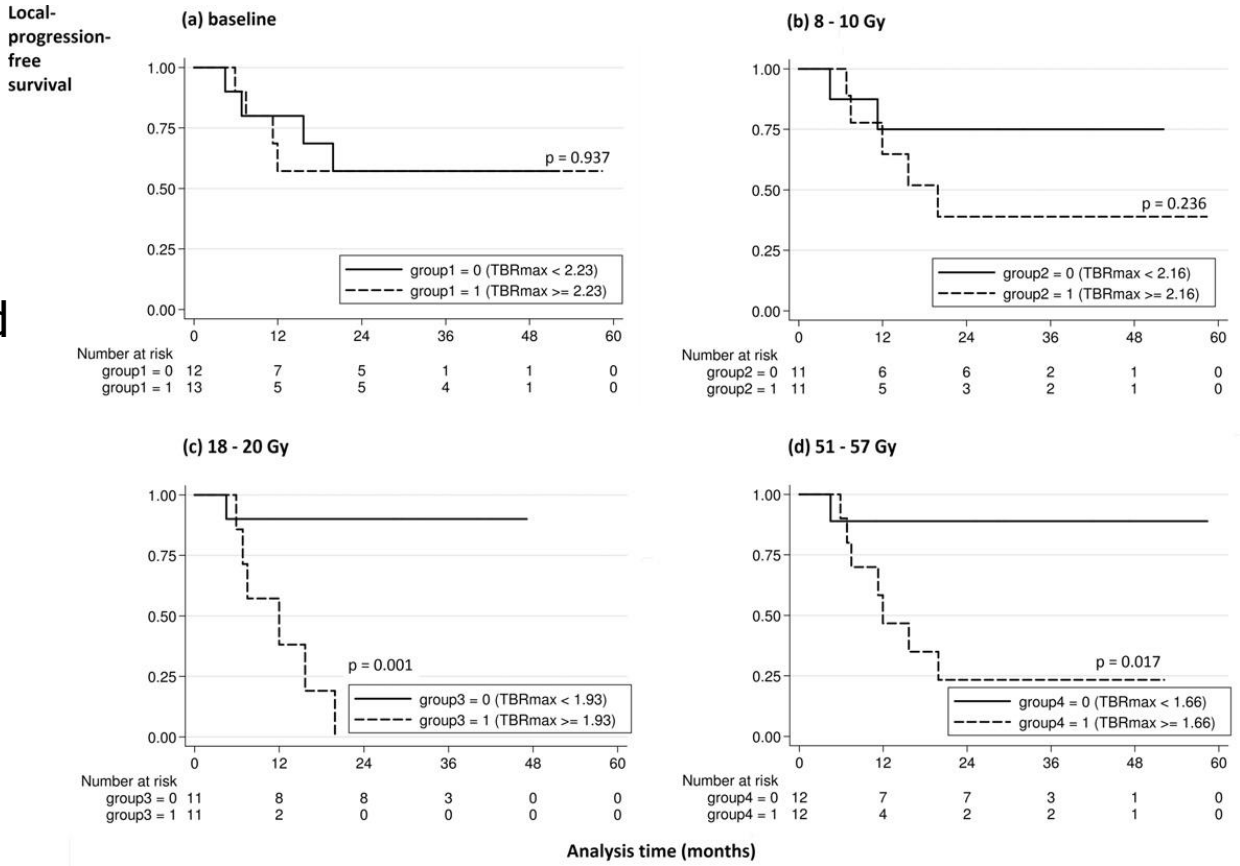
- Significantly lower variation of tumor volumes using combined MR/PET with respect to MRI.

S. Leibfarth, Tübingen

Segmentation of radioresistant areas of the tumor: Hypoxia PET Imaging with [^{18}F]-FMISO

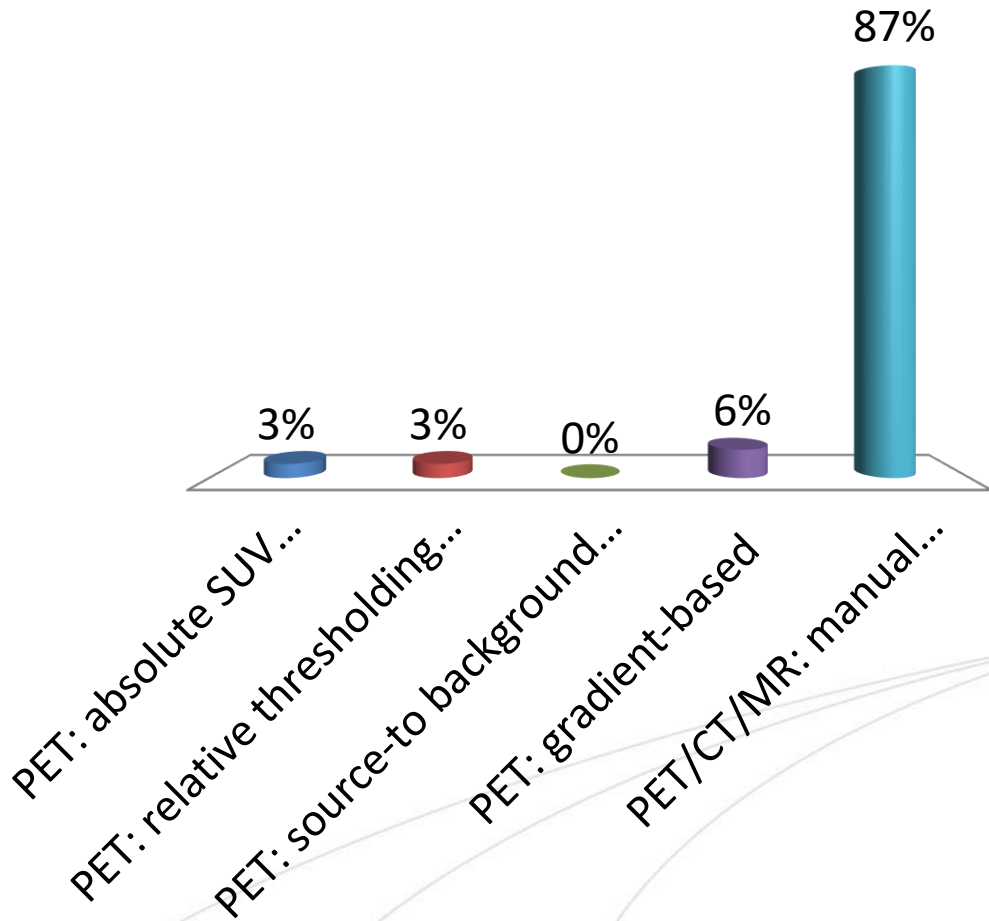
Zips D et al. Radiother Oncol 2012;105(1):21-8.

- N=25 HNC patients
- FMISO PET/CT in week 0, 1, 2, and 5
- Different imaging parameters evaluated @ 4h pi
  - HV (T/Bg: 1.4, 1.6, 1.8, 2.0)
  - TBR_{max}
  - SUV_{max}
- Correlation with LPFS in week 2



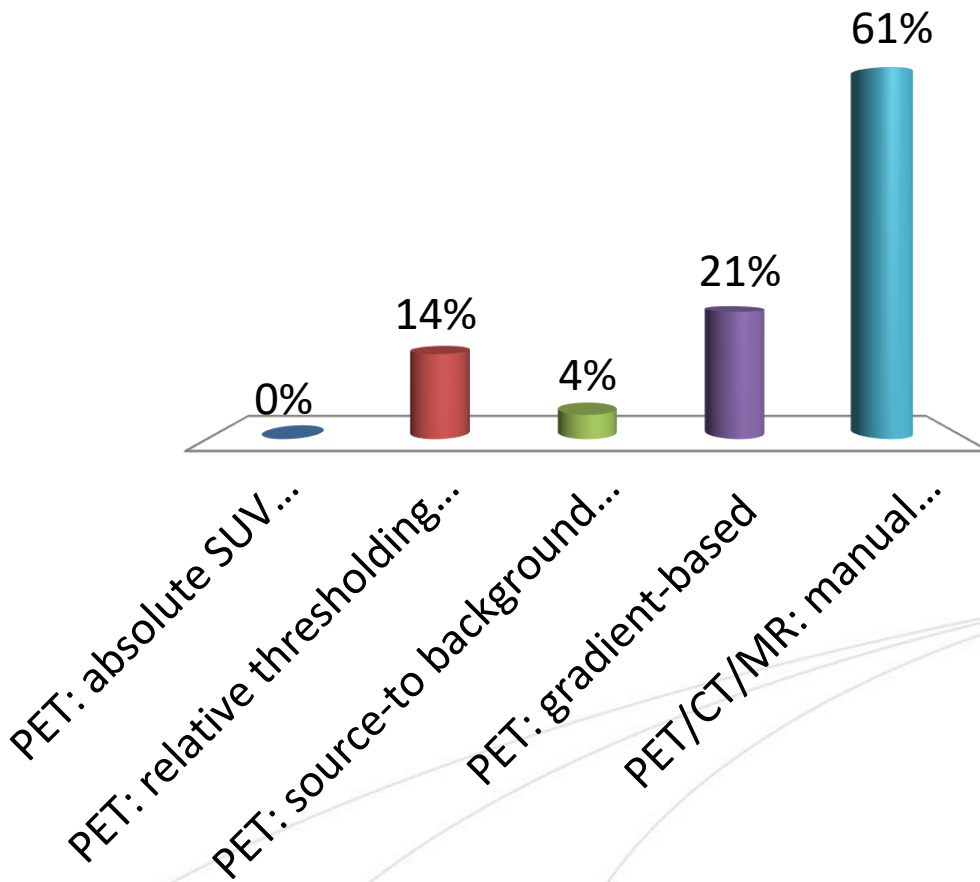
Which contouring method is in your opinion most *accuracte*?

A. PET: absolute SUV thresholding (e.g. SUV=2.5)
B. PET: relative thresholding (e.g. 40% SUV_{max})
C. PET: source-to background methods
D. PET: gradient-based
E. PET/CT/MR: manual following standardized protocol



Which contouring method is in your opinion most *practical to implement*?

A. PET: absolute SUV thresholding (e.g. SUV=2.5)
B. PET: relative thresholding (e.g. 40% SUV_{max})
C. PET: source-to background methods
D. PET: gradient-based
E. PET/CT/MR: manual following standardized protocol



Summary/Conclusion

Functional Image based RT target volume delineation

- Improves accuracy of contouring
- Gives robust volumes

PET-based contouring

- Different automatic contouring methods available
- Large differences in complexity but also in accuracy and robustness
- Validation is crucial

Multi-modality imaging for contouring

- May again improve target volume delineation
- Validation is difficult
- Potential for functional imaging based therapy adaptation

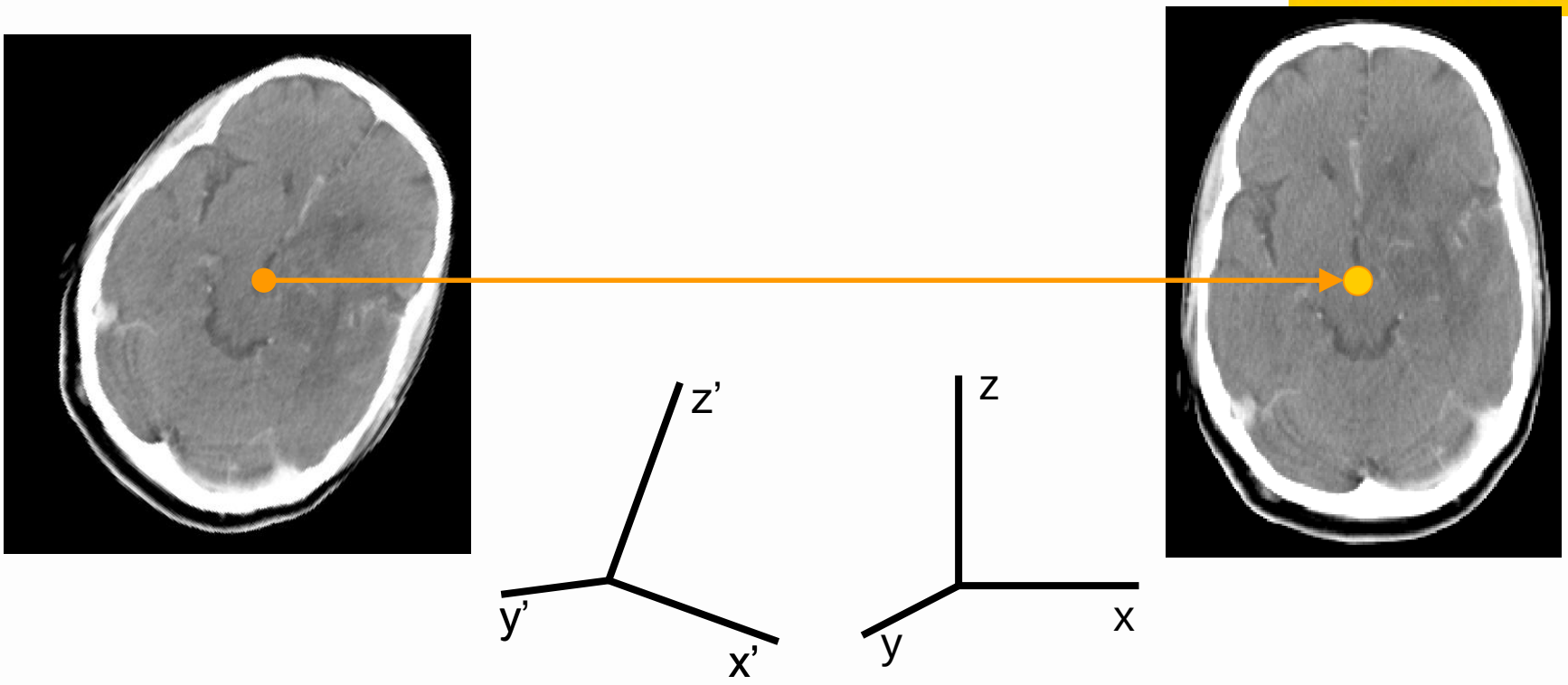
Image-based delineation of radioresistant tumor sub-volumes

- Eg. Hypoxia PET, Diffusion MRI, …

Registration

Uulke van der Heide

Image registration



- The process of transforming different sets of data into one coordinate system
- The process of associating each voxel in one image with the corresponding voxel in the other image

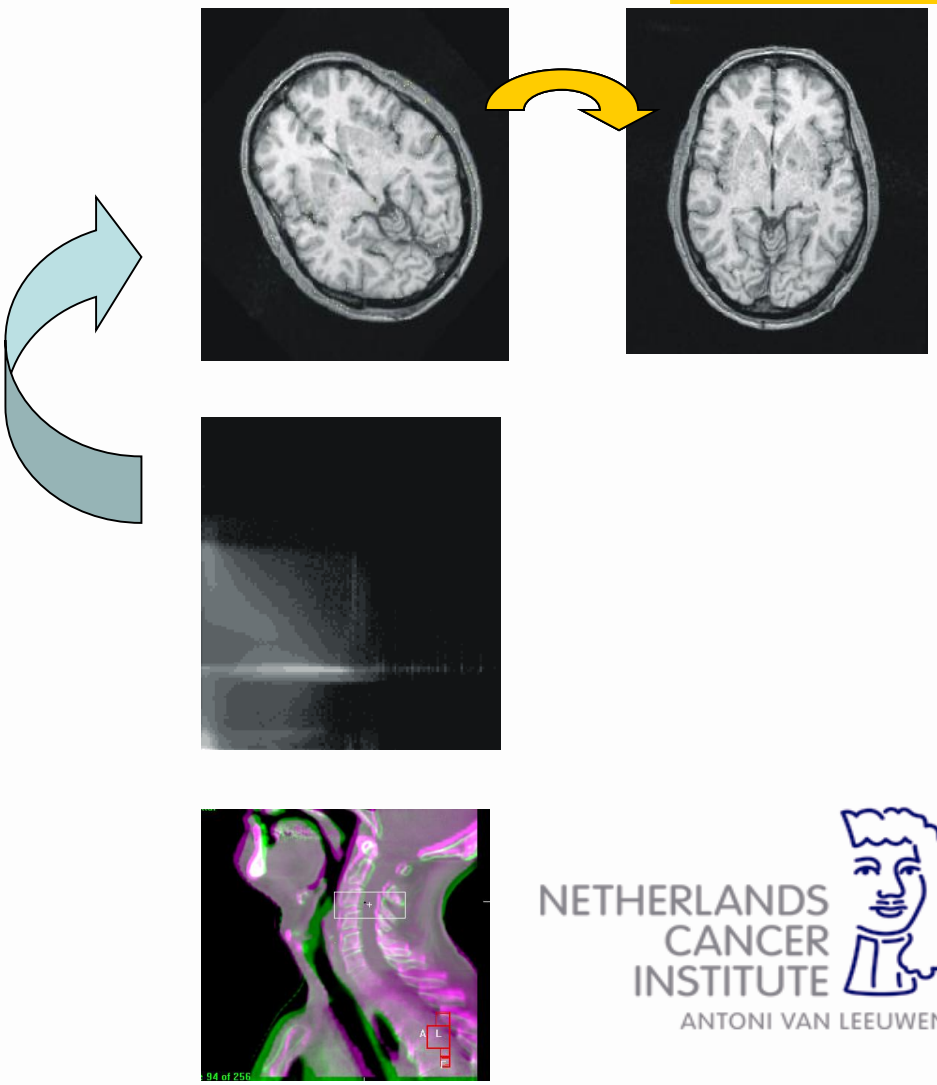
Manual registration

- Simple ‘algorithm’
  - Manually shifting and rotating one image across the other and verify if it ‘looks ok’.
- Difficult in 3-D
- Not very precise
- Appropriate for gross alignment

- Automatic registration is more versatile

steps of the registration process

- transformation
- similarity assessment
- visualization



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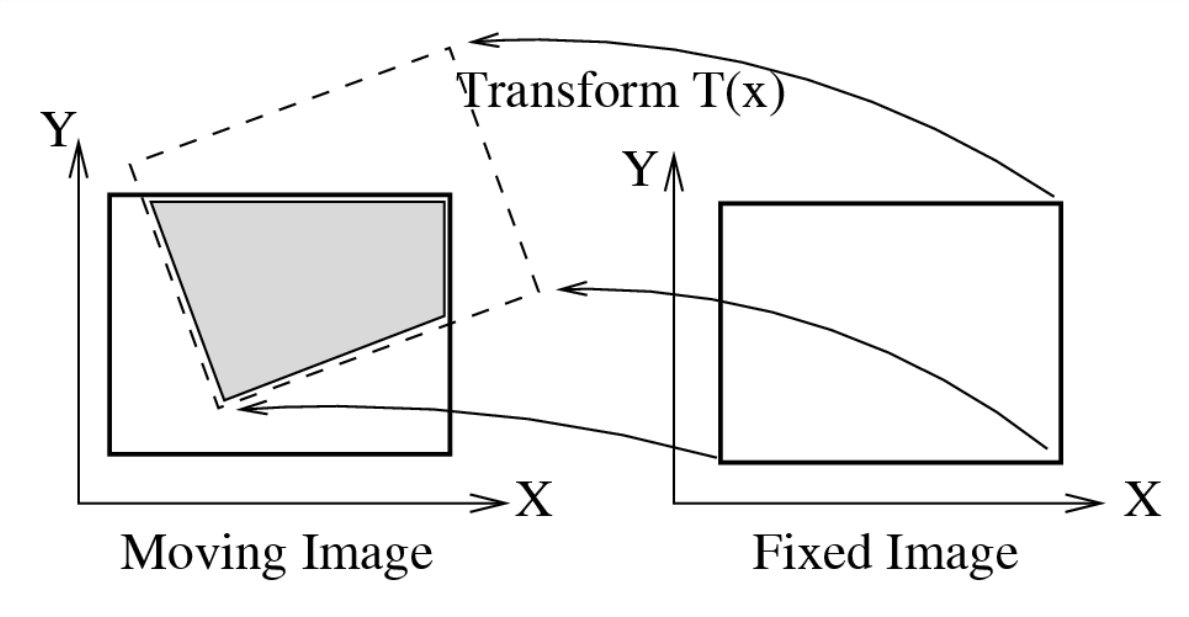
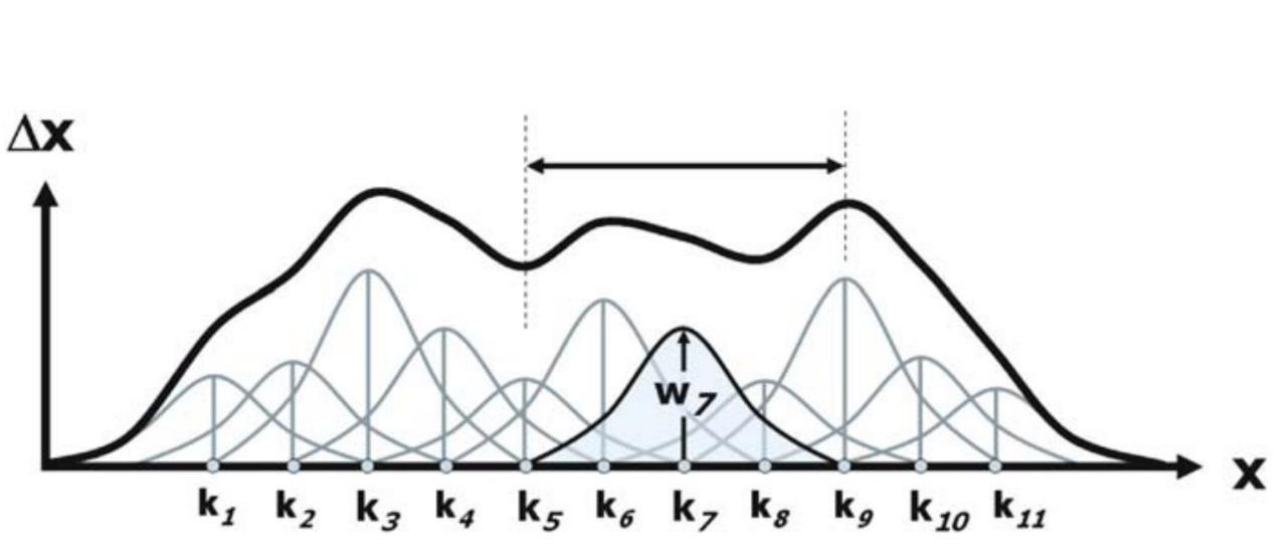
Transformation

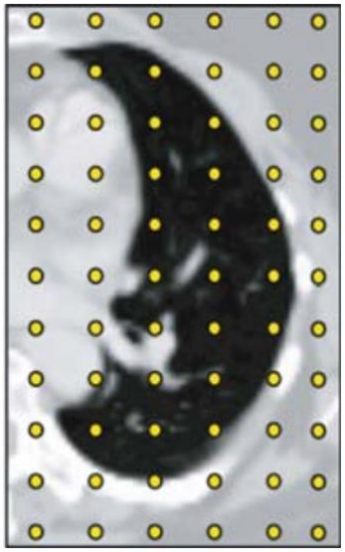


- Rigid transformation (translations, rotations)
- Deformable registrations

Deformable registration

B-Splines

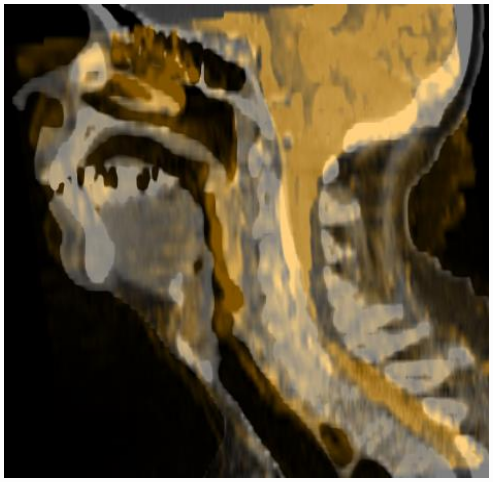




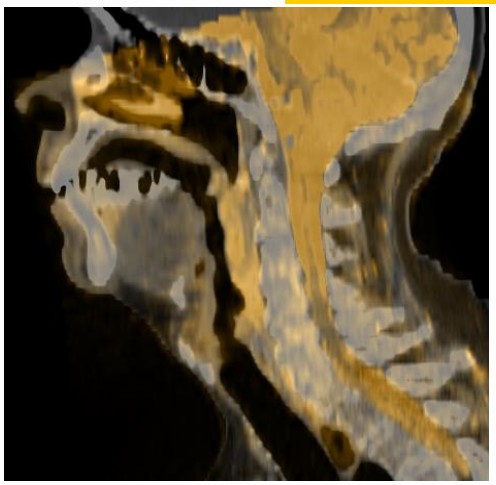
- Regular grid of ‘control points’
- Optimization of the registration by shifting them relative to one another

Deformable registration of PET/MR and (PET/)CT

Fusion of CT (grey) and MR (orange)

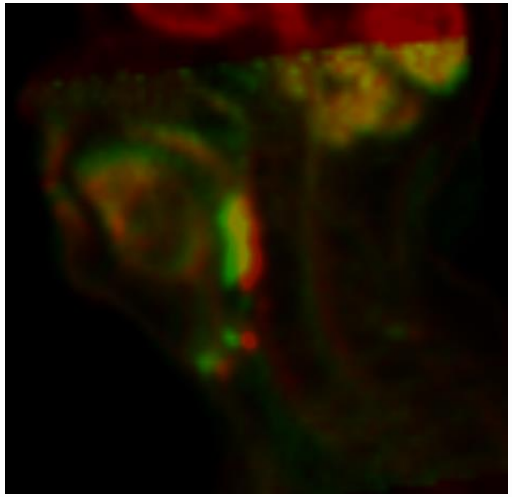


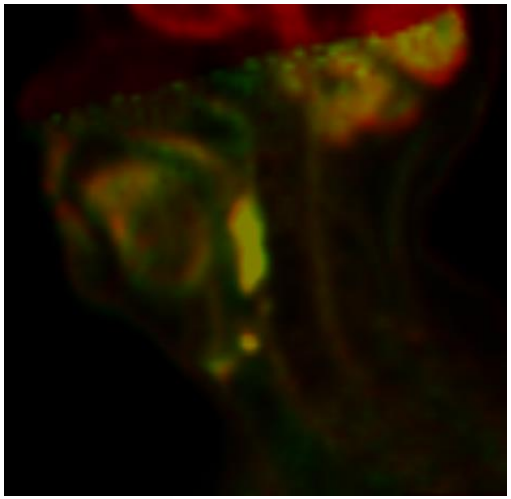
after rigid registration



after deformable registration with LMI+BEP

Fusion of the two PET datasets

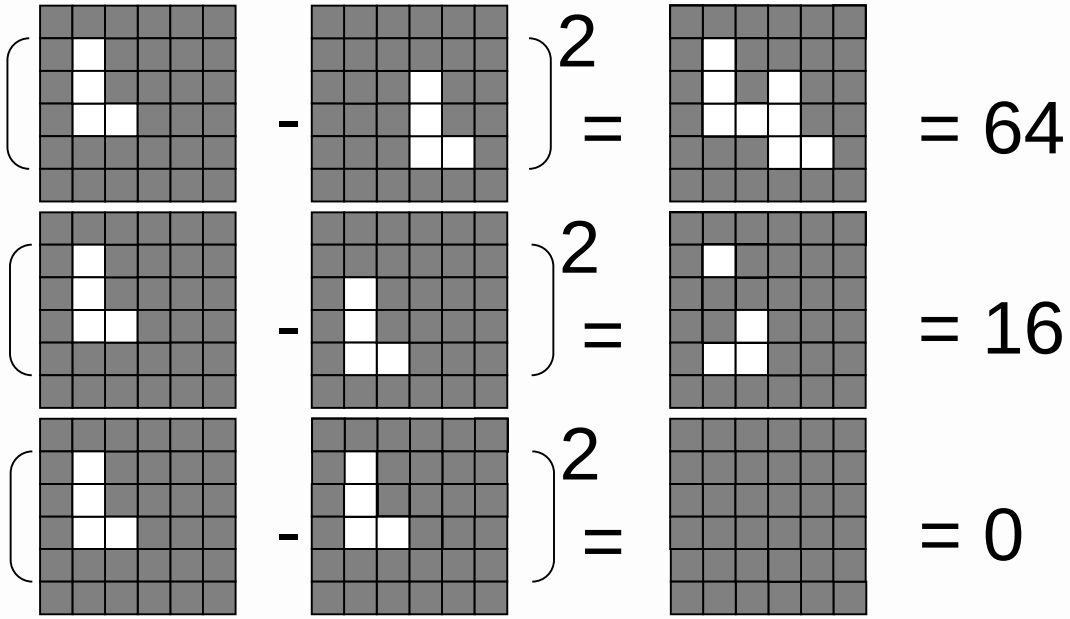




Courtesy Daniela Thorwarth

Similarity metrics

- How good is the registration result?
- For automatic registration this needs to be summarized in a single number.



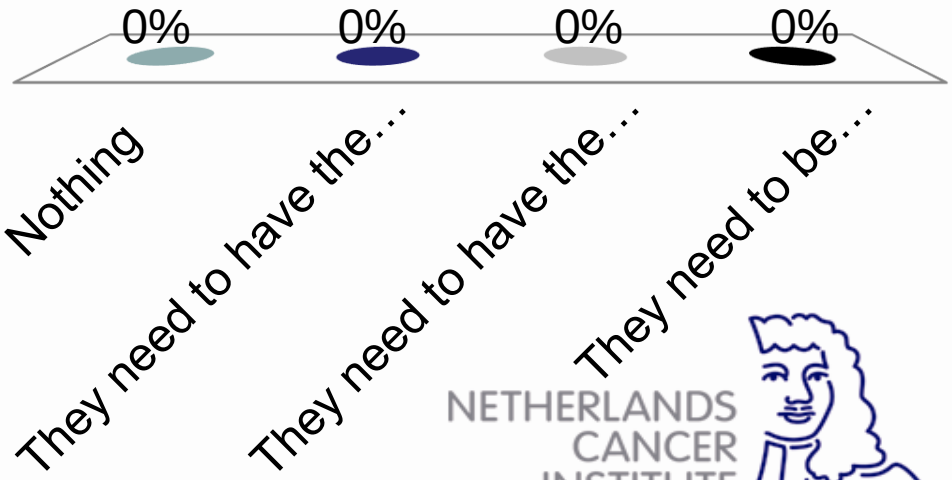
What properties are required for the two images to be registered with a correlation metric?

a. Nothing

b. They need to have the same voxel size

✓ c. They need to have the same contrast type

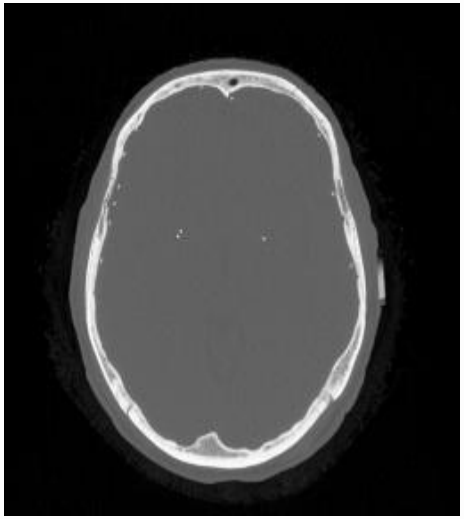
d. They need to be measured at the same time point (day)

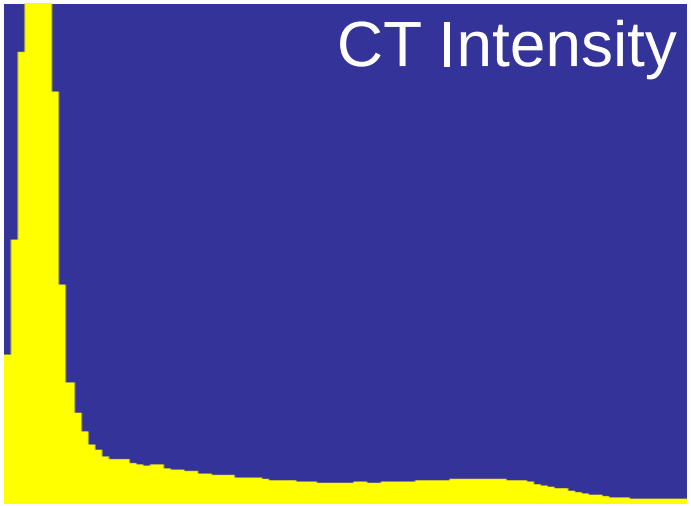


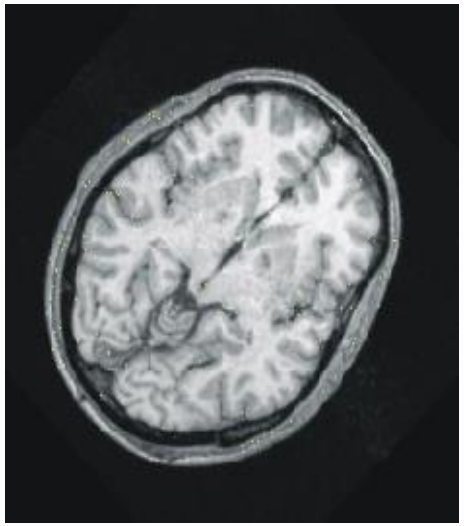
Similarity metrics

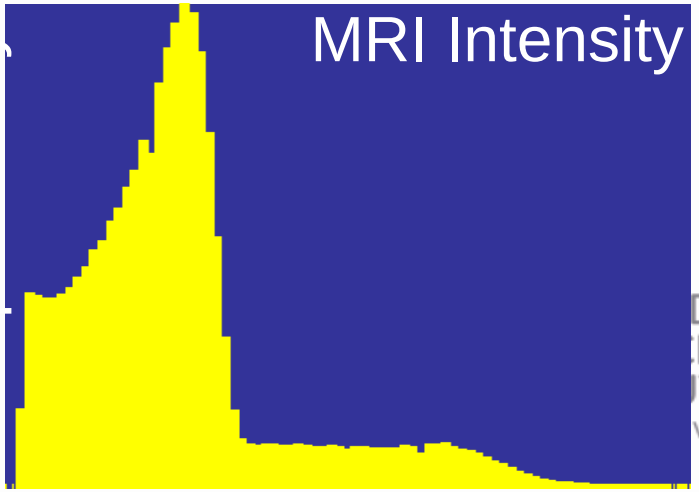
- Root mean square of difference
- Correlation ratio
- Mutual information
- Etc……

How to register images from different modalities?

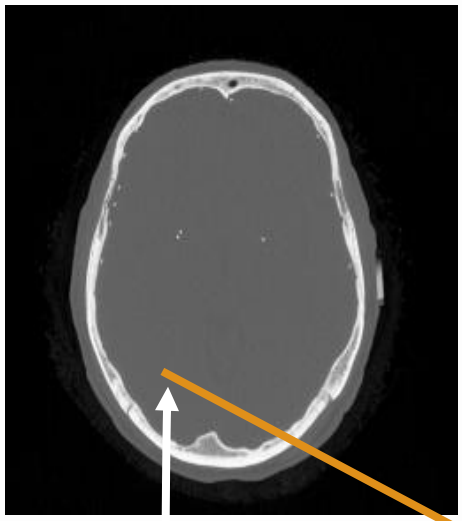


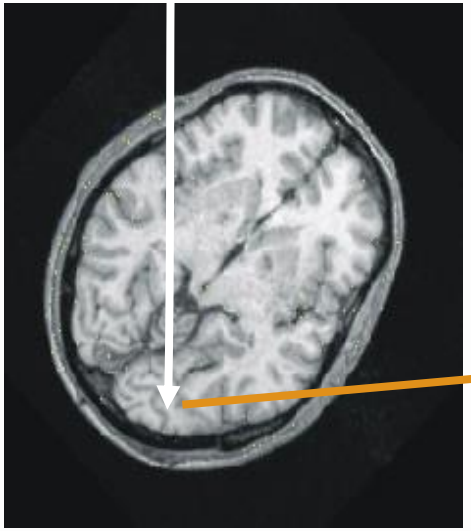


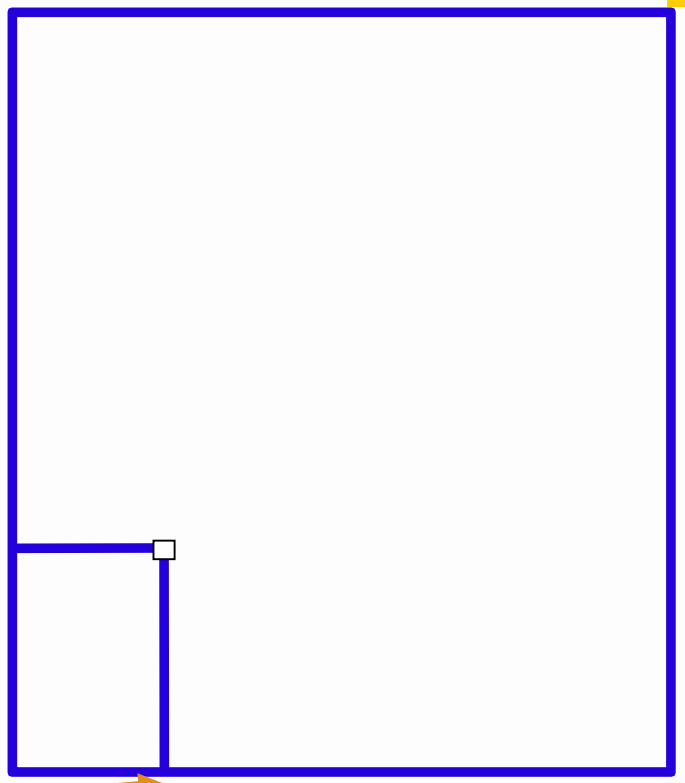




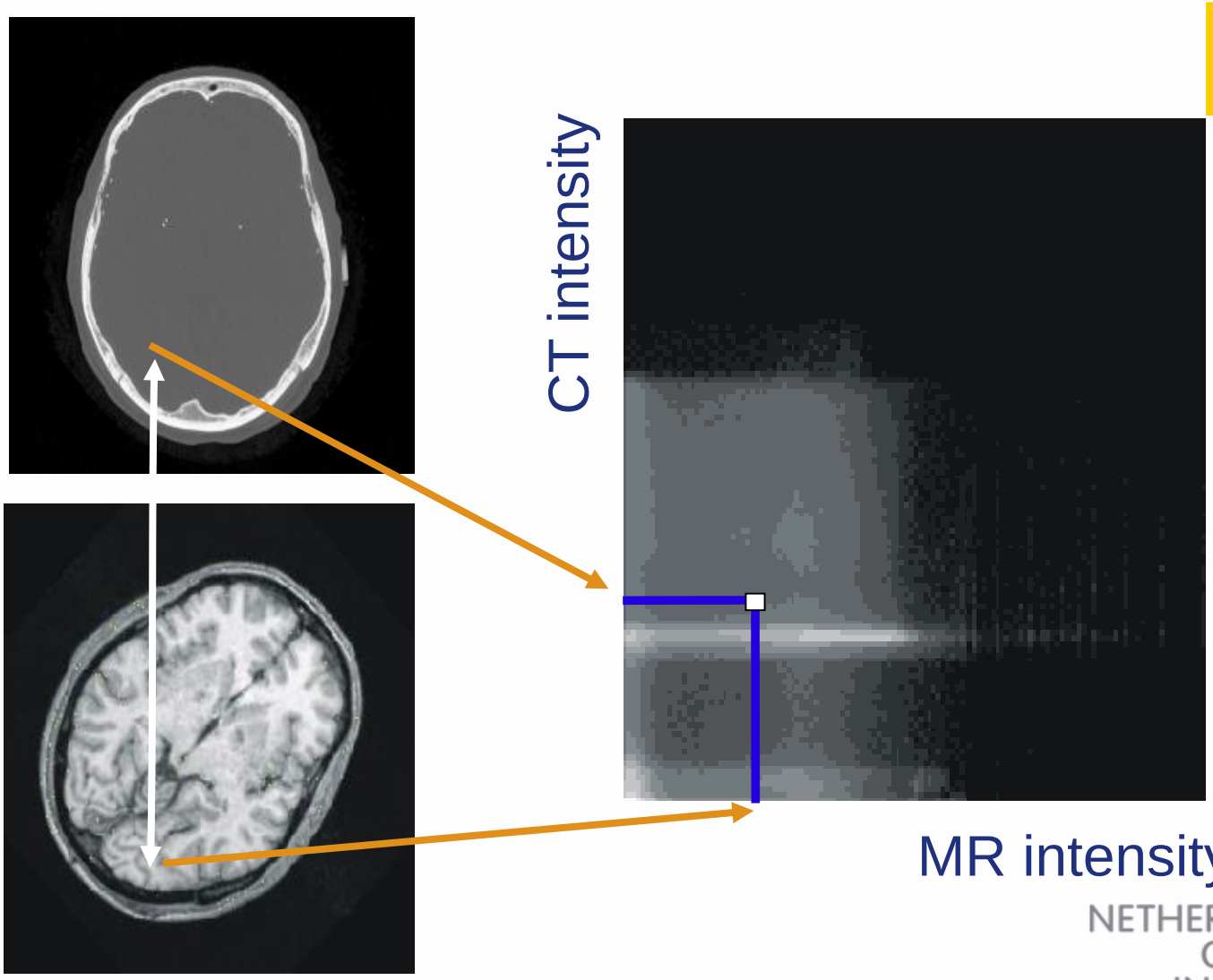
Joint histogram







Joint histogram



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Joint histogram

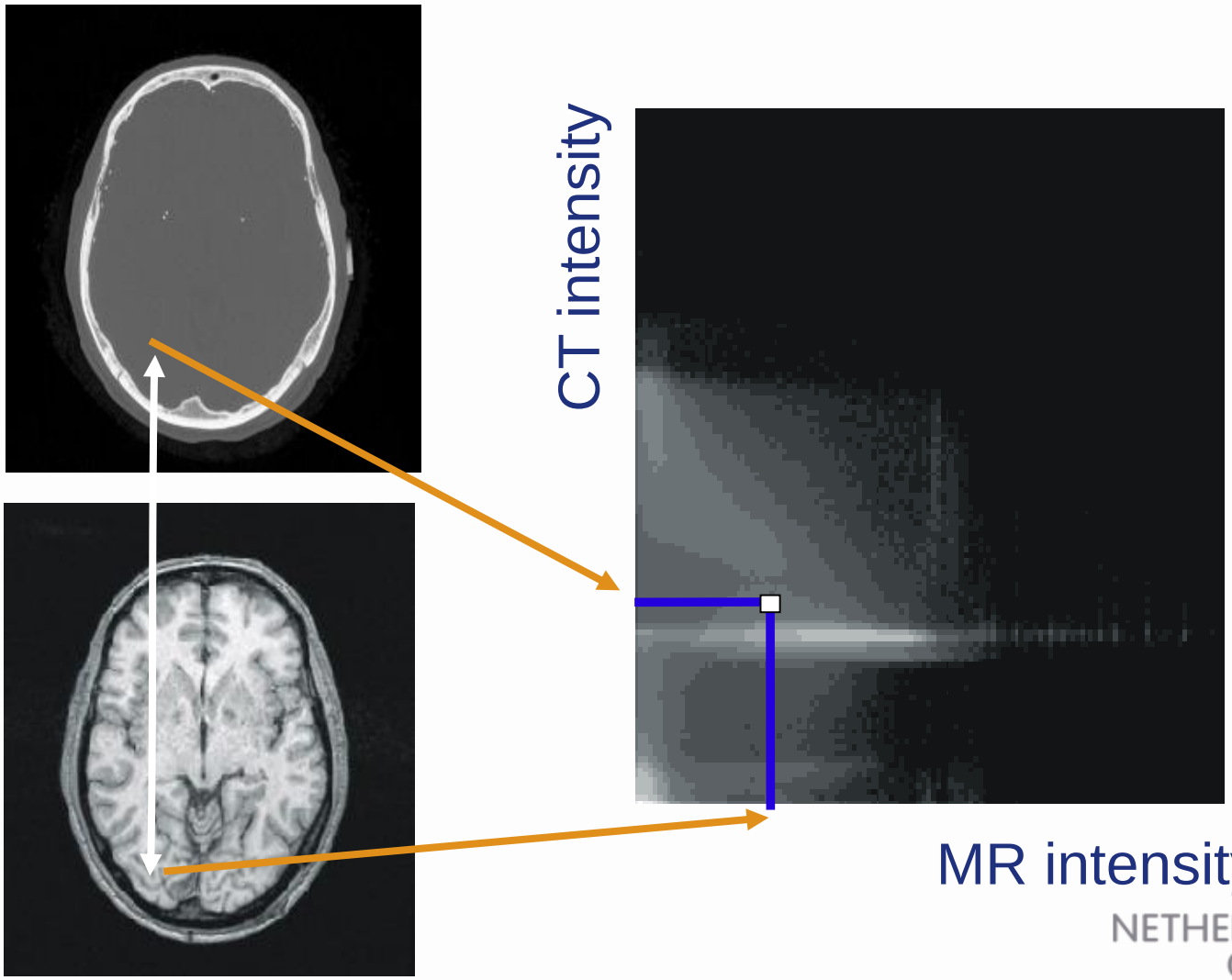

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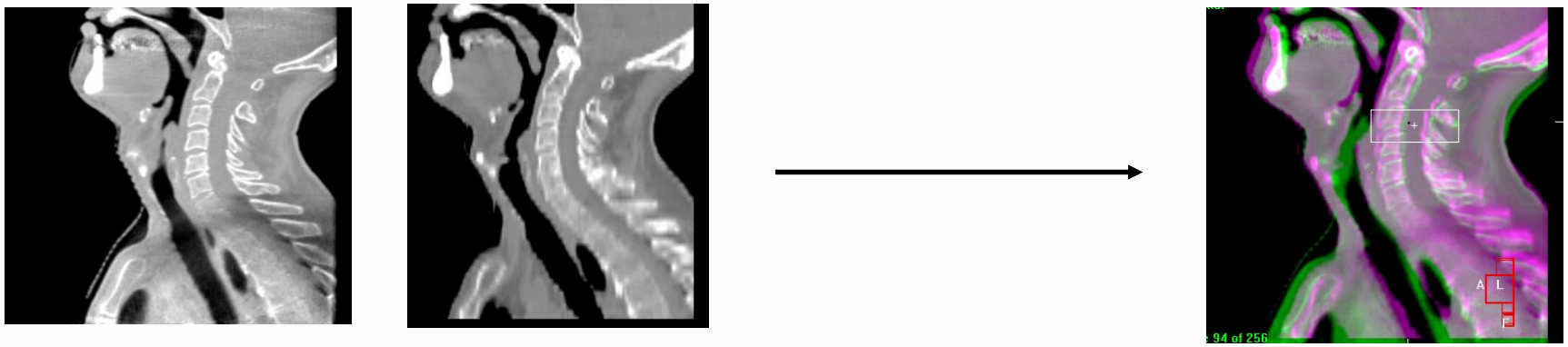
Image fusion

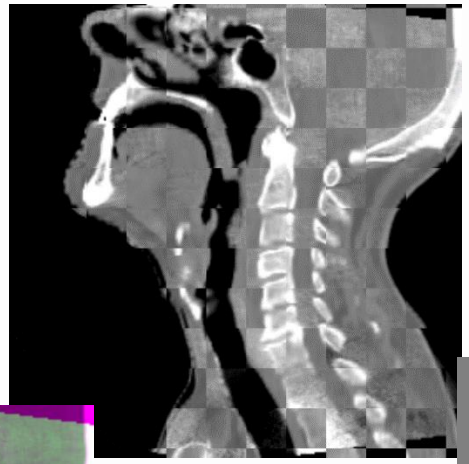
- Combine the information of two scans

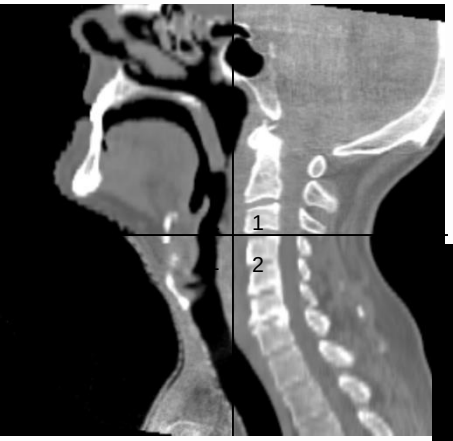


- Allows viewing and validation of registration result

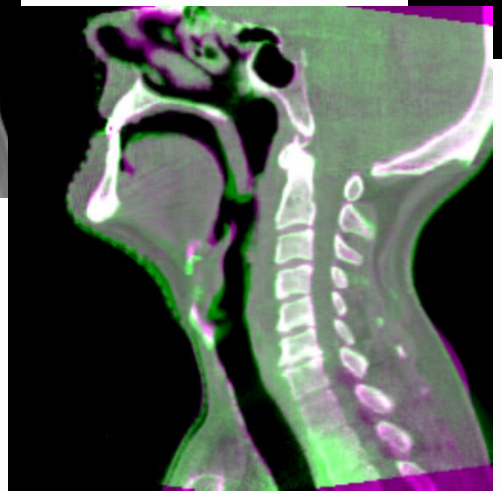
Image fusion

Checker



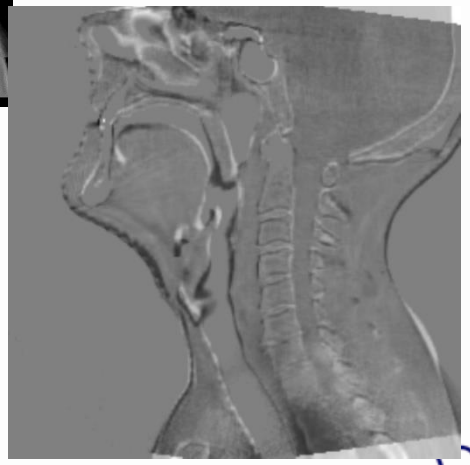


sliding window



Overlay

Substract



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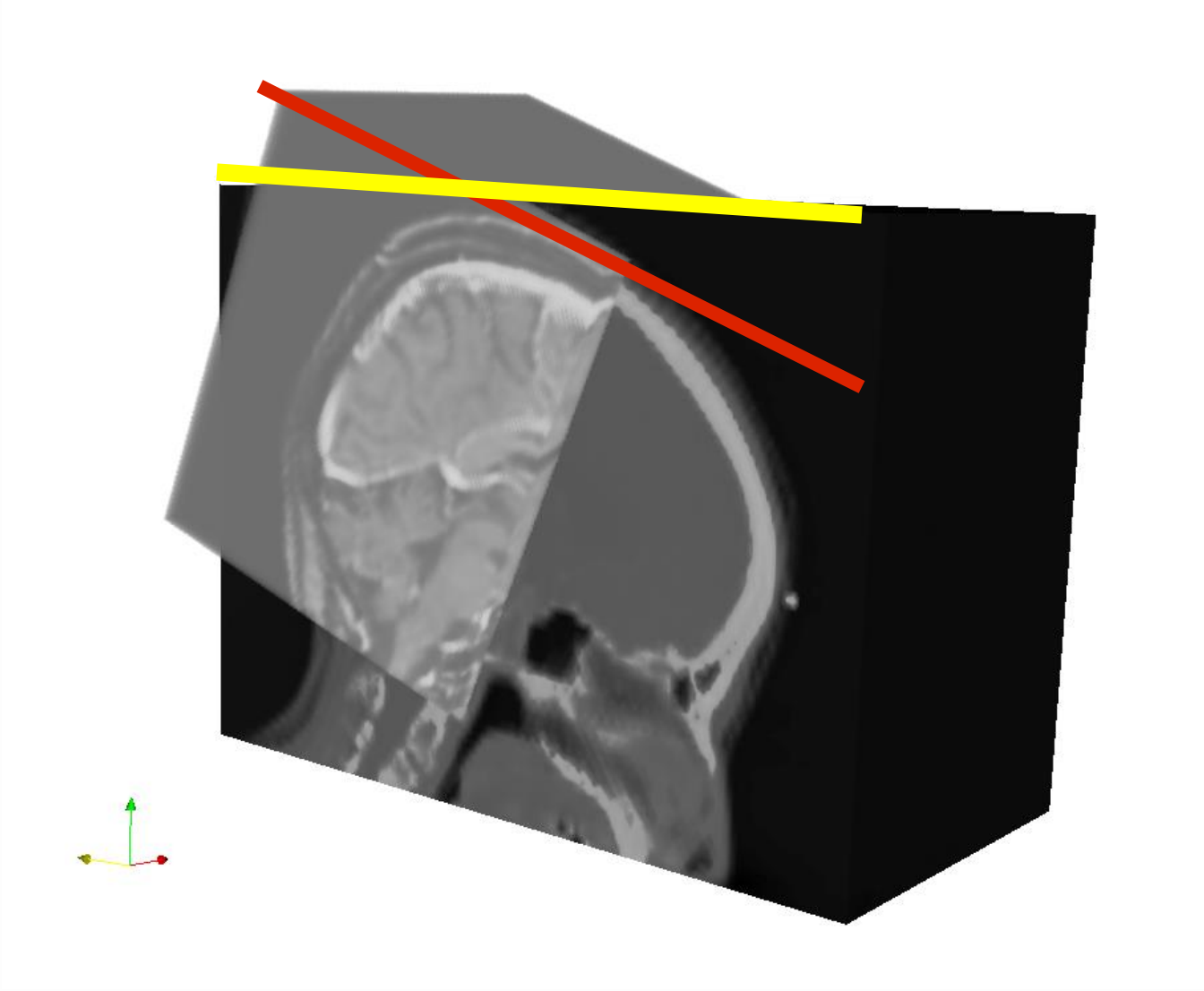
Resampling

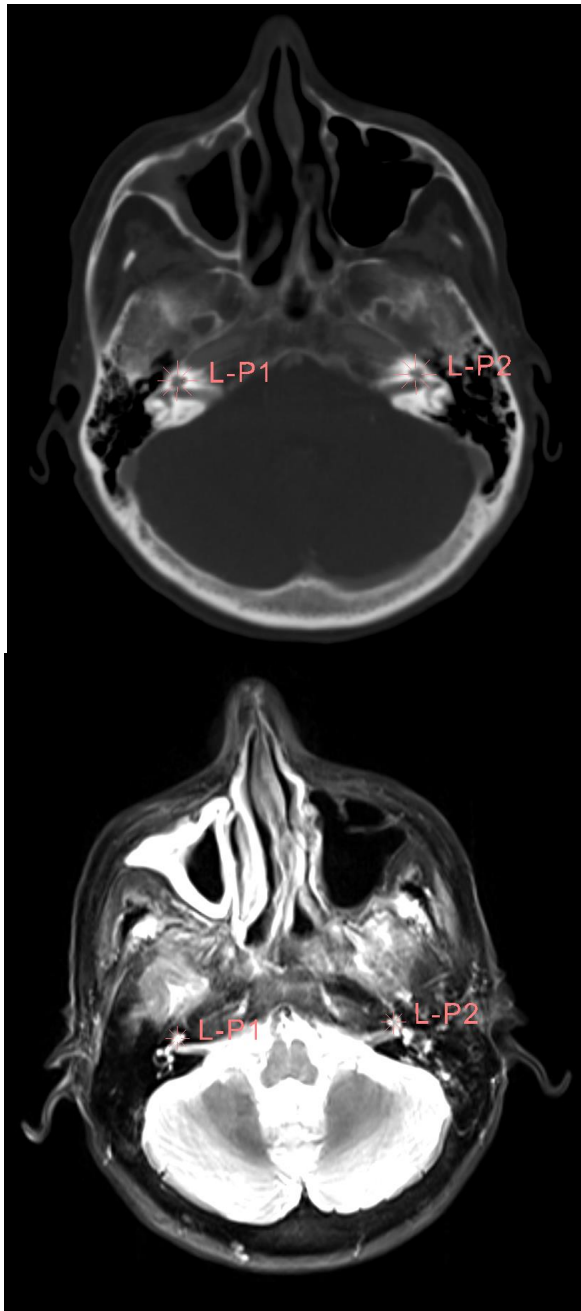


Validation

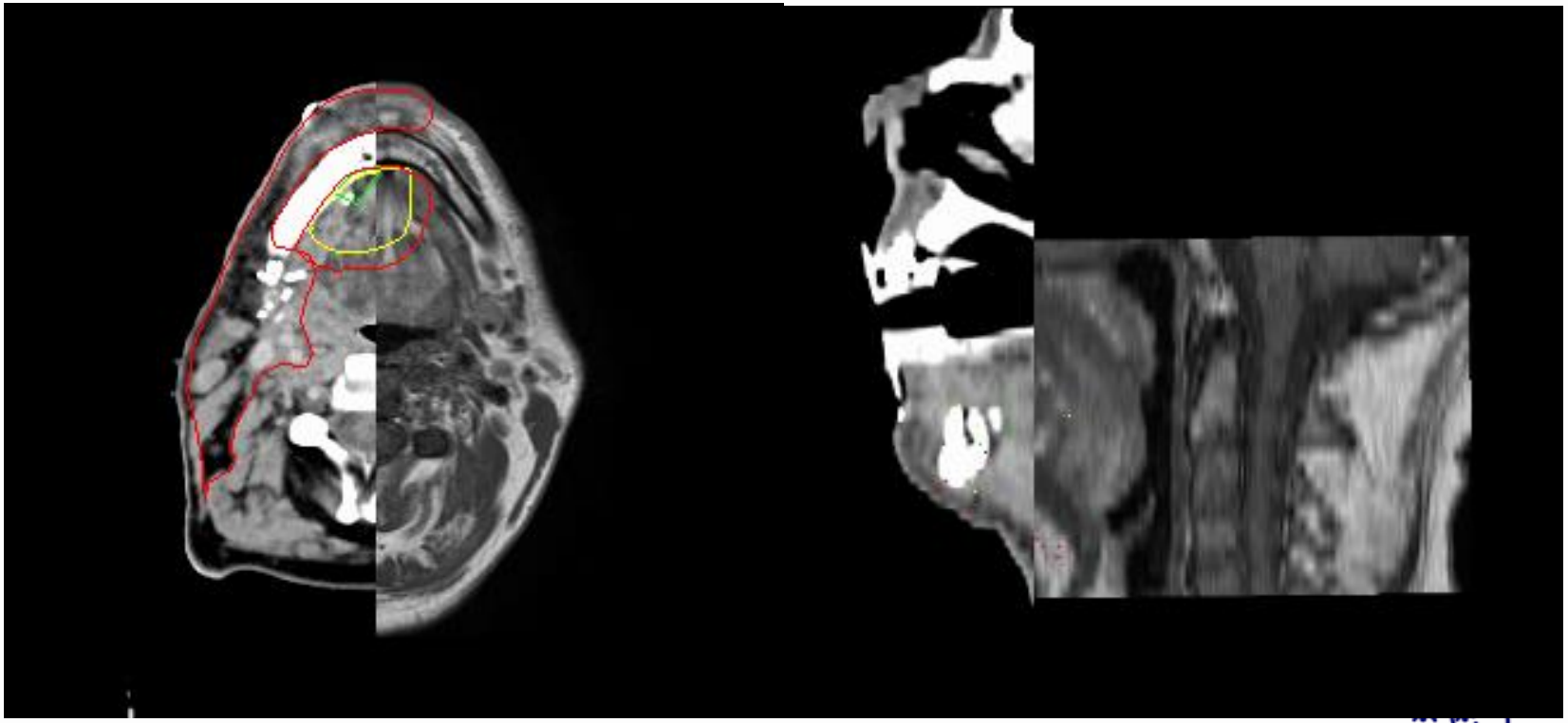
- Landmarks on 2 images
  - The distance between corresponding points should be minimal
- Dice similarity index of contoured structures

$$DSI = \frac{2\left|A \cap B\right|}{\left|A\right| + \left|B\right|}$$

- …



What if images don’t match?



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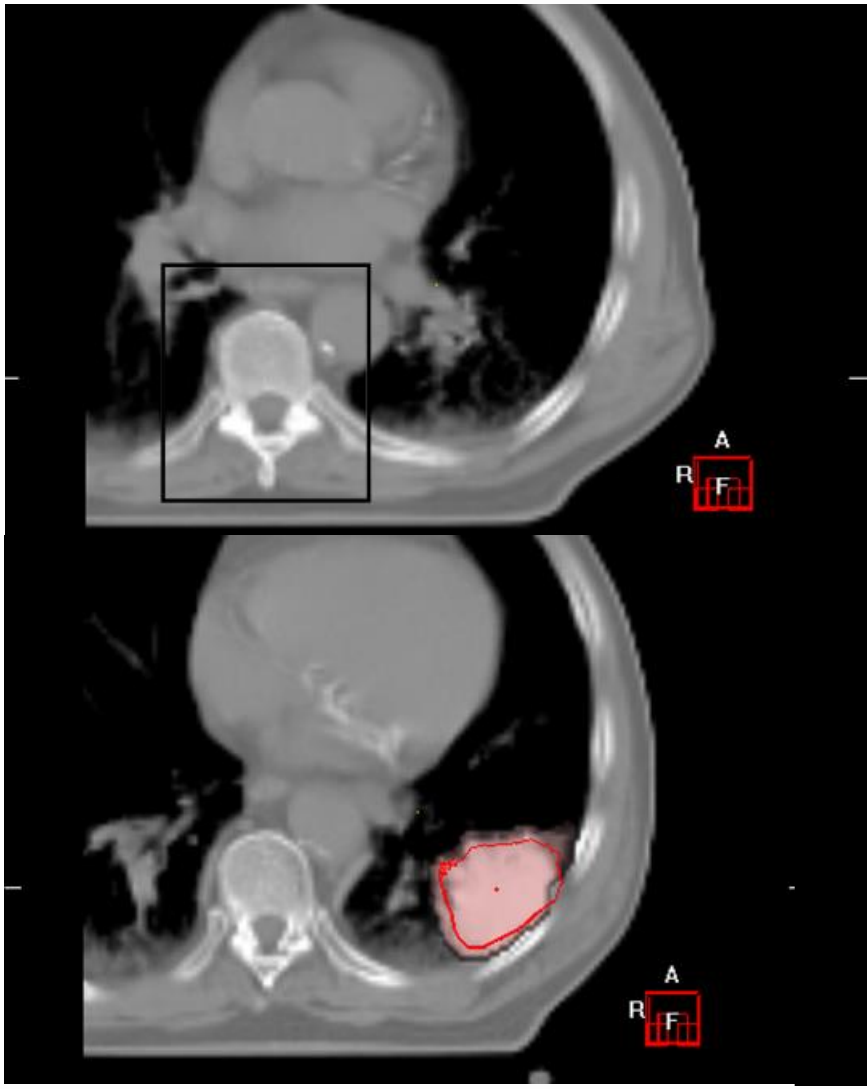
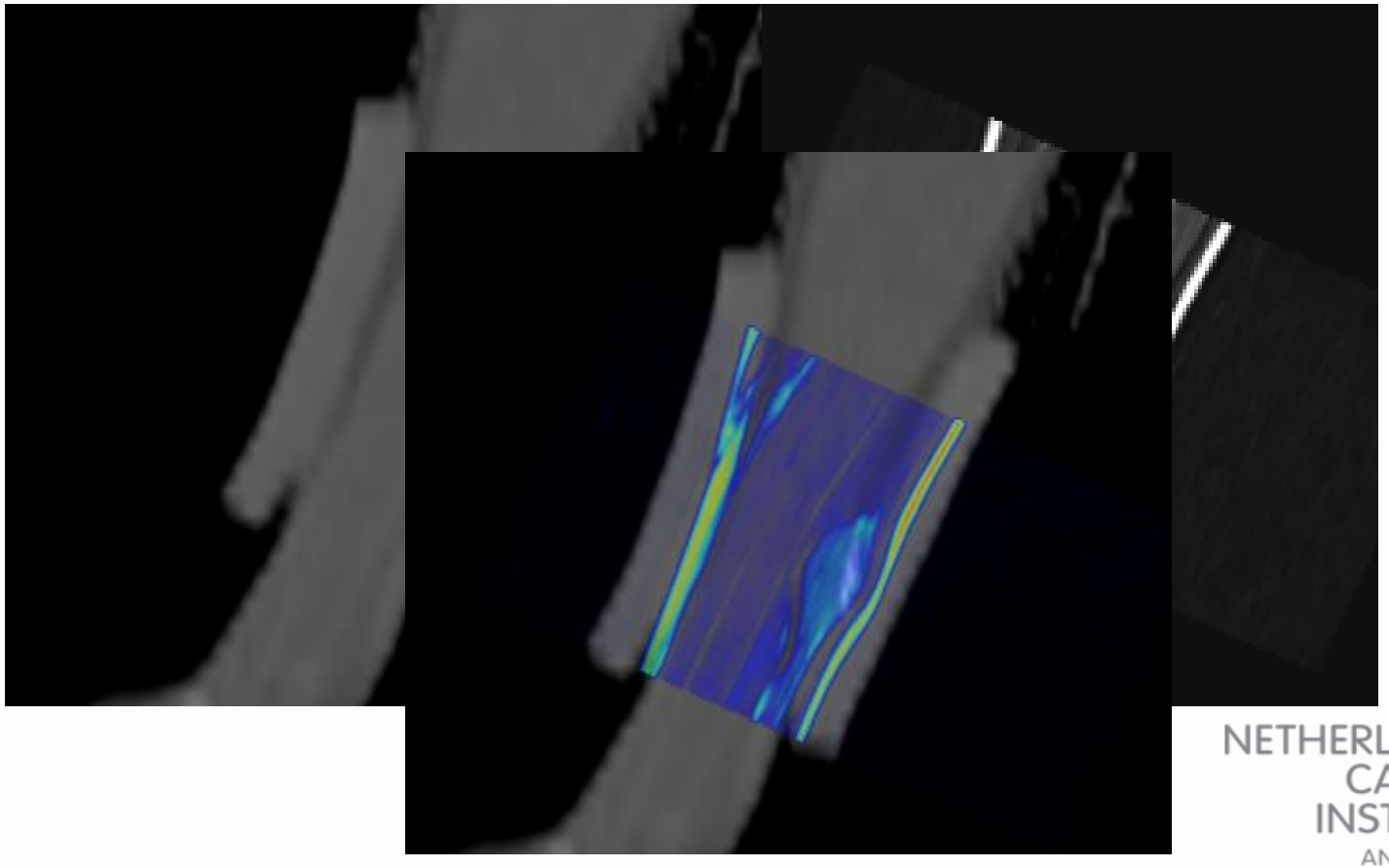
What if images are deformed

- Select part of the image to register
  - Perpendicular (clipbox)
  - Free shape (ROI)
  - …
- Deformable registration



Example: registration of MRI and CT of sarcoma in arm

Are there sufficient common structures in the images?



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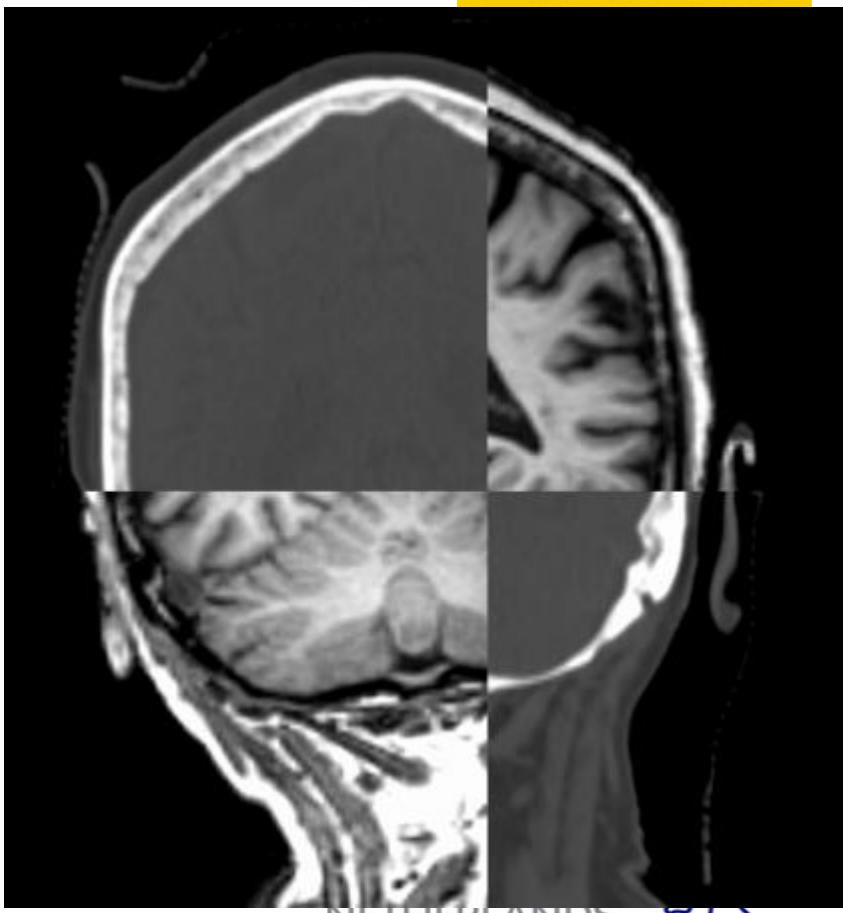
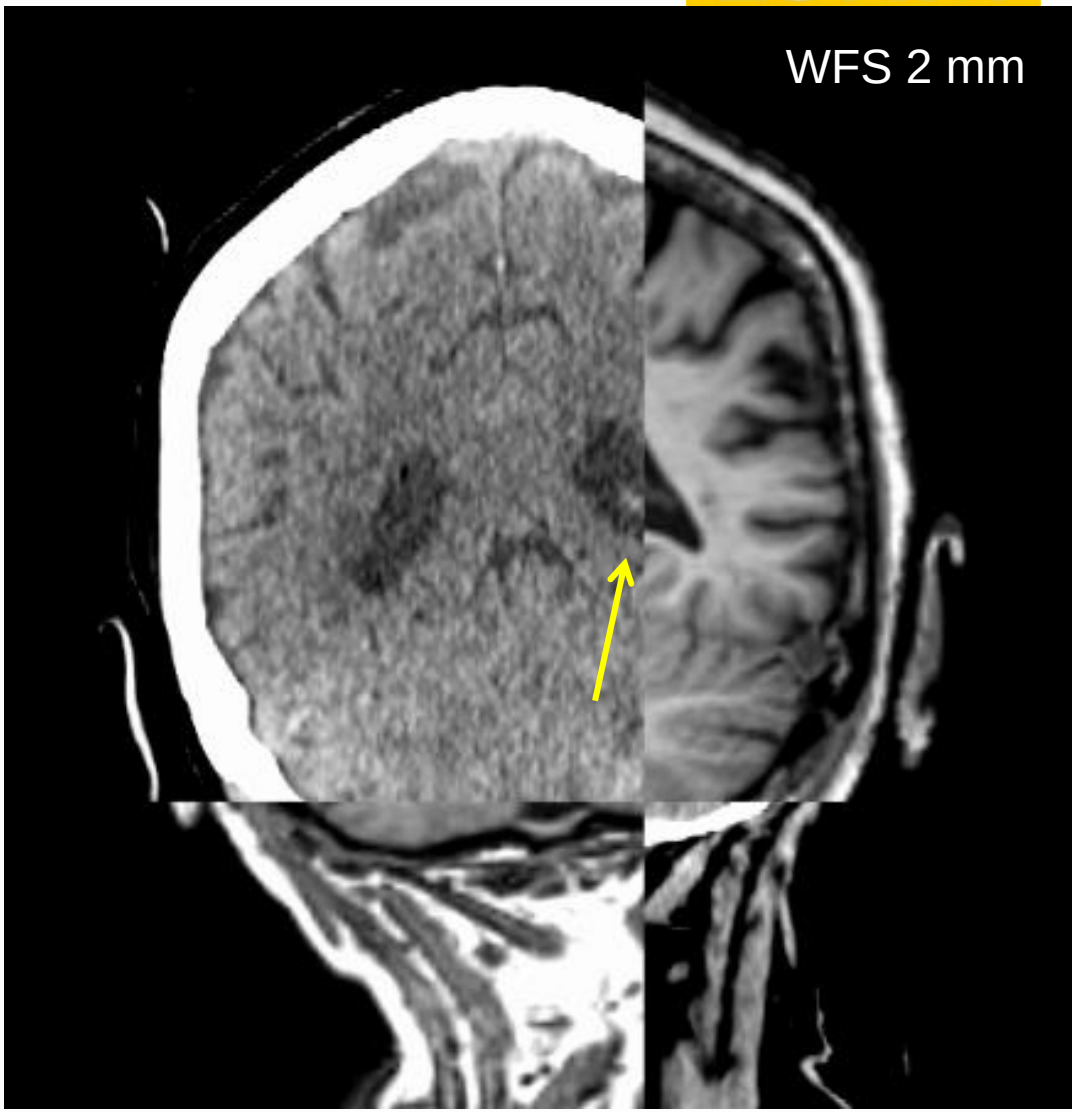
Example: registration of CT and MRI of brain

- Cortical bone:
  - CT: bright
  - MRI: dark
- Bone marrow
  - CT: grey
  - MRI: grey
- Skin
  - CT: dark grey
  - MRI: bright



water-fat shift

- The signal from water and from fat are not imaged at the same location
- This is usually a tunable parameter in MRI
- Reduction of the water-fat shift costs SNR



In your clinic, do you ONLY use MRI and PET scans for target delineation that were made specifically for RT?

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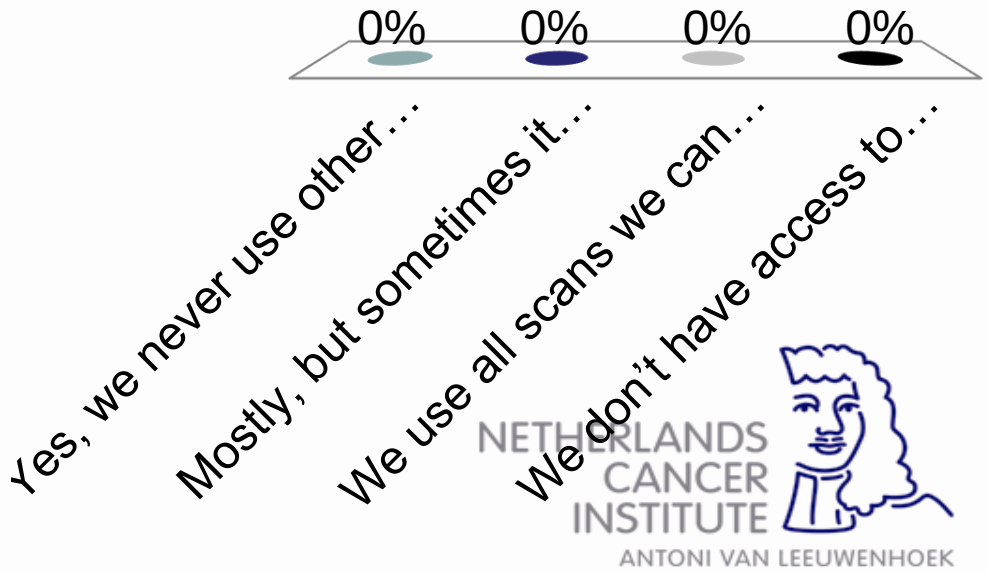
a. Yes, we never use other scans
b. Mostly, but sometimes it is inevitable to use other scans
c. We use all scans we can get
d. We don't have access to scans made specifically for RT



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Practical considerations

Make images in RT position

- Use flat table top
- Use fixation devices, masks

Consider the use of the images

- Diagnostic
  - Decide if a target volume should be irradiated or not
- Delineation
  - Use one imaging modality to identify the boundaries of a target, that isn't visible on the planning CT scan

Summary

steps in registration

- Transformation
  - Rigid / deformable
- similarity assessment
  - Correlation / mutual information
- Visualization
  - resampling
- Validation
  - Corresponding landmarks / structures

Summary

- The registration method depends on the available images and on the clinical use

- Registration has to be based on features that are clearly visible in both image modalities.
  - Don’t ‘put the spot on the spot’

- Make scans in treatment position to minimize deformation
  - Deformable registration can be risky

What if no RT images are available?

- Do not register, use side by side
- Consider increasing the PTV margin
- If a local registration is possible, make sure
  - the registration can be validated on structures AROUND the tumor
  - You don’t simply put the ‘spot on the spot’
  - the registration is not used for other purposes (i.e. delineation of lymph nodes, organs at risk etc.)

Acknowledgements

- Alexis Kotte (Utrecht)
- Daniela Thorwarth (Tübingen)
- Peter Remeijer (Amsterdam)

MRI and CT for Head & Neck Tumours

Frank Pameijer, MD, PhD

- Departments of Radiology and Radiation Oncology
- University Medical Center, Utrecht
- The Netherlands

No disclosures

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Head and Neck cancer: Imaging?

- Imaging results in more accurate TNM-staging compared to clinical examination alone!
- Clinical examination and imaging are complementary modalities
  - Findings should be discussed in multidisciplinary setting

Multidisciplinary H&N Oncology meeting

- UMCU: every Wednesday 13.30-16.00
  - All new patients
  - All known patients with new event

Objectives

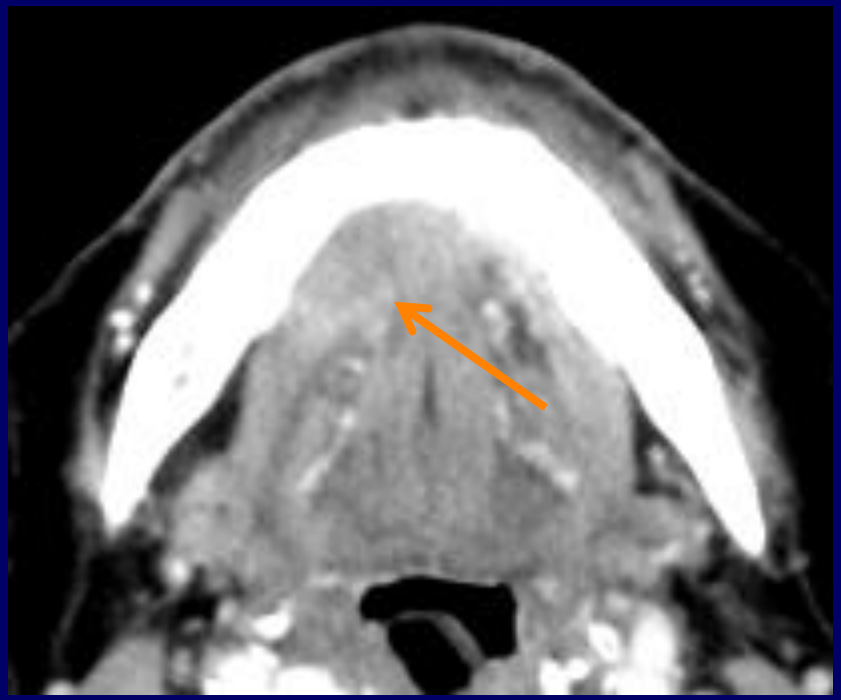
Imaging techniques for evaluation H&N ca.

- Conventional X-ray
  - Panoramic dental X-ray
- Ultrasound
- **CT**
- **MRI**
- PET

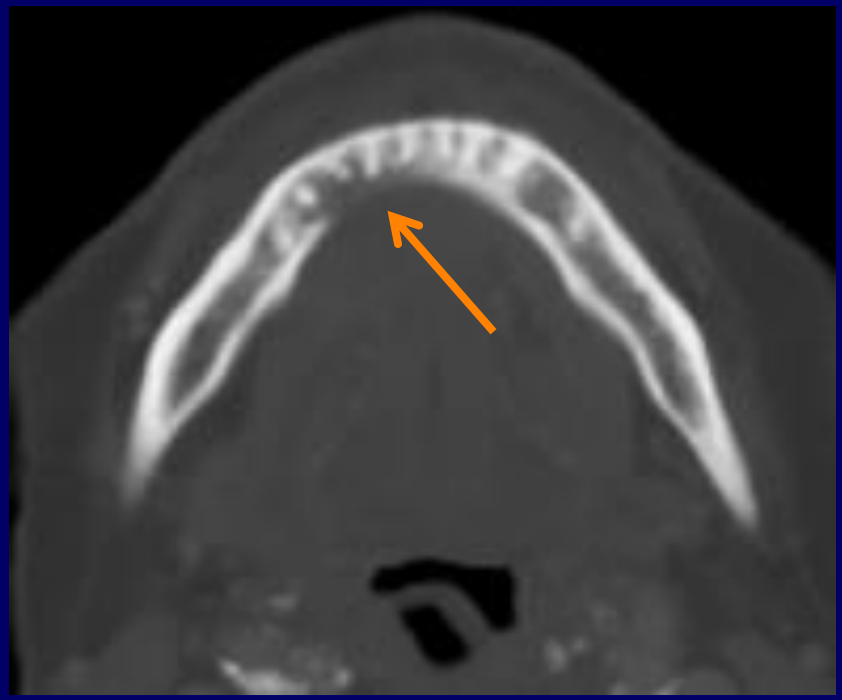
CT

- Advantages:
  - Quick, widely available, cheap
  - Superior bone detail
  - Preferred method for nodal staging
- Disadvantages:
  - Radiation exposure
  - Administration of iodine-containing agents
  - Inferior soft tissue contrast (vs MRI)
  - Dental filling metallic artifacts

Superior bone detail
Floor of mouth ca.

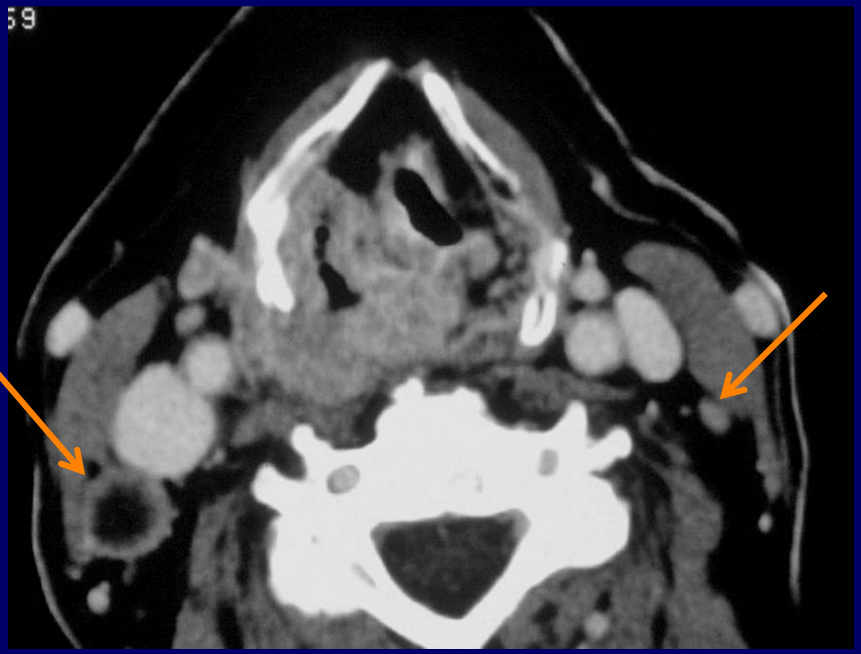


Soft tissue window

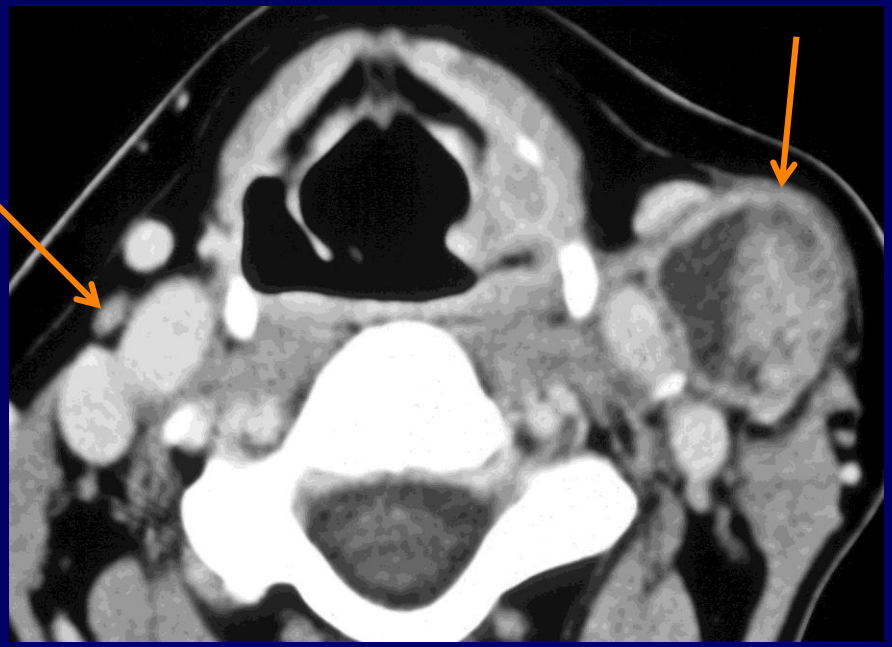


Bone window

Nodal staging



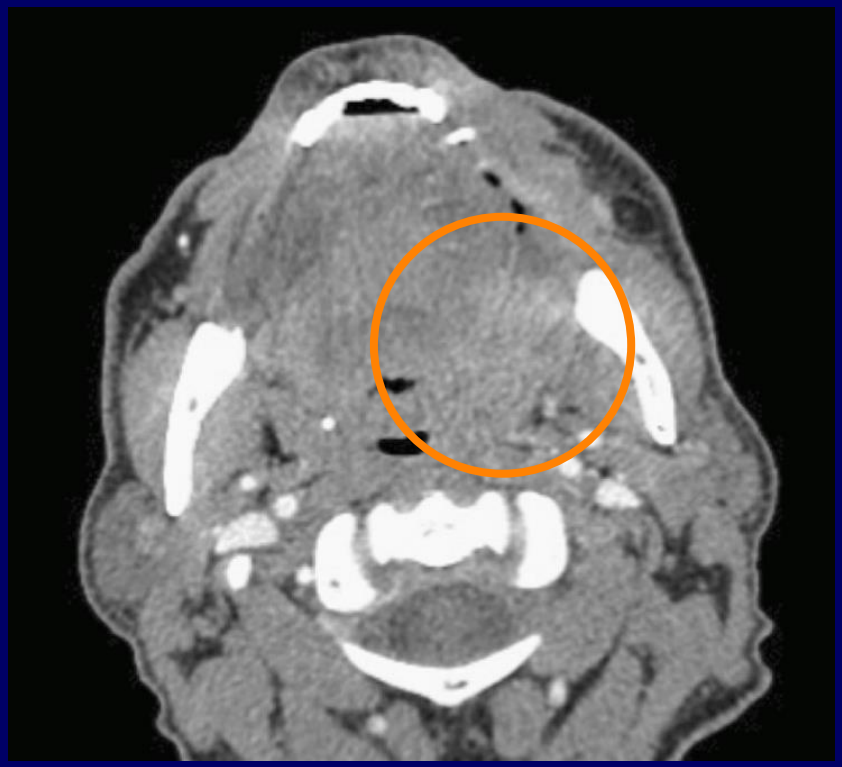
Hypopharyngeal ca.



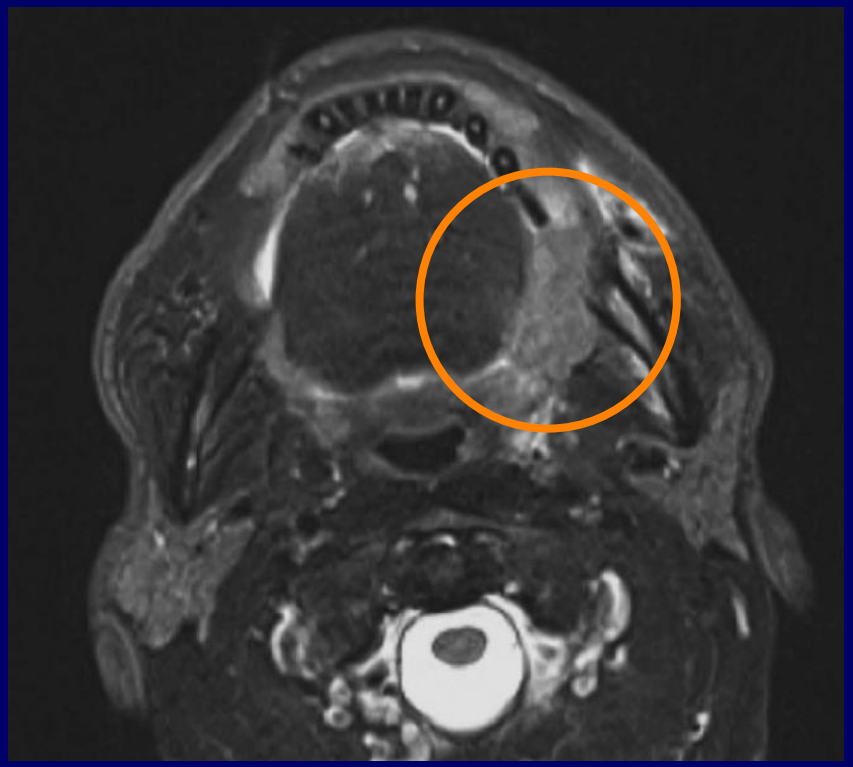
Supraglottic laryngeal ca.

Inferior soft tissue contrast (vs. MRI)

Oropharyngeal carcinoma

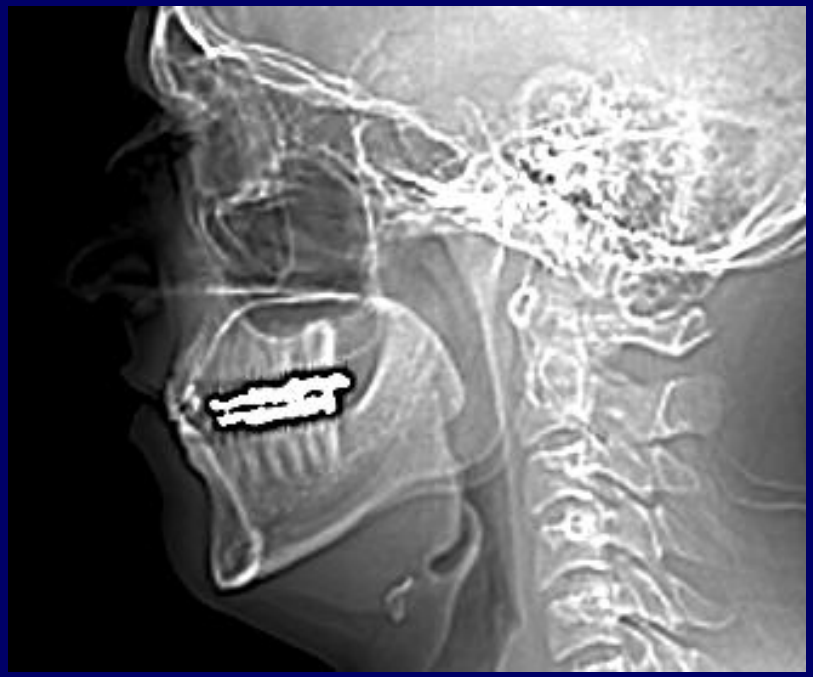


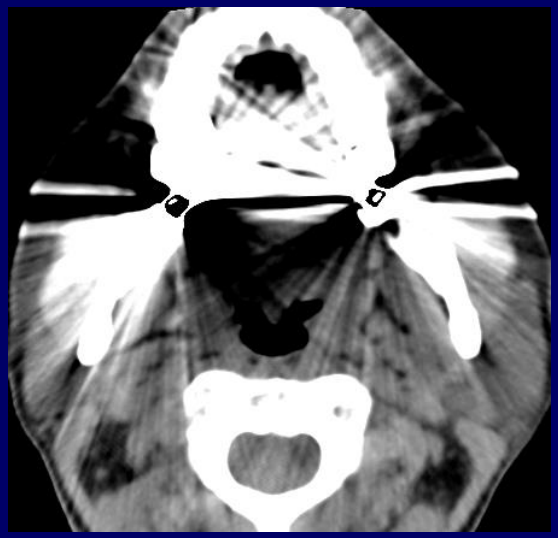
CECT



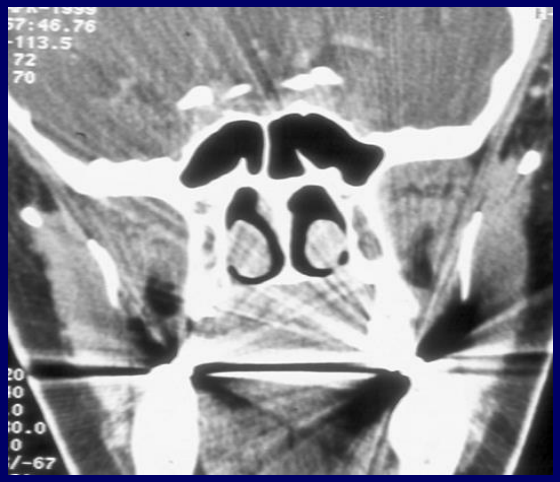
T2 DIXON-FS MR

CT: Dental metallic fillings

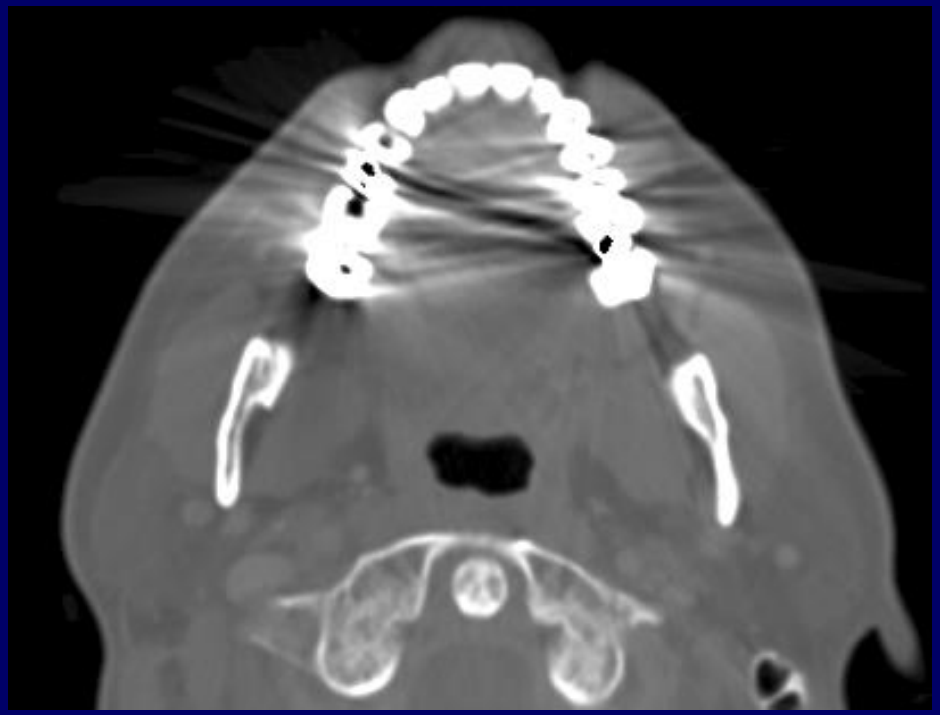




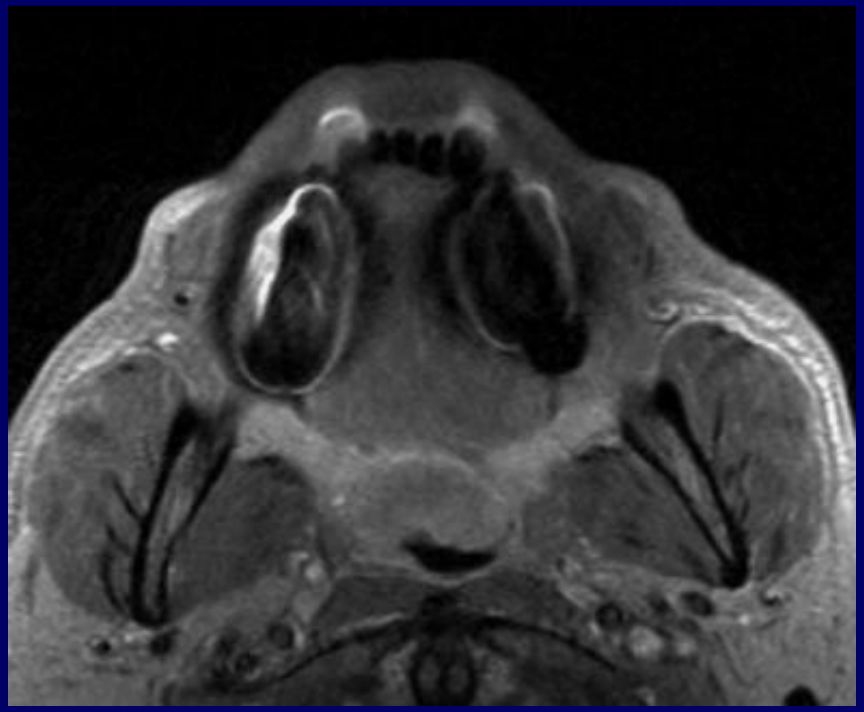
‘Streak’ artifacts



Dental filling artifacts: CT / MRI



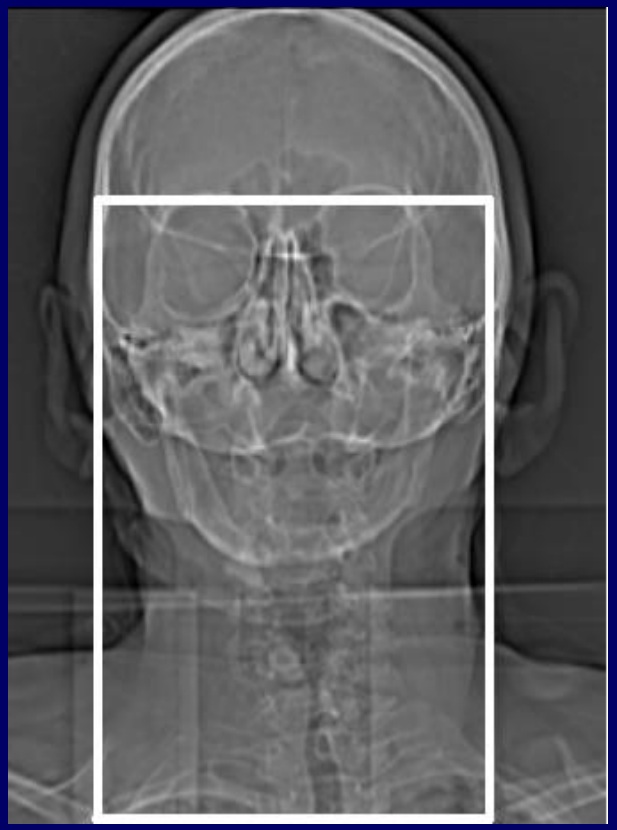
CT



MRI

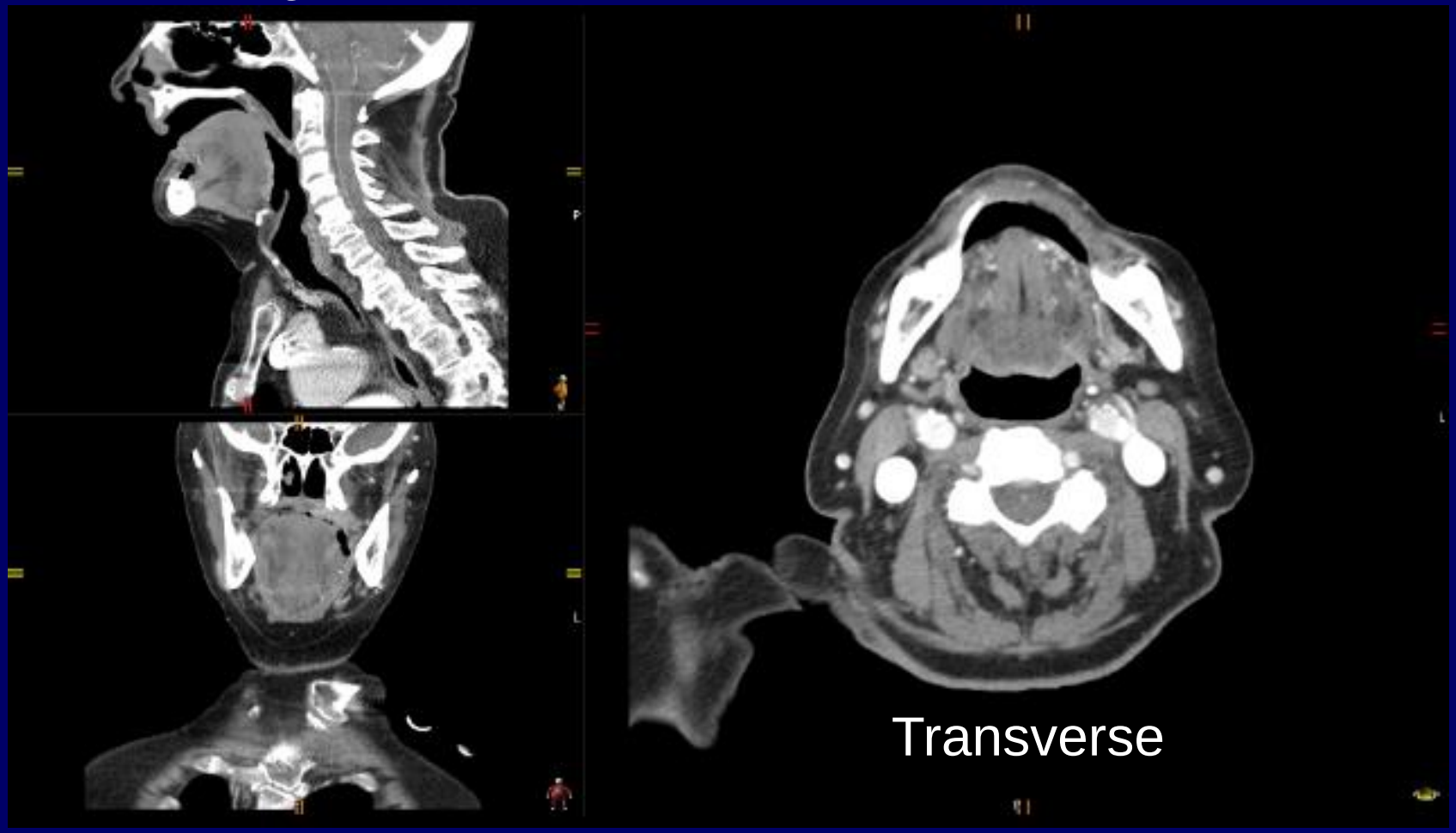
Multi-detector Spiral CT Neck

- ‘Box’ acquisition
  - Upper orbit / lung apex
- Scanning time: +/- 7 sec.
- +/- 400 sections: 1,5mm
  - Reconstructions: 3mm
  - Standard directions (3)



Standard directions

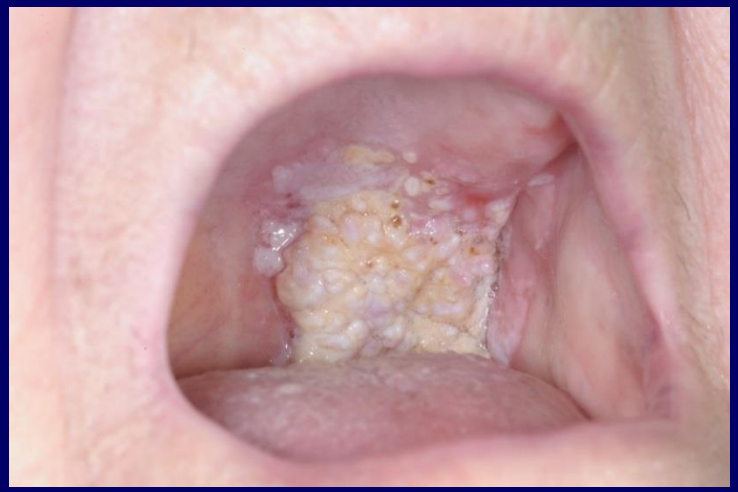
Sagital



Coronal

Daily practice: CT

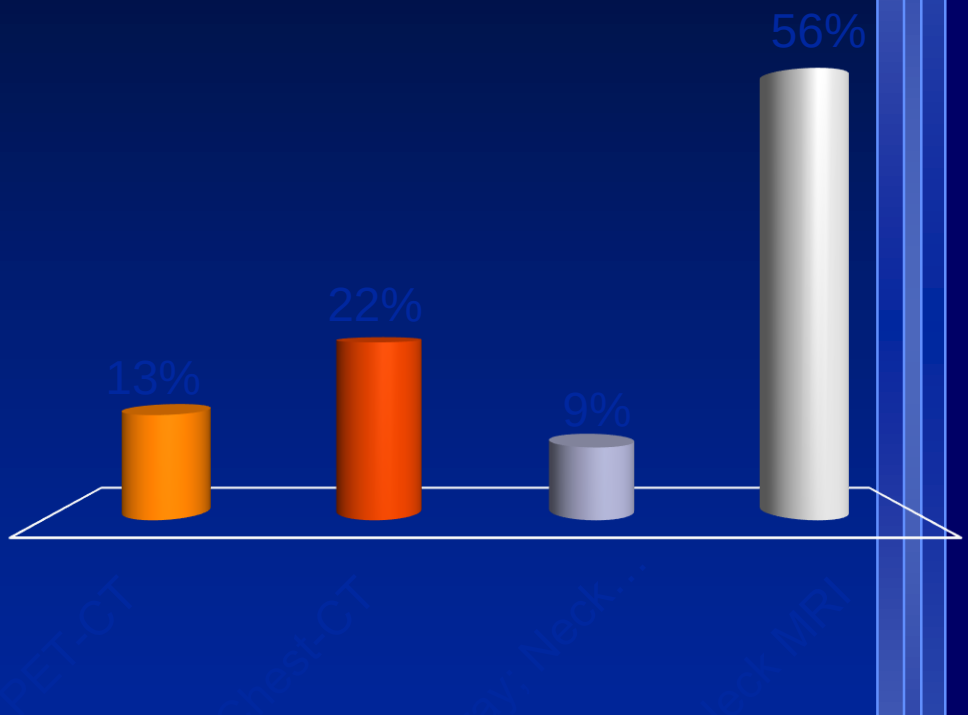
- Female, 89 years
- Since several months painful mouth
- Examination:
  - Lesion soft palate
  - 3,0 cm (T2)



- Biopsy: Squamous cell carcinoma (SCC)

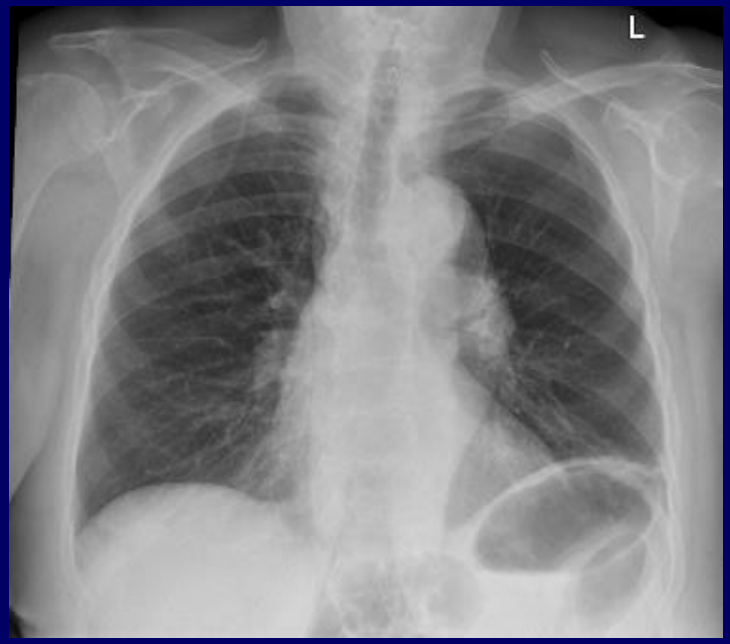
Preferred radiological workup?

A. PET-CT
B. Neck-/Chest-CT
C. Chest Xray; Neck Ultrasound; Neck CT
D. Chest-CT;Neck MRI

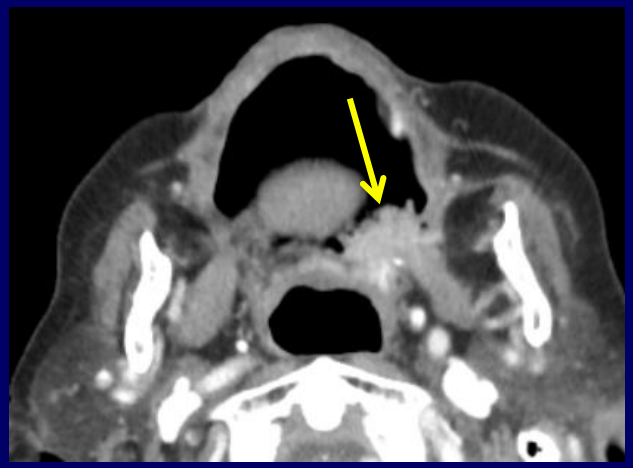


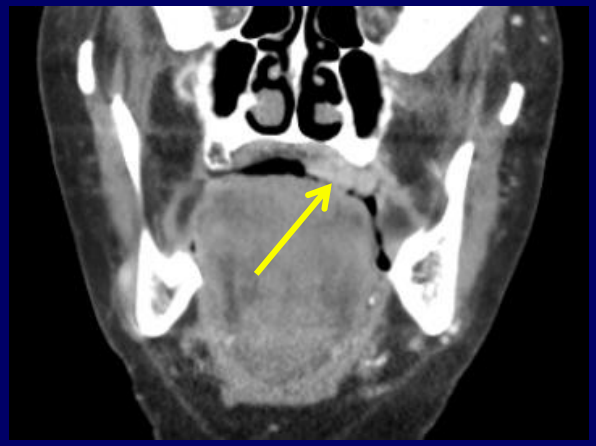
Radiological work-up

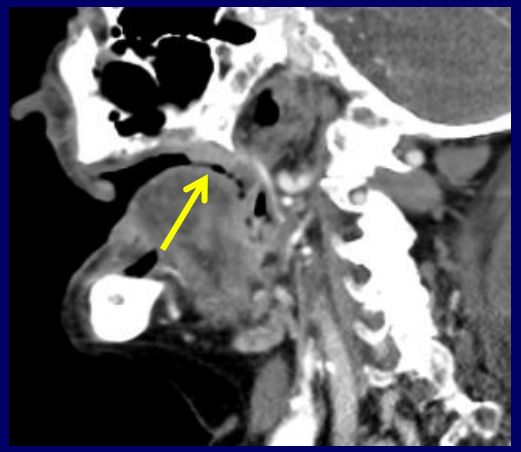
- Chest X-ray
  - Normal
- US Neck
  - Normal nodes
  - No FNAC
- CT Neck

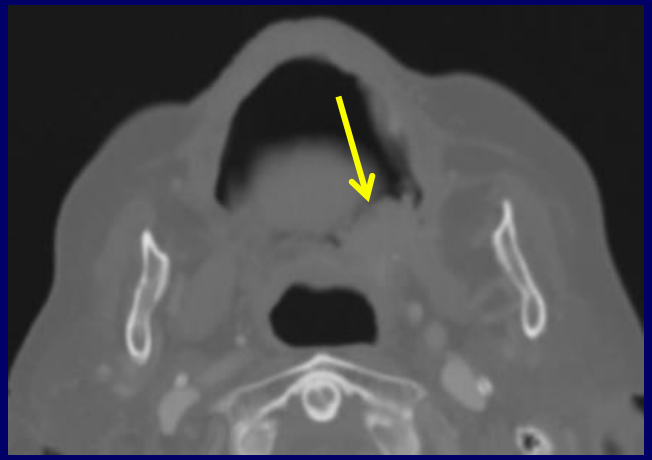


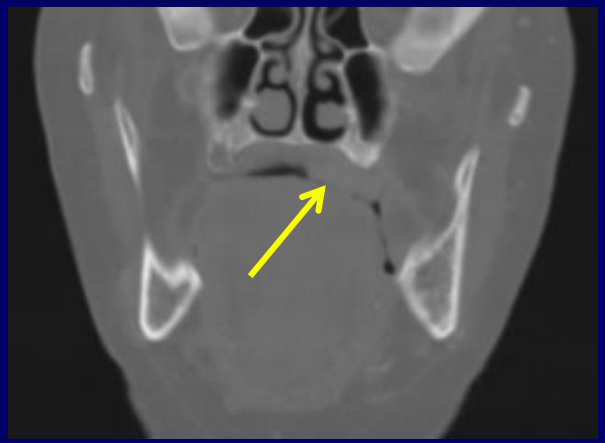
Soft tissue window

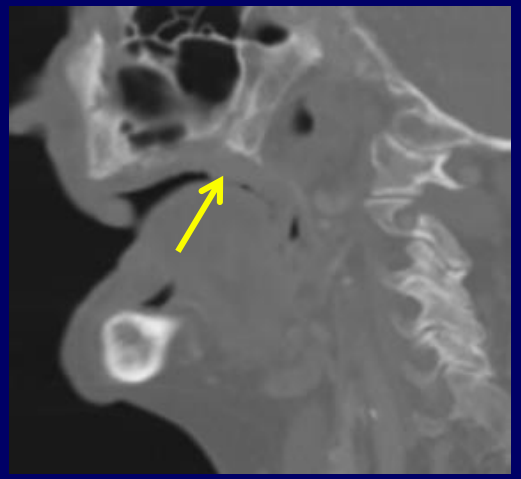












Bone window

Multidisciplinary H&N meeting

- T2N0 maxillar ca.
- Treatment
  - Partial maxillectomy
  - Palatal obturator

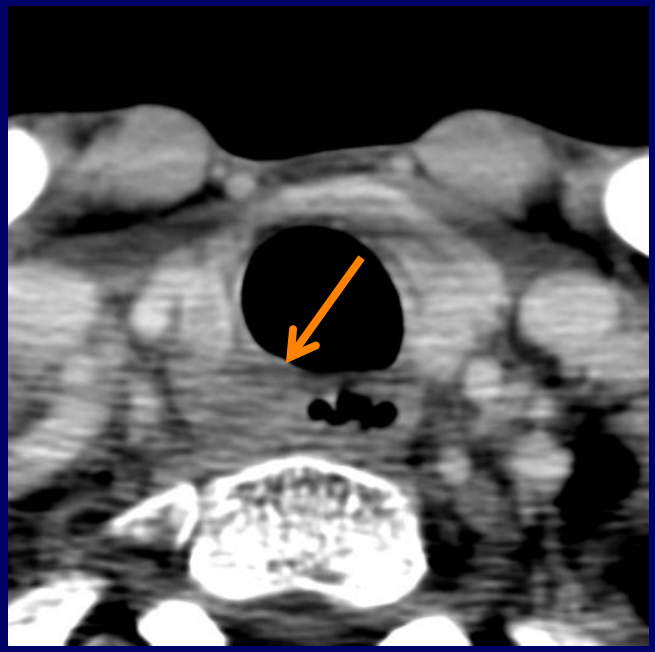
Obturator after maxillectomy

- Path report: verrucous ca. Ø 4,8 cm, near positive surgical ventral margin (<1mm)
- **Conclusion**:
  - pT3N0M0
  - In view of age: clinical follow-up (no post-op RT)

Magnetic resonance imaging (MRI)

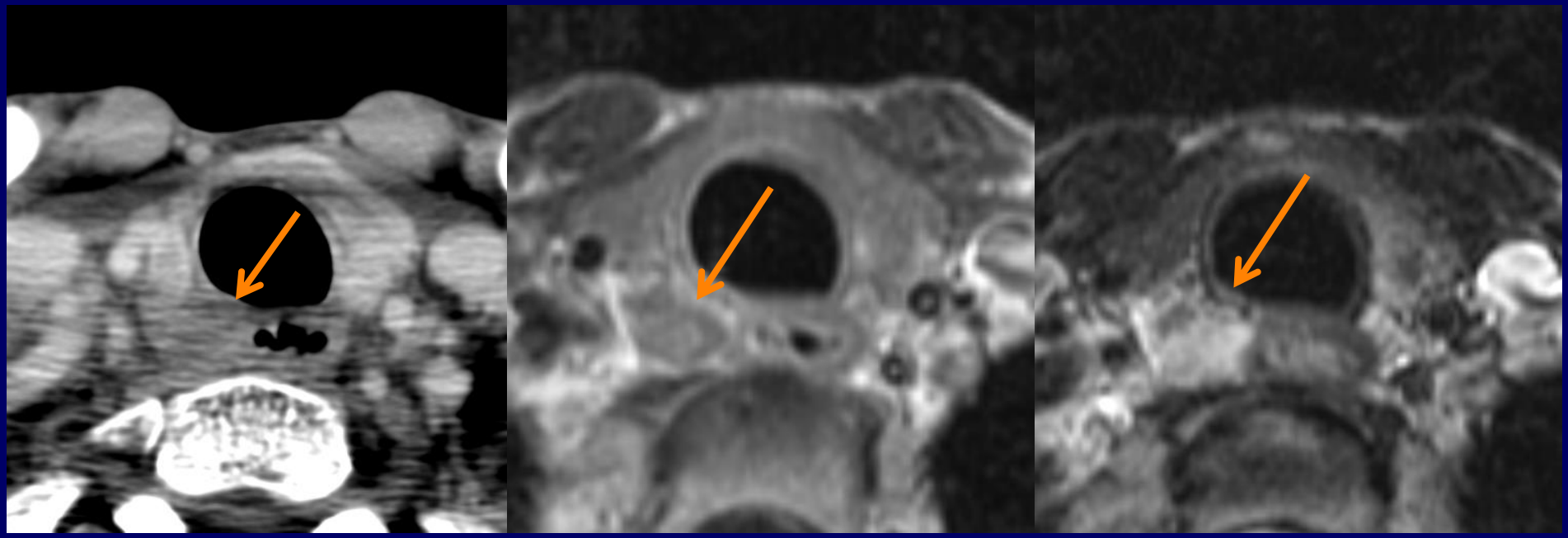
- Advantages:
  - No radiation
  - Allergies to iv contrast (Gadolinium) extremely rare
  - Superior soft tissue contrast (vs. CT)
  - Less dental filling metallic artifacts
- Disadvantages:
  - Limited availability; expensive
  - Long acquisition time => ↑motion degradation
  - More contraindications (claustrophobia, ICD, CI, etc.)

Superior soft tissue contrast (vs. CT)
Patient with hoarseness



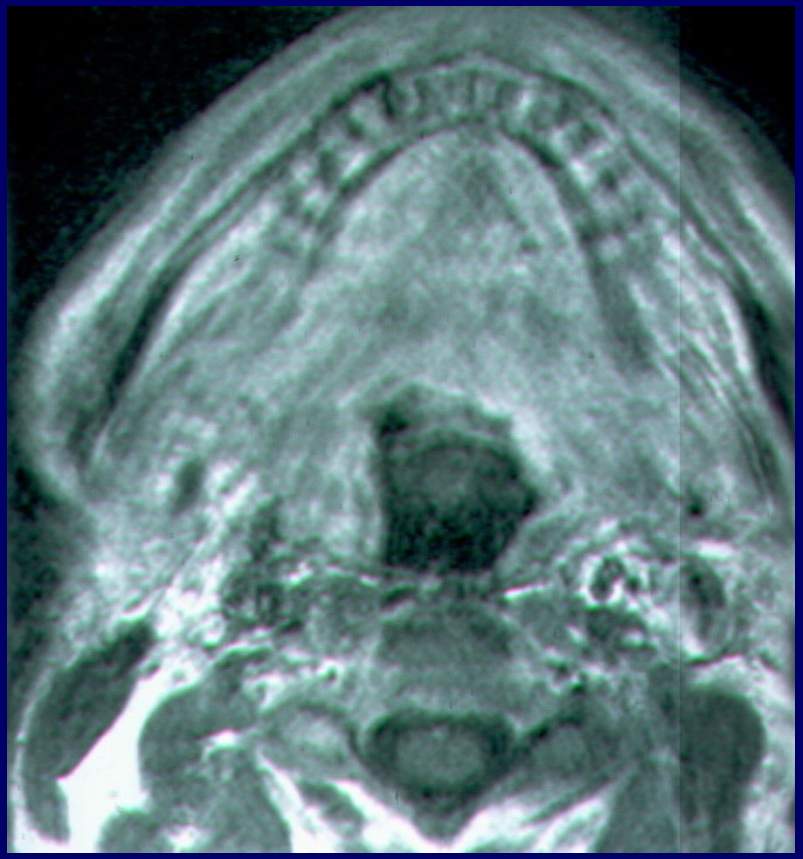
CT: esophageal ca. ?

Superior soft tissue contrast (vs. CT)
Patient with hoarseness

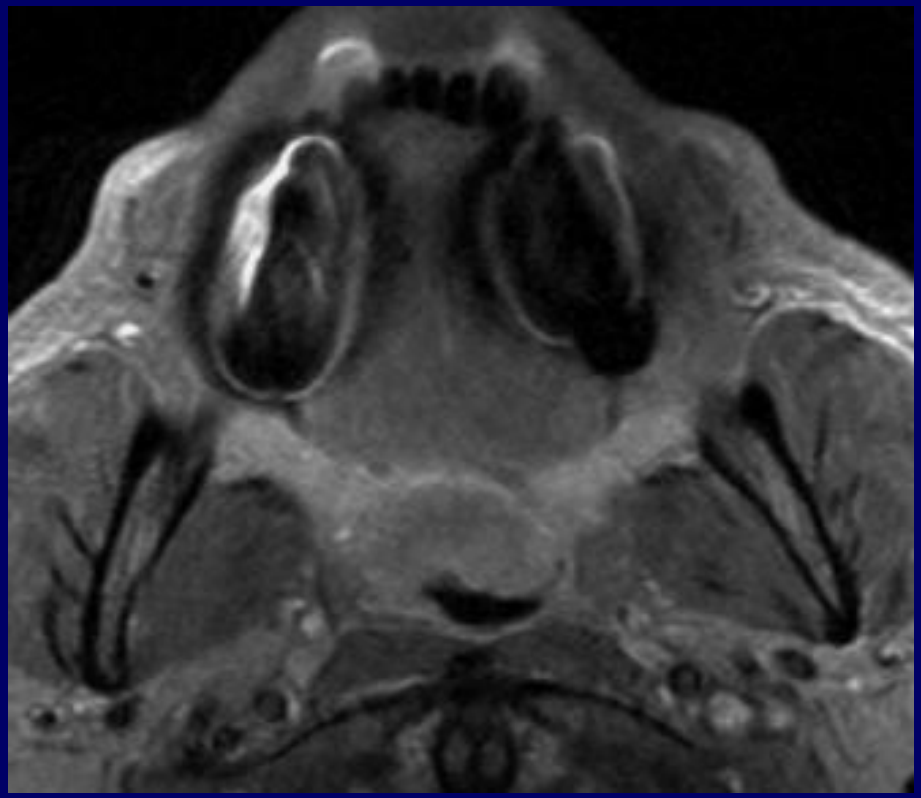


Lymph node metastasis lung ca.

Artifacts



Movement



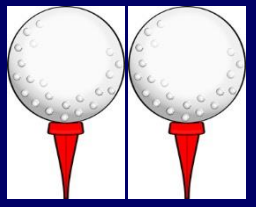
Dental fillings

Technique

Classic sequences:

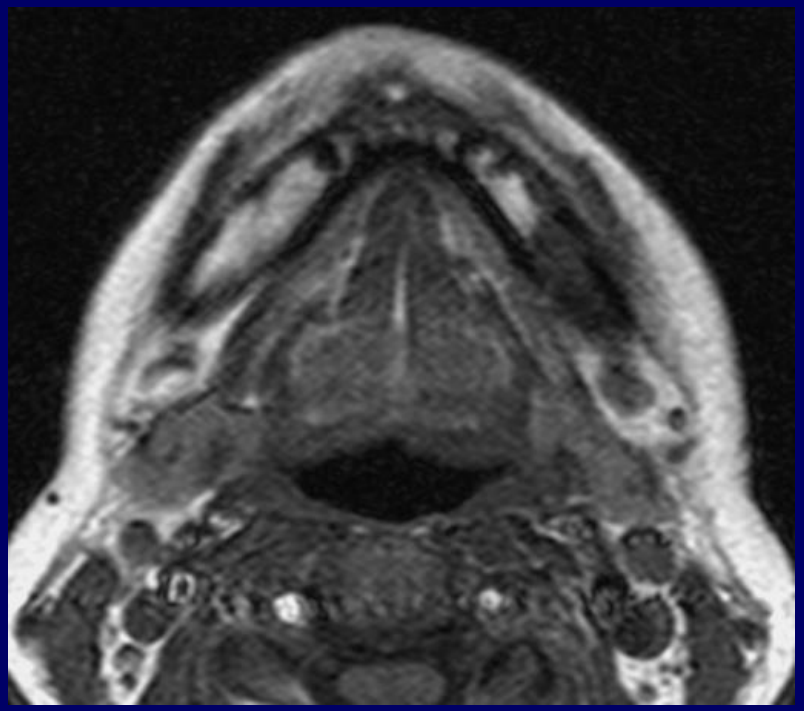
- T1
  - Without / with i.v. contrast
  - Fatsuppressed

- T2

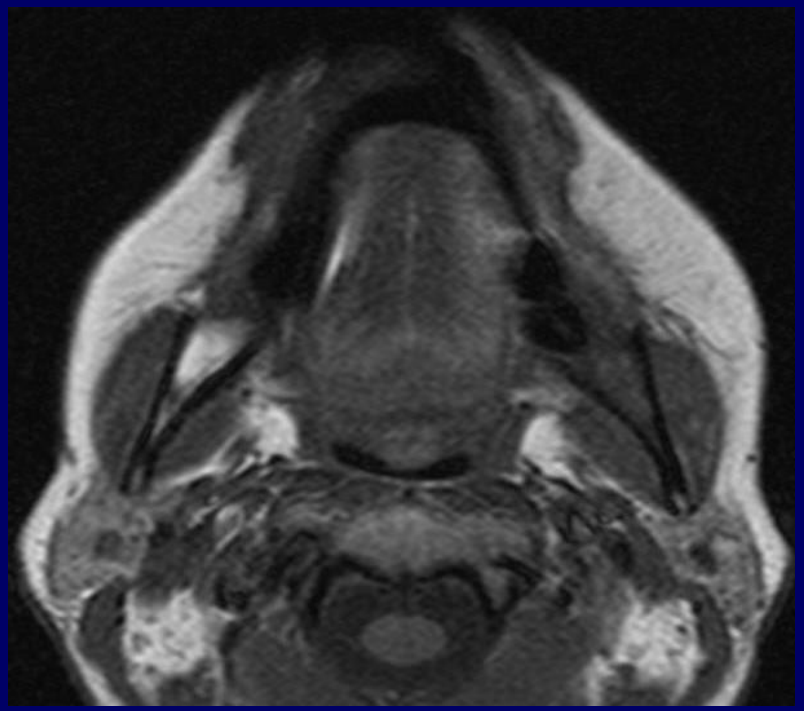


T1 without i.v. contrast

- “Fat is your friend” (anatomical orientation)



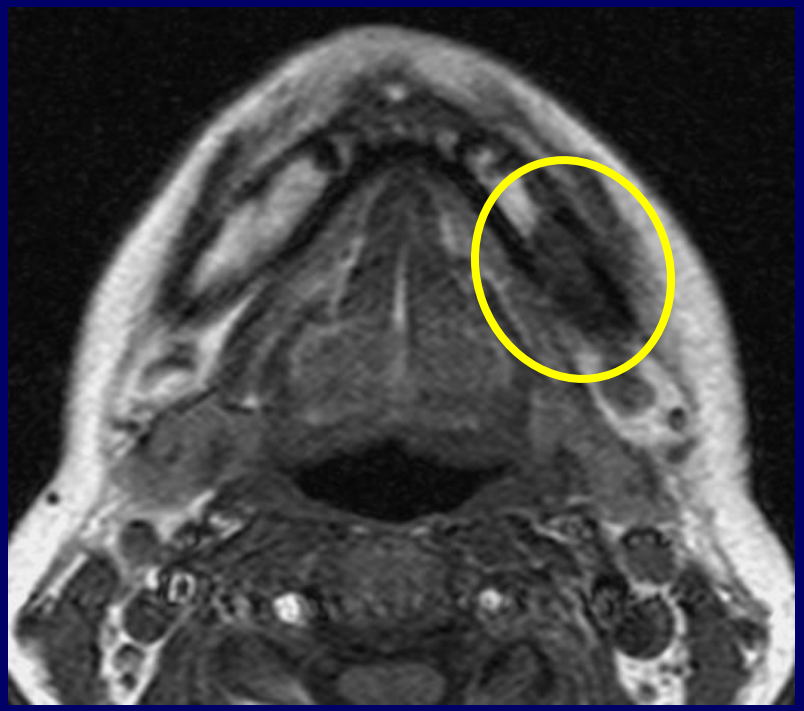
T1



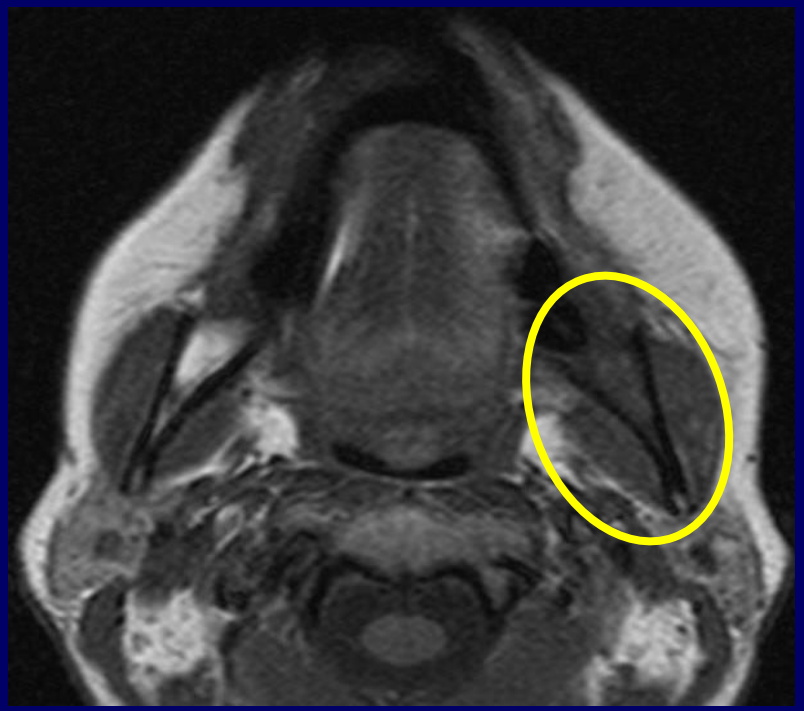
T1

T1 without i.v. contrast

- “Fat is your friend” (anatomical orientation)



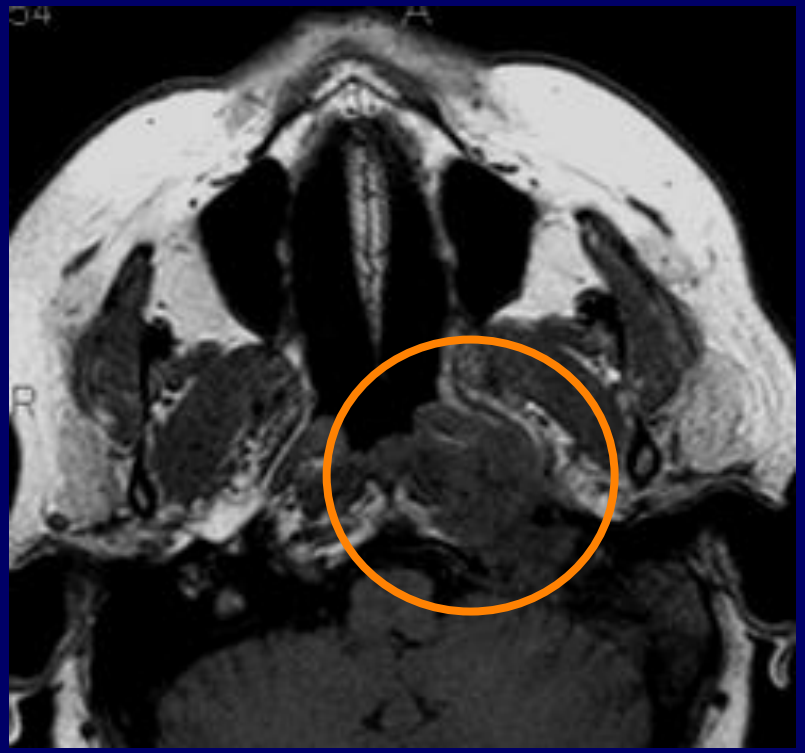
T1



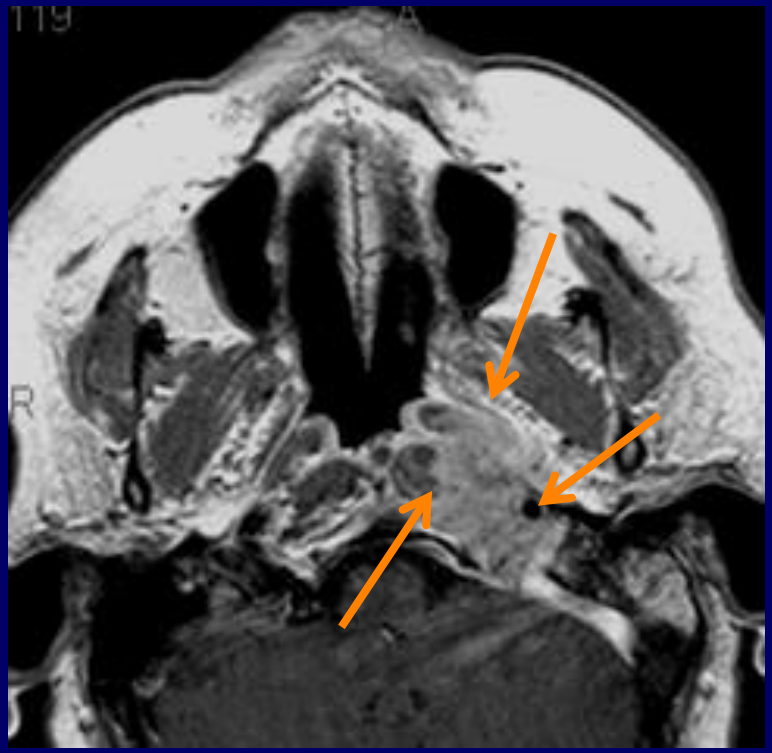
T1

T1 with contrast

- Better delineation of enhancing lesions from surrounding musculature



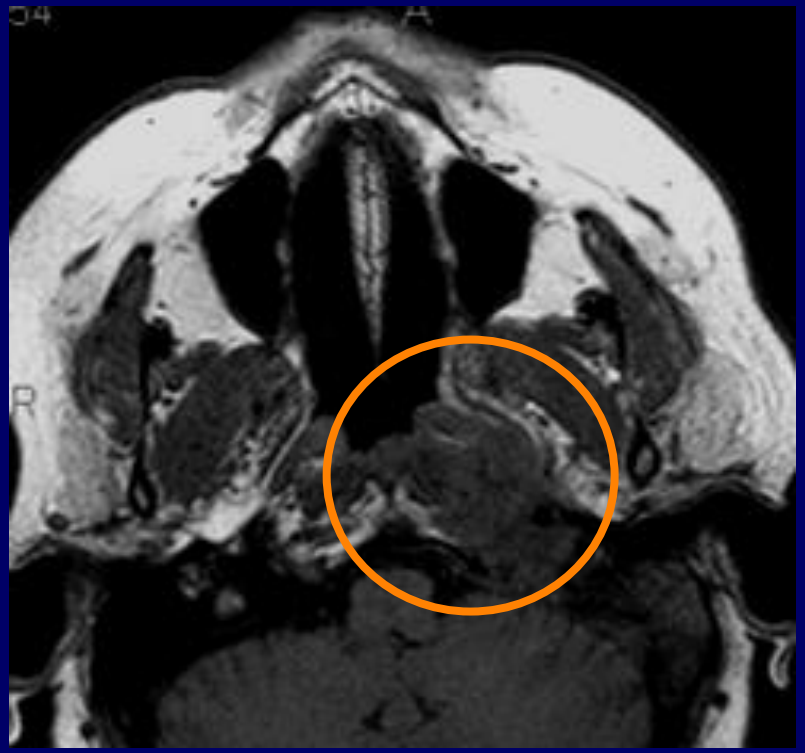
T1

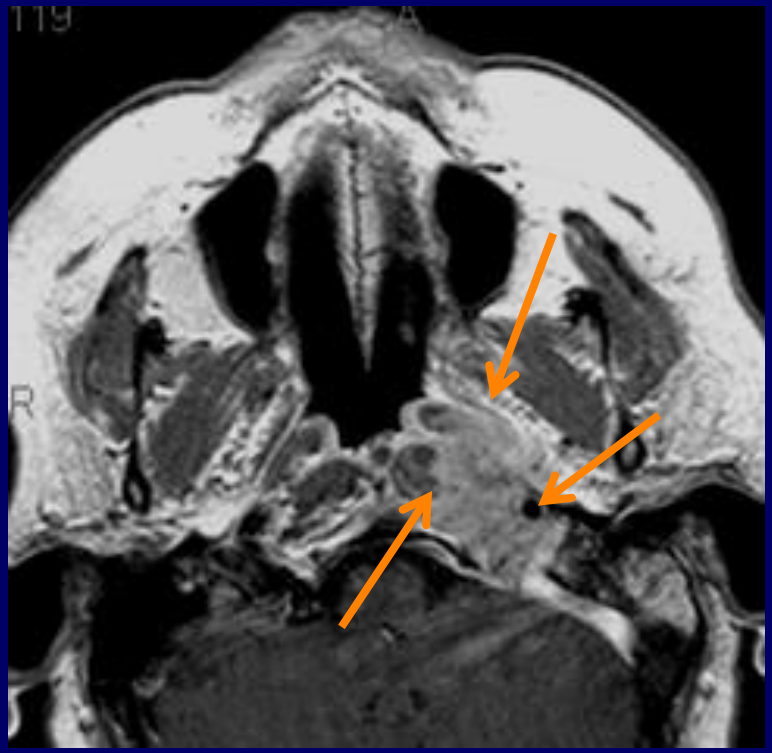


T1 + C

T1 with contrast

- Better delineation of enhancing lesions from surrounding musculature

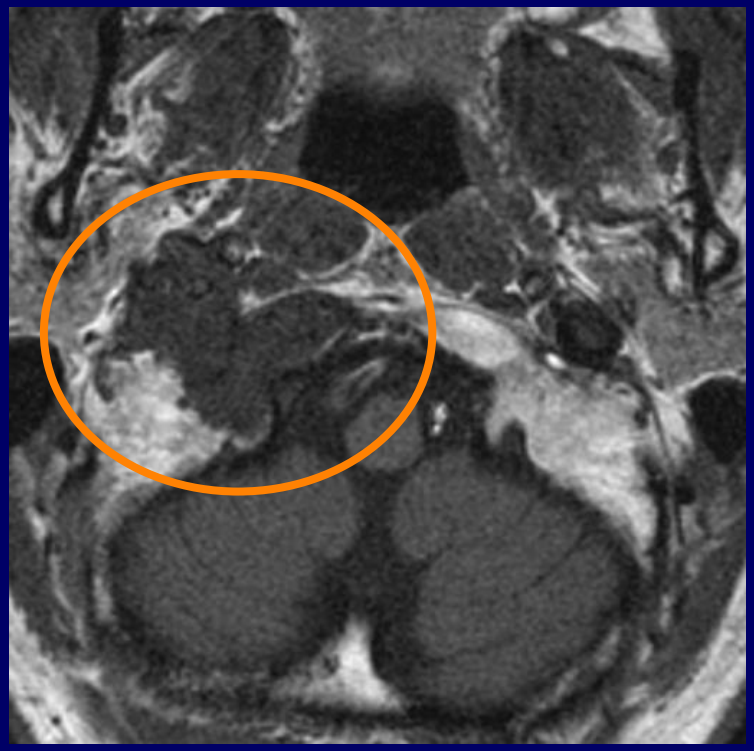




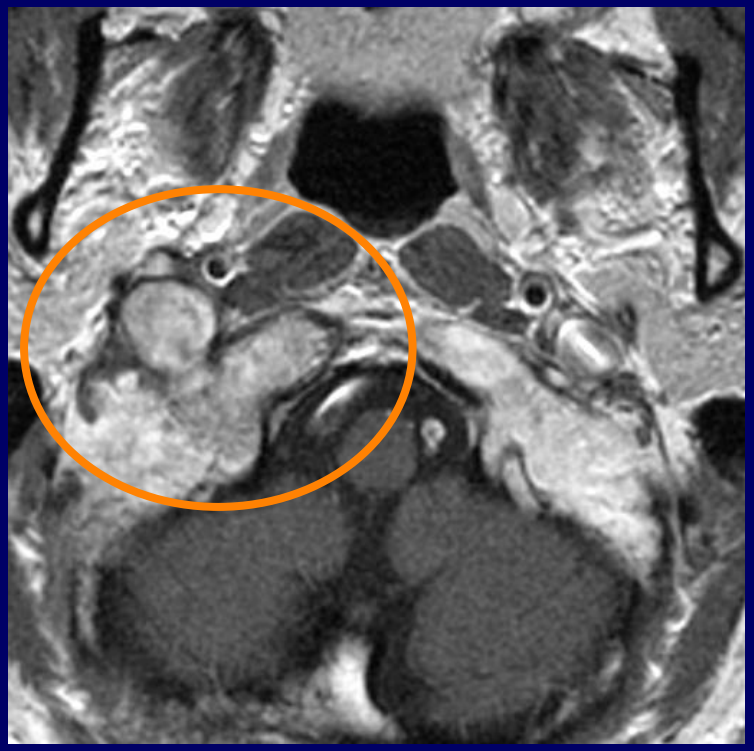
Nasopharyngeal ca.

T1 with contrast

- May obscure visualization of lesions within fatty bone marrow!!!



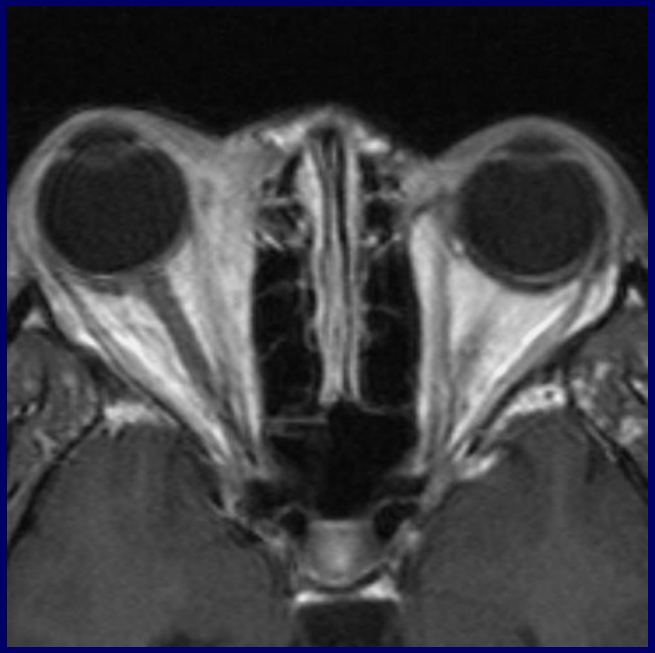
T1 without



T1 + C

T1 + C + Fat Suppression (FS)

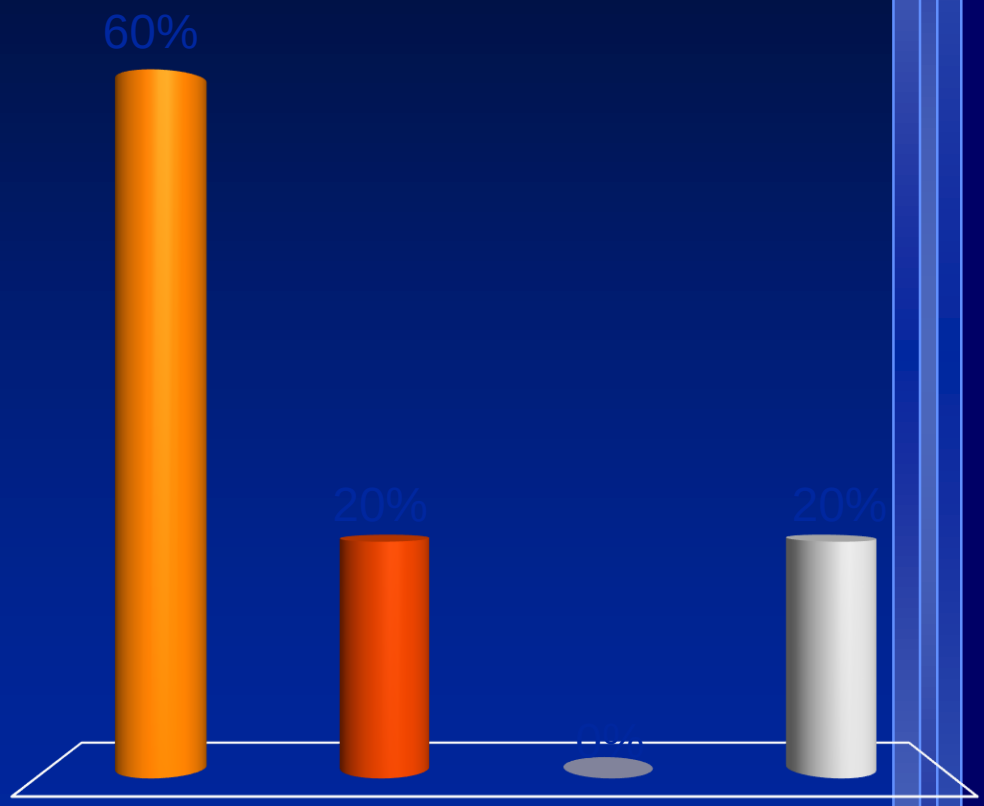
- Superior delineation of enhancing lesions when surrounded by fat



T1 + C

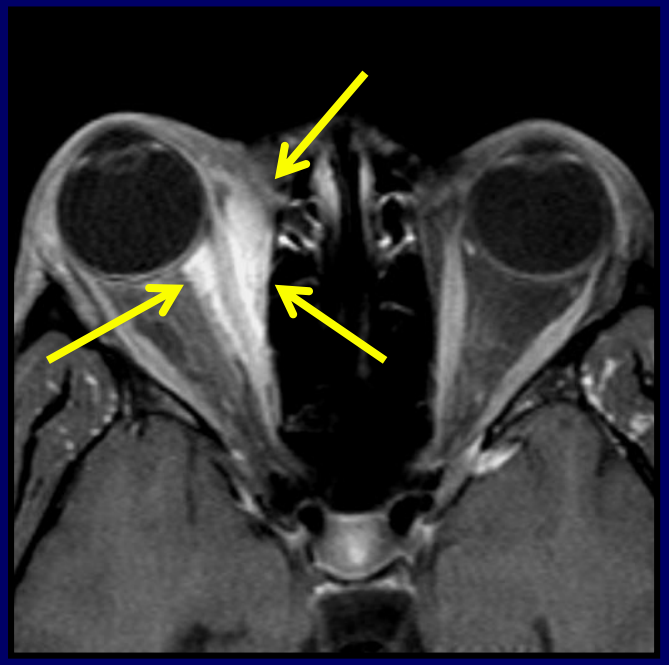
Orbital lesion(s) located in

A. Right orbit
B. Left orbit
C. No lesion
D. Both orbits

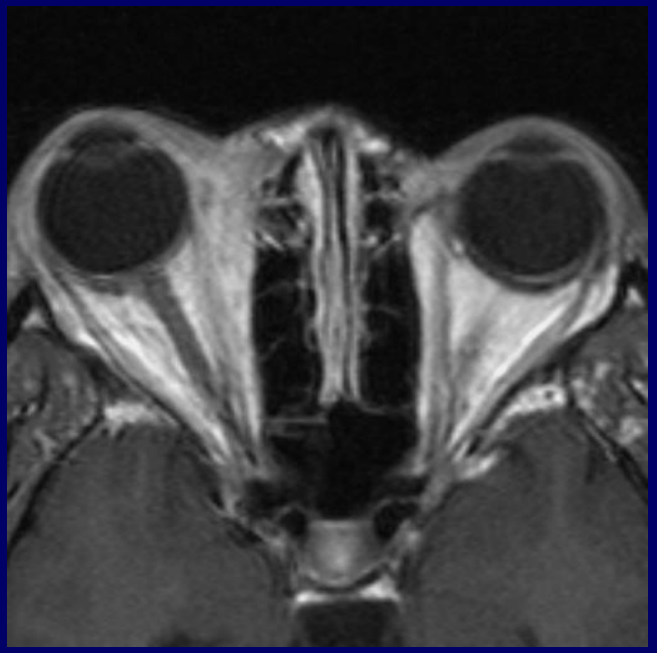


T1 + C + Fat Suppression (FS)

- Improved delineation of enhancing lesions surrounded by fat



T1 + C + **FS**



T1 + C

Technique

Classic sequences:

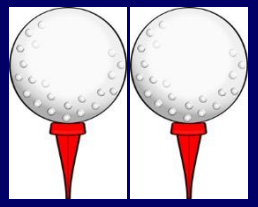
- T1
  - Without / with i.v. contrast
  - Fatsuppressed (FS)

Technique

Classic sequences:

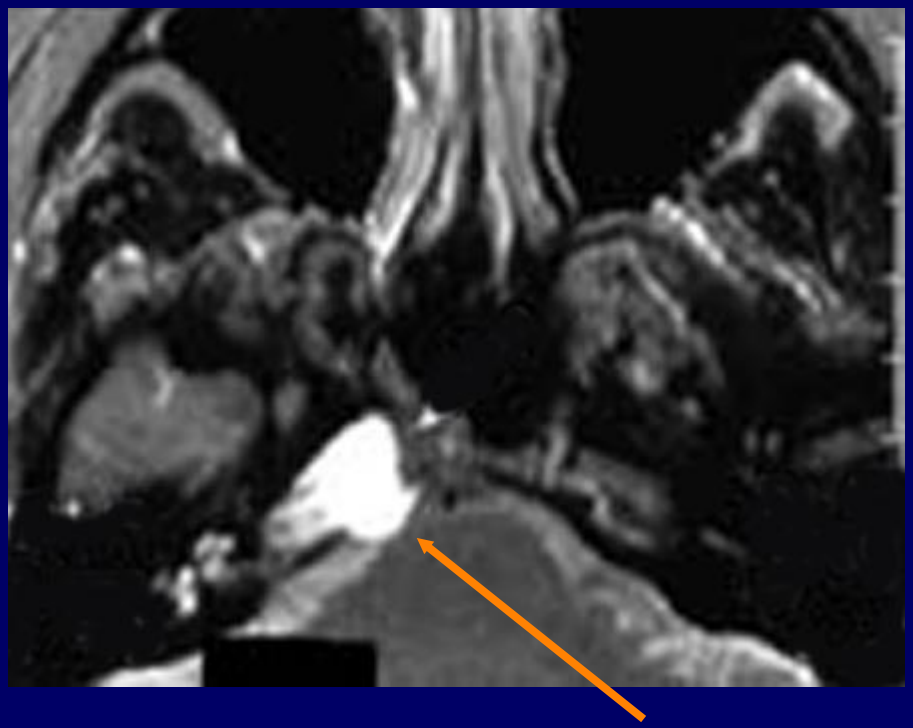
- T1
  - Without / with i.v. contrast
  - Fatsuppressed (FS)

- T2

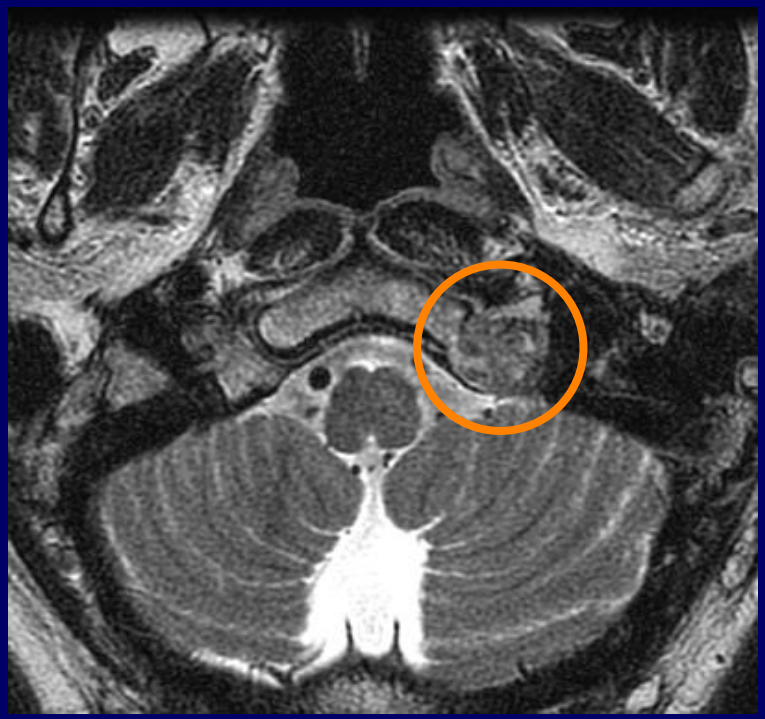


T2

- May be helpful for narrowing of differential diagnosis



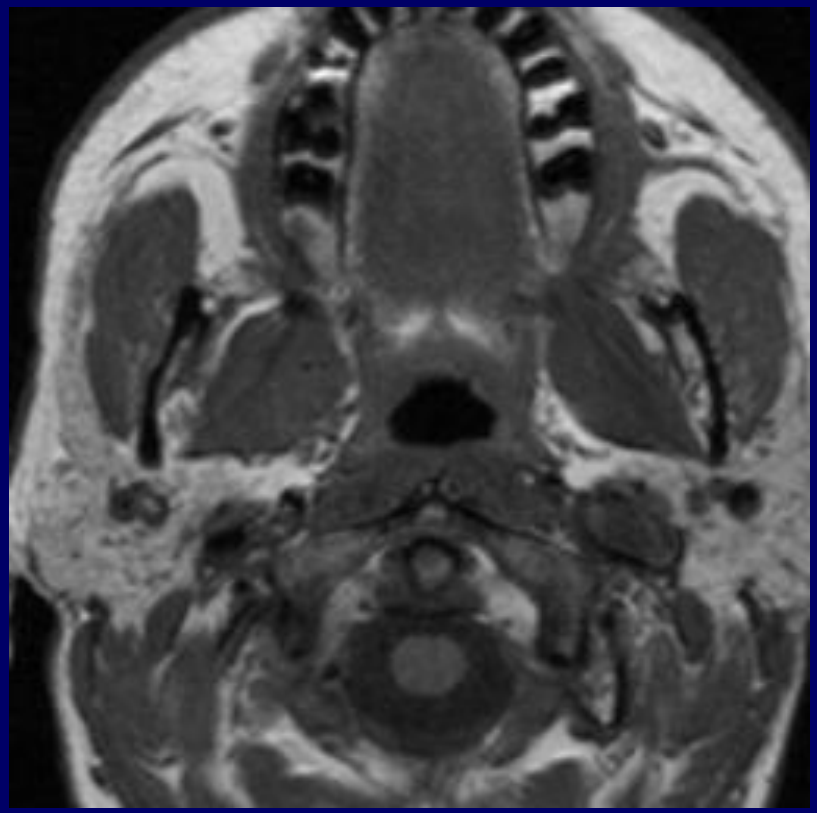
Chondrosarcoma



Metastasis

T2

- May be helpful for lesion detection

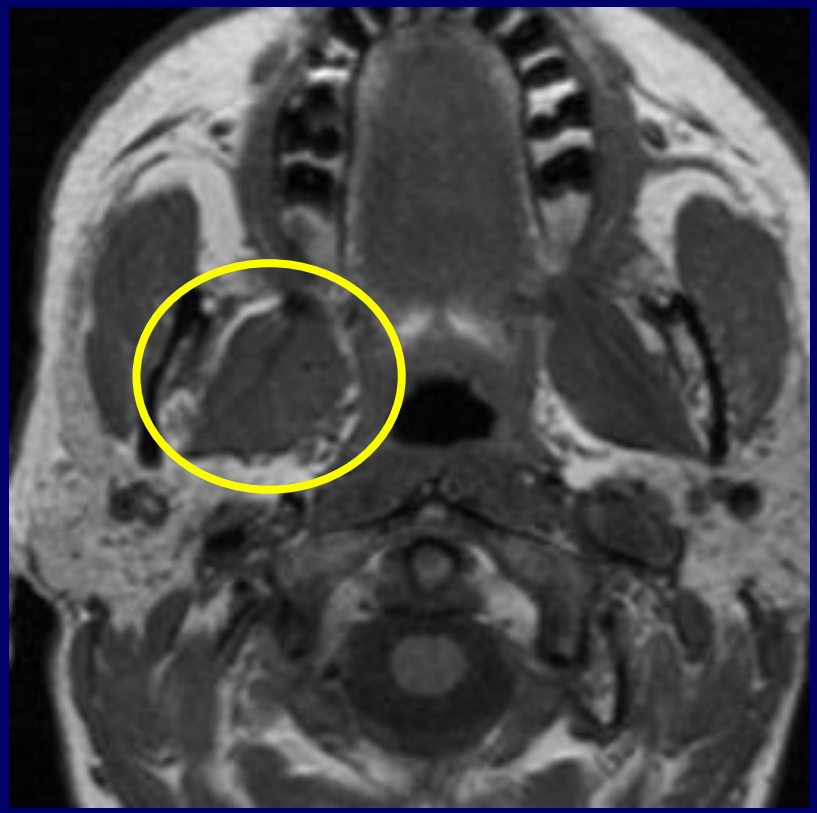


T1

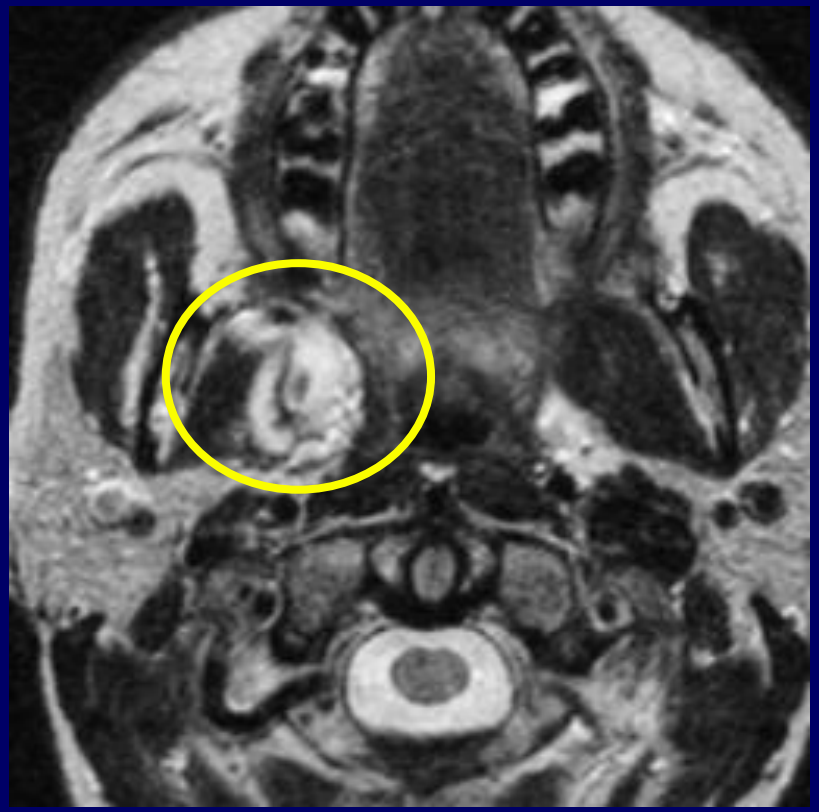
T2

T2

- May be helpful for lesion detection



T1



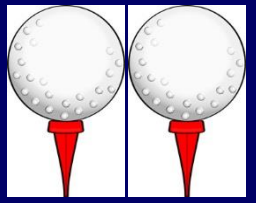
T2

Technique

Classic sequences:

- T1
  - Without / with i.v. contrast
  - Fatsuppressed

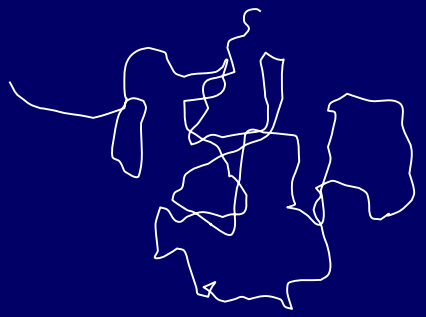
- T2



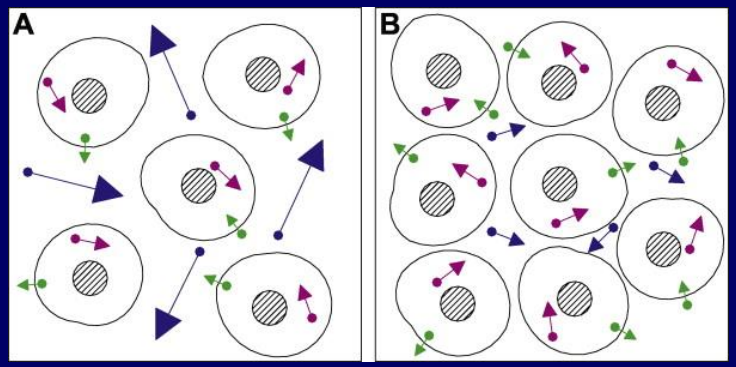
- **New sequences**

Diffusion weighted imaging (DWI)

- Microscopic mobility of water
- Normal tissue:
  - Brownian motion of water molecules
  - No restriction of movement
- Hypercellular tissue (tumor)
  - Restricted diffusion of water



Normal tissue



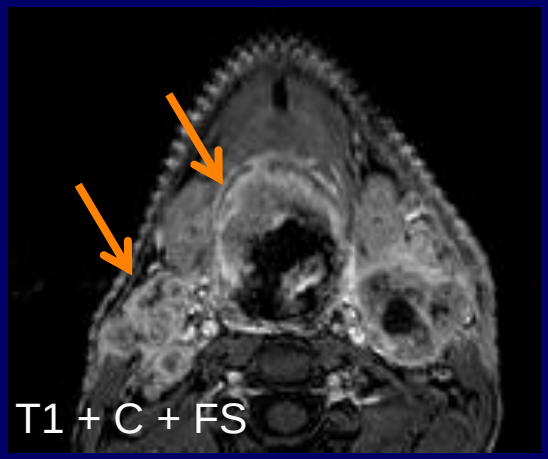
Hypercellular tissue

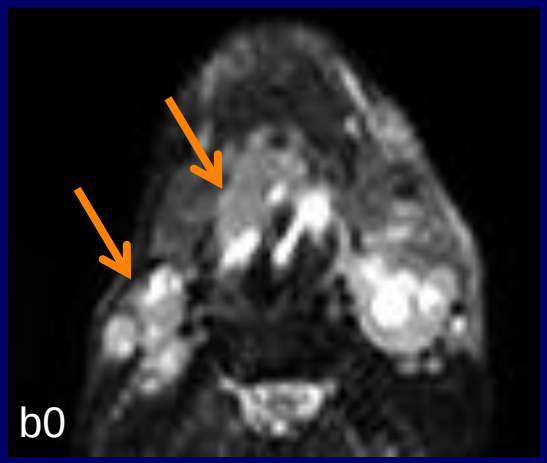
DWI

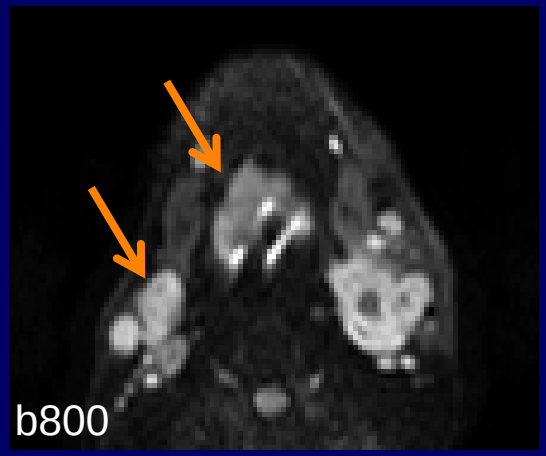
- Totally different from T1 / T2 etc.
- DWI gives information about the microstructure of tissue

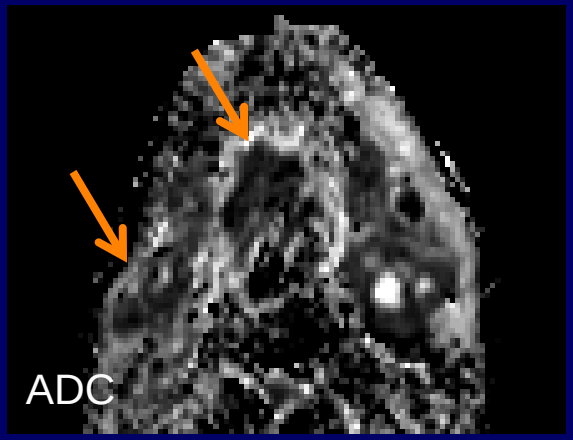
- Typical DWI sequence
  - B0: not sensitive to diffusion (“T2-image”)
  - B ‘high’ (800 – 1000): very sensitive
  - ADC (apparent diffusion coefficient)

Typical DWI sequence









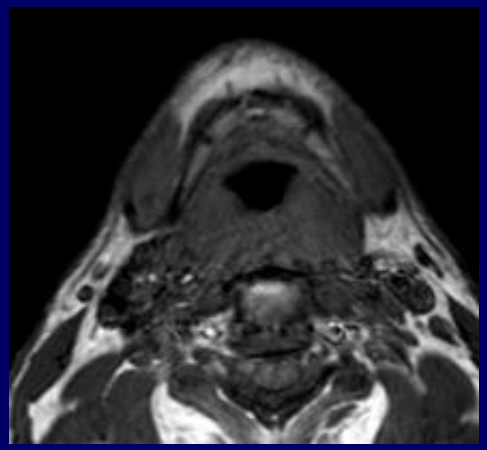
Base of tongue carcinoma with bilateral neck nodes

DWI

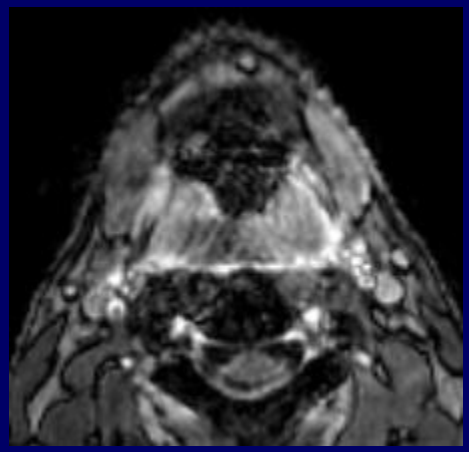
- Primary setting ??

- Future:
  - Detection of recurrence
    - vs PET
  - Early response monitoring

Detection of recurrence
Posterior pharyngeal wall ca.



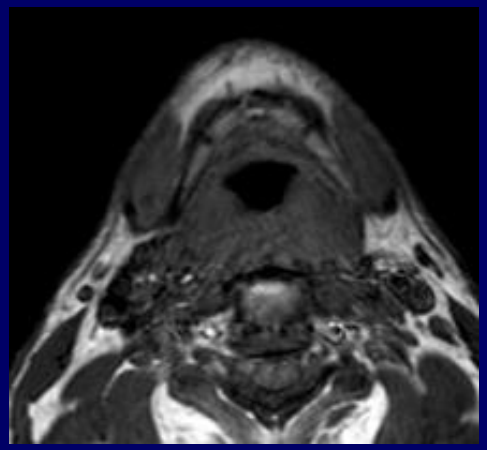
T1



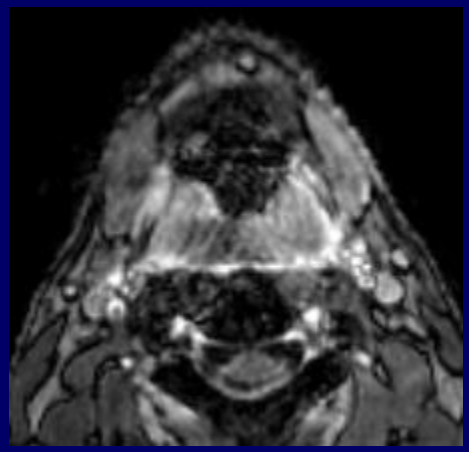
T1 + C

Pre-Tx

Detection of recurrence
Posterior pharyngeal wall ca.

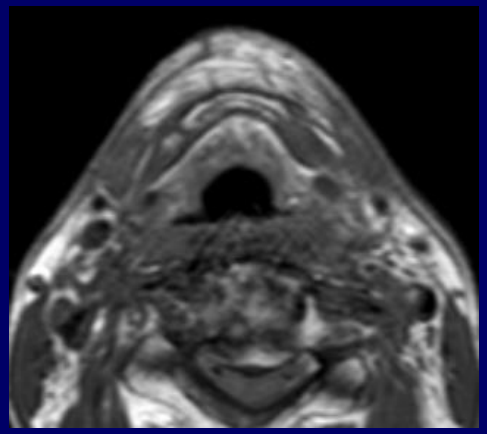


T1

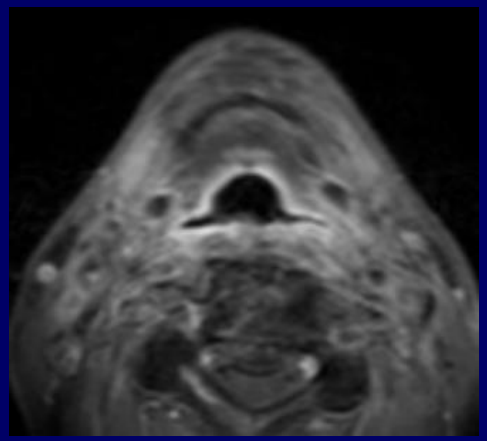


T1 + C

Pre-Tx



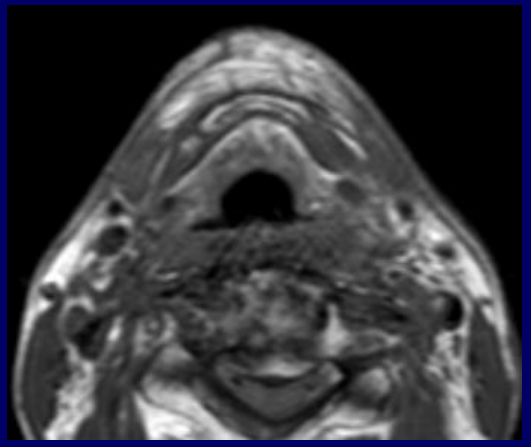
T1



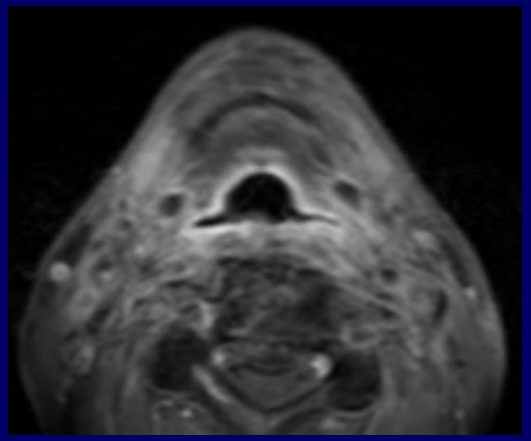
T1 + C

Post
Chemo-RT

Detection of recurrence
Posterior pharyngeal wall ca.



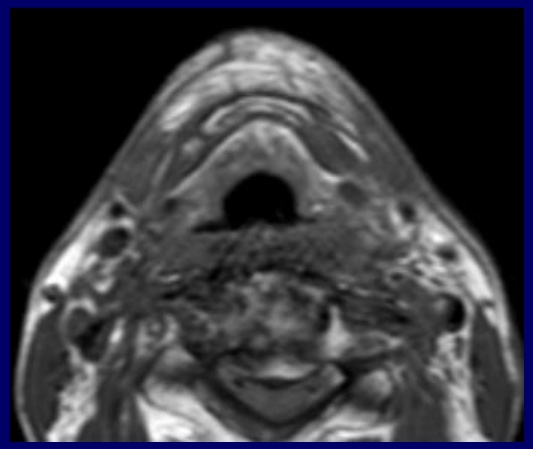
T1



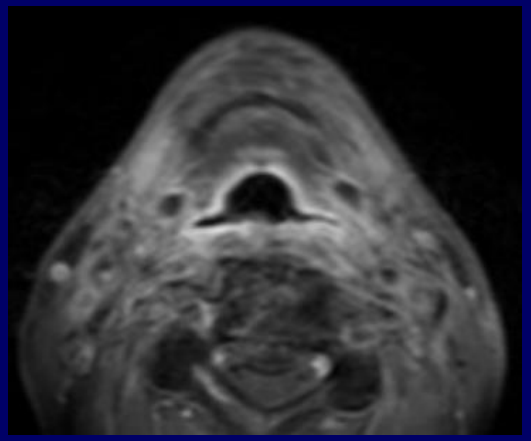
T1 + C

Post
Chemo-RT

Detection of recurrence
Posterior pharyngeal wall ca.

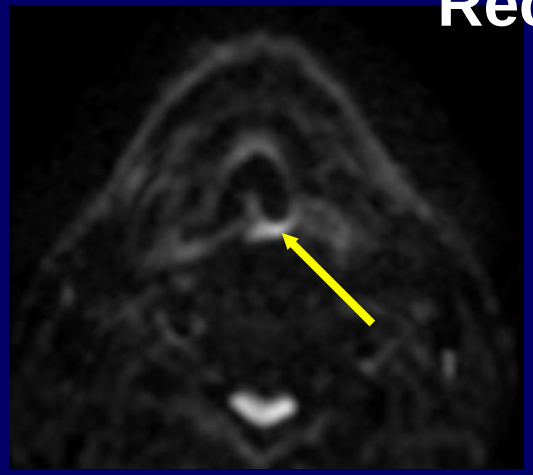


T1

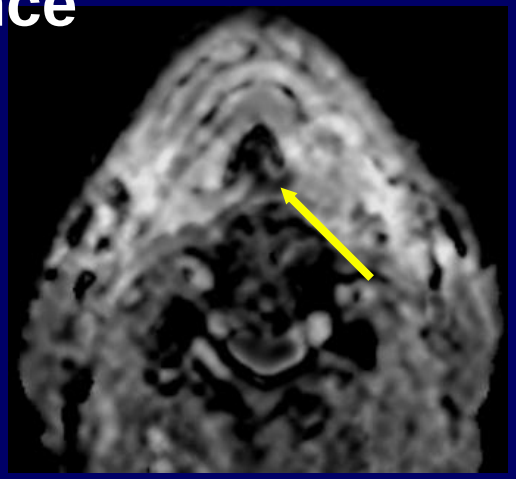


T1 + C

Biopsy: Recurrence



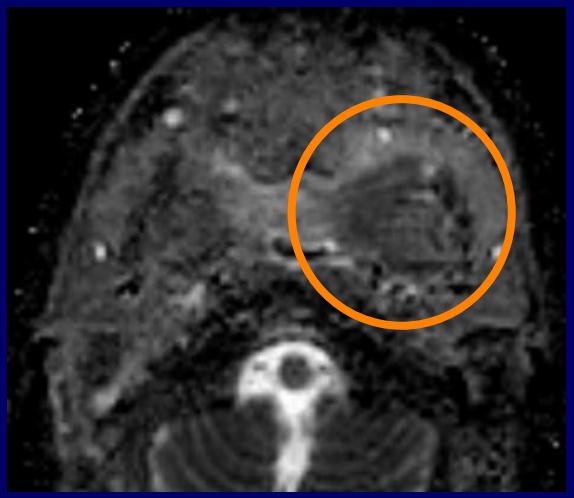
DWI B1000



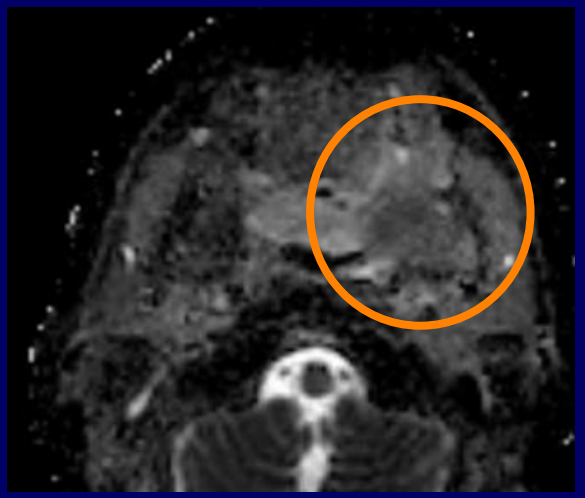
ADC

Early response monitoring: tonsillar ca.

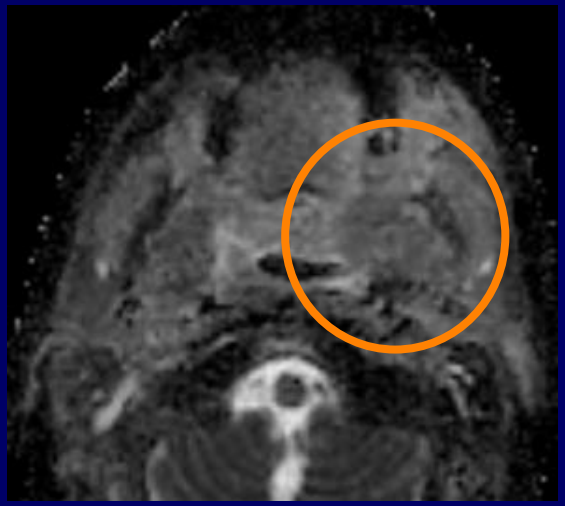
ADC



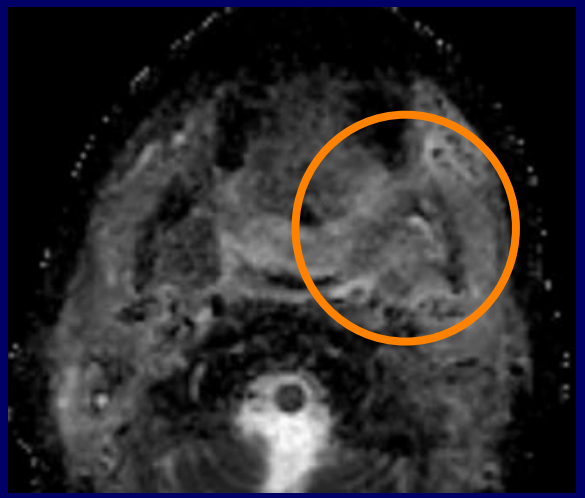
Pre-RT



1 week RT



2 weeks RT



3 weeks RT

MRI and CT for Head & Neck Tumours

Frank Pameijer, MD, PhD

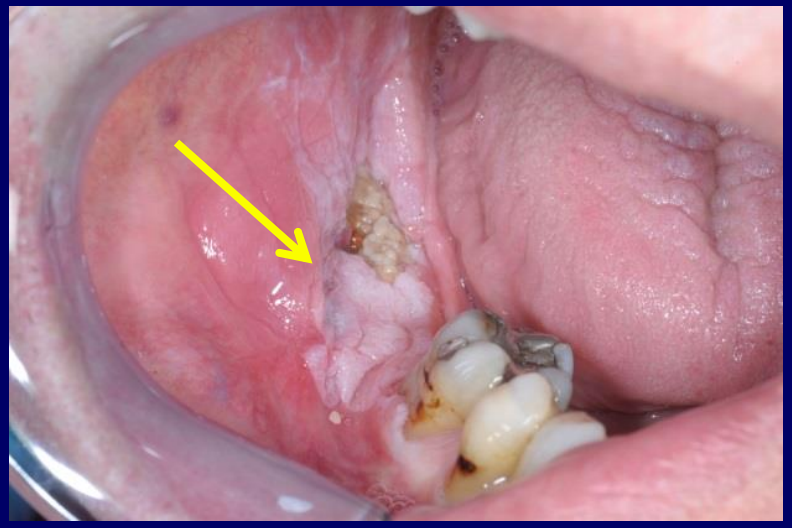
- Departments of Radiology and Radiation Oncology
- University Medical Center, Utrecht
- The Netherlands

No disclosures

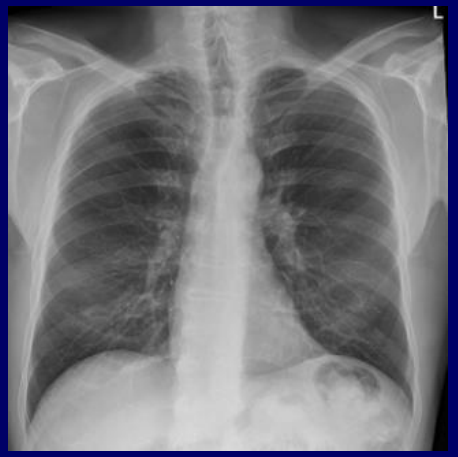
ESTRO School

Daily practice: MRI

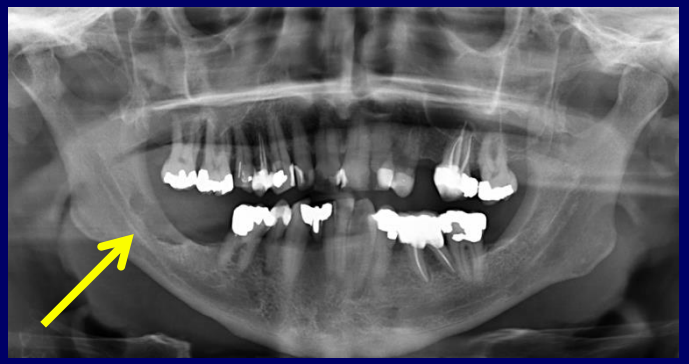
- Male, 65 years
- 42 pack years
- Recently extraction 48
  - No healing
- Examination:
  - Tumor right gingival ridge
  - 2,5 x 3,5cm (T2)
  - Invasion of mandible? (T4a)
- Biopsy: Squamous cell carcinoma (SCC)



Radiological work-up

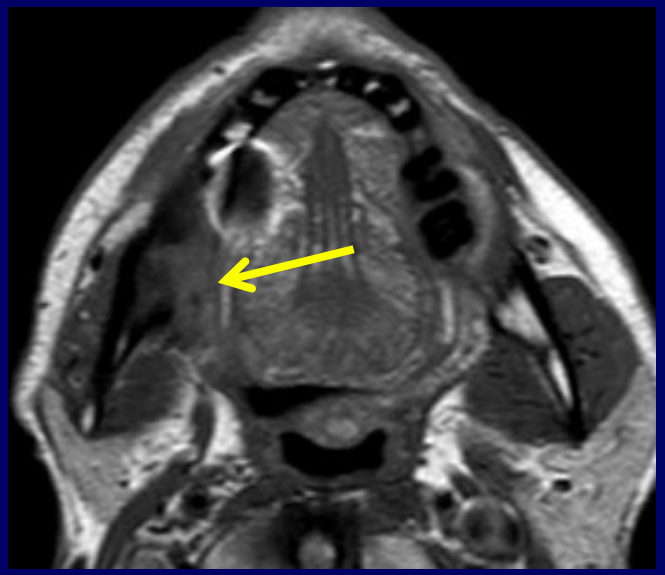


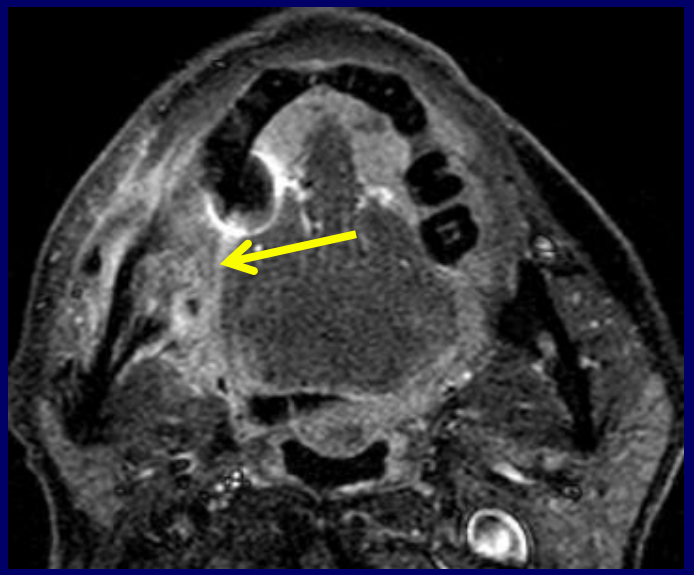
- Chest X-ray: normal
- US Neck:
  - FNAC right neck Level I / II
  - Cytology report: no malignant cells
- Panoramic dental X-ray



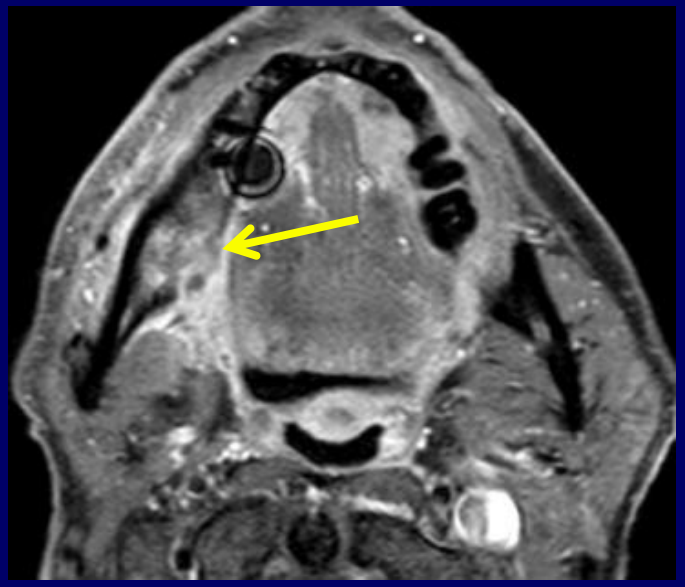
- MRI

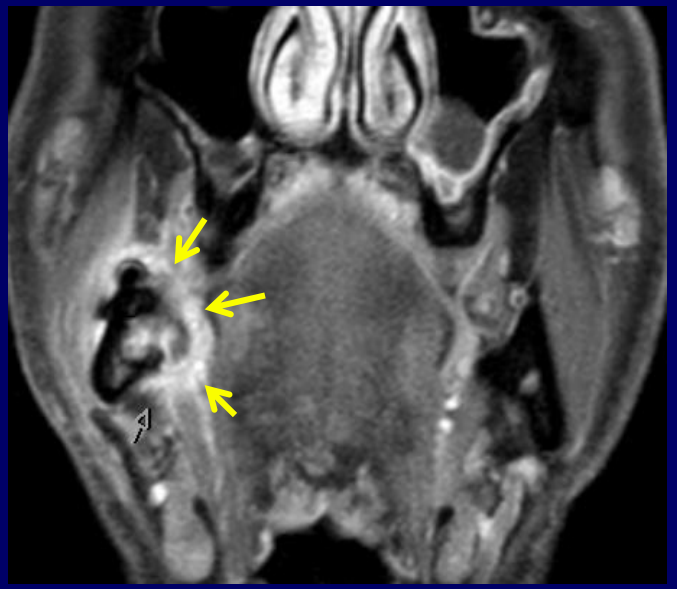
T1





T2

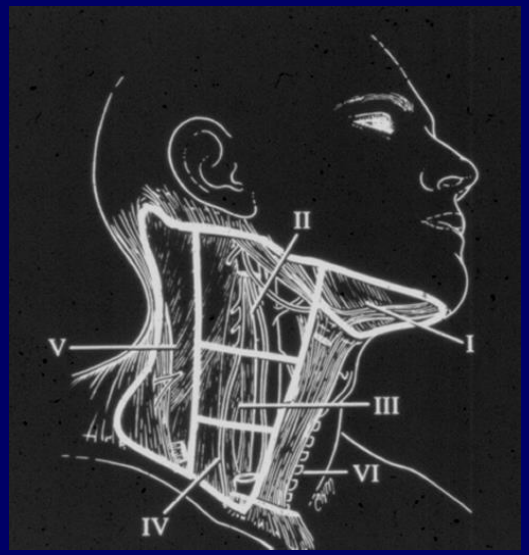




T1 + C + FS

Multidisciplinary H&N meeting

- T4aN0 right gingival carcinoma
- Treatment
  - Segmental mandibular resection
  - Neck dissection level I-III
- Path report
  - Tumor excision: radical
  - Neck dissection level I-III: no lymph node mets
- **Conclusion**:
  - pT4aN0M0
  - Clinical follow-up (no post-operative RT needed)



MRI and CT for Head & Neck Tumours

Frank Pameijer, MD, PhD

- Departments of Radiology and Radiation Oncology
- University Medical Center, Utrecht
- The Netherlands

No disclosures

ESTRO School

FDG PET/CT for RT planning of head-neck tumors

Wouter Vogel
NKI-AVL, Amsterdam

May 2017, Bordeaux
Course on Molecular Imaging and Radiation Oncology

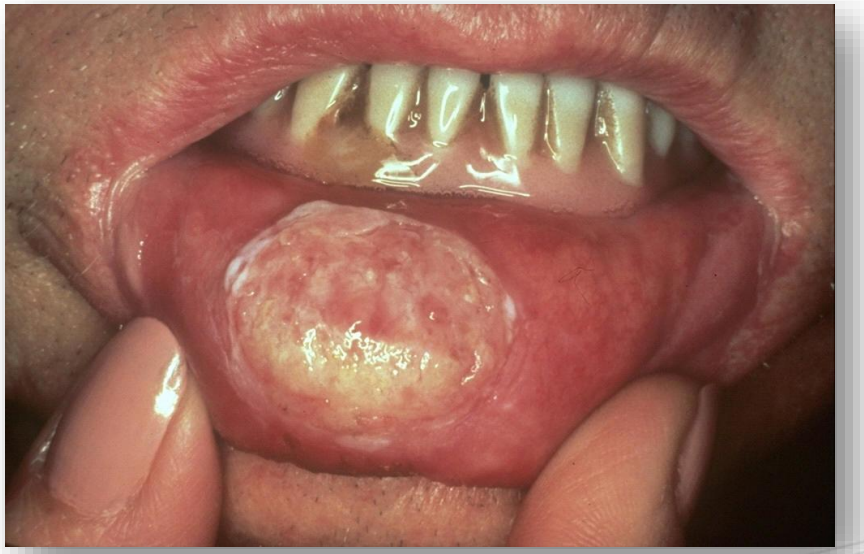
Topics

- Diagnostic value

- Radiotherapy planning
  - Primary tumour delineation
  - Selection of lymph nodes

Cancer in the head and neck area

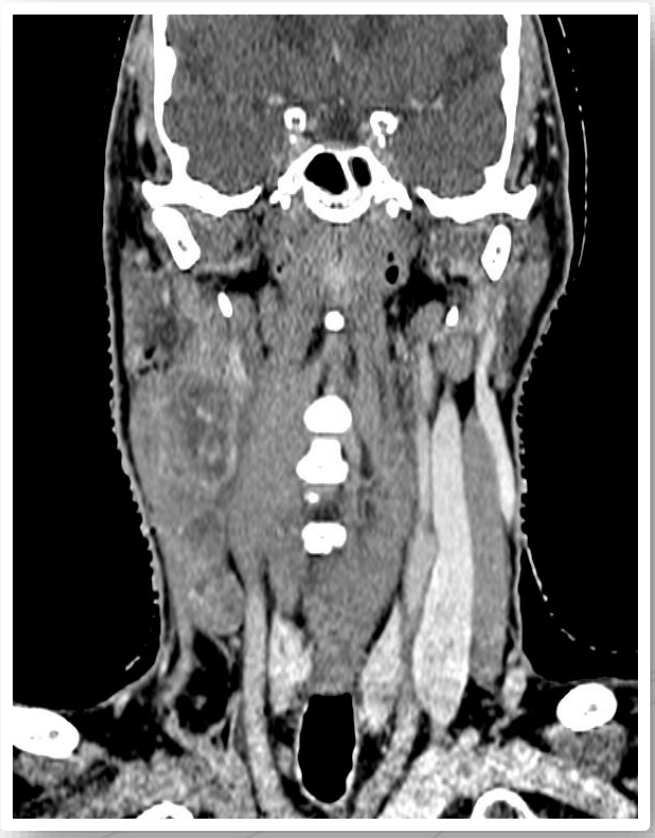
- Squamous cell carcinoma
- Mucosal origin
- Aggressive
- Curative intent



A lot of information is needed for treatment

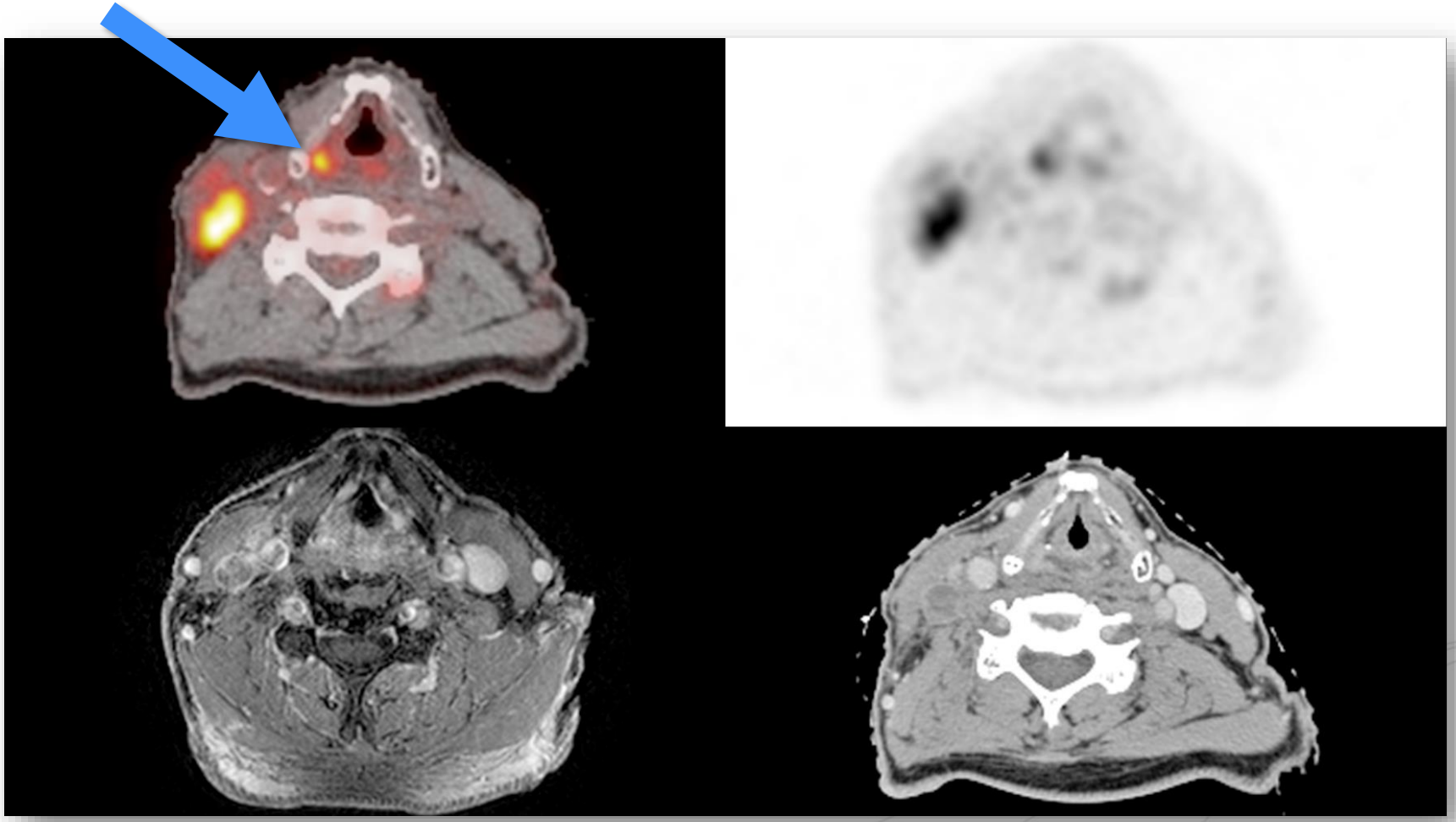
Standard imaging with CT

- Anatomical orientation
- Normal organs
- Tumour locations
- Electron density map



In addition: endoscopy, blind biopsies, MR, US, US/fna, FDG PET

Primary tumour detection



Diagnostic value

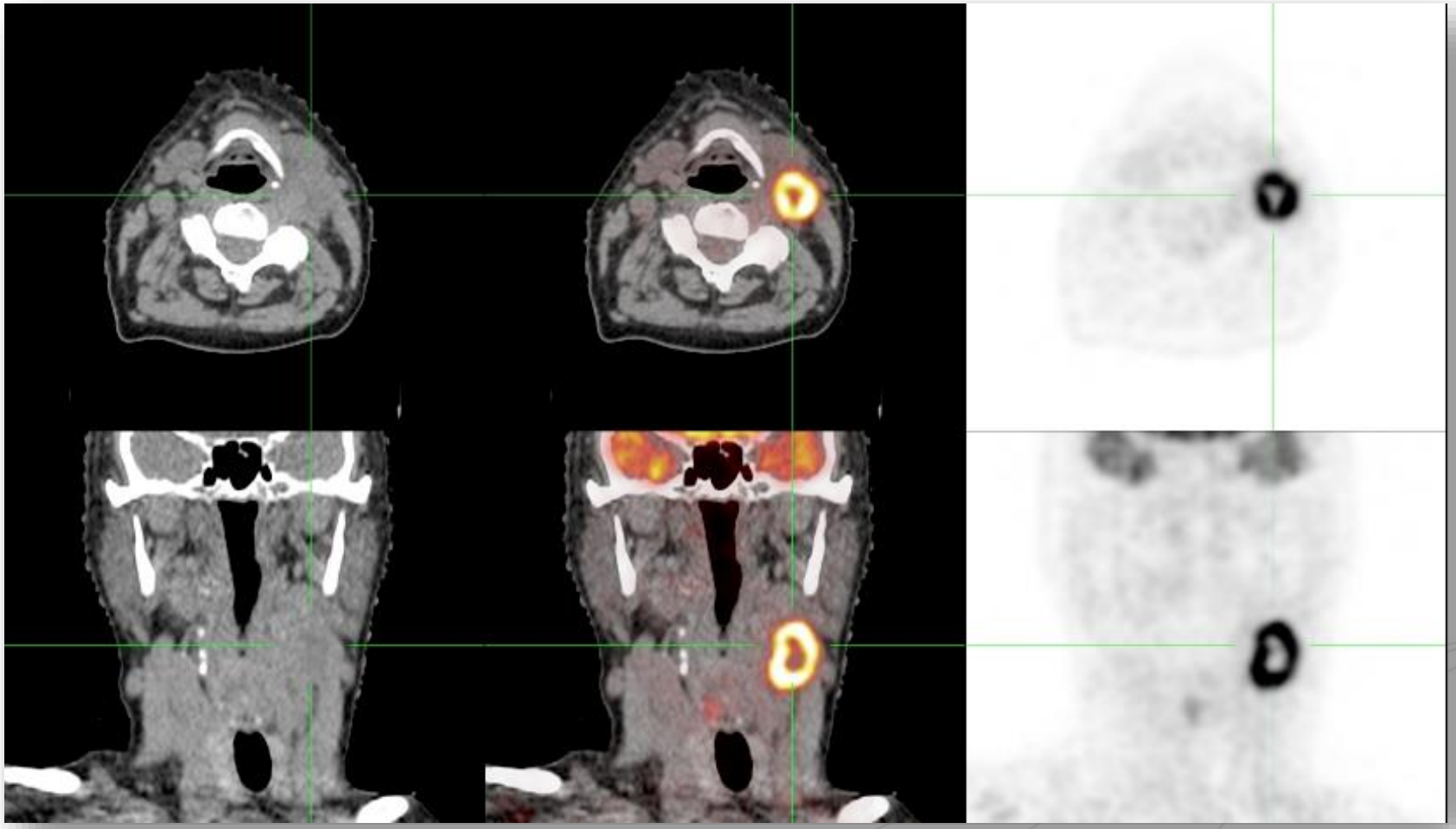
- Prior to panendoscopy: **29%**
- After panendoscopy: **25%**

Rusthoven, Review, Cancer 2004;101: 2642 – 2649
Johansen, DAHANCA-13, Head Neck. 2008;30(4):471-8.

Impact on radiotherapy

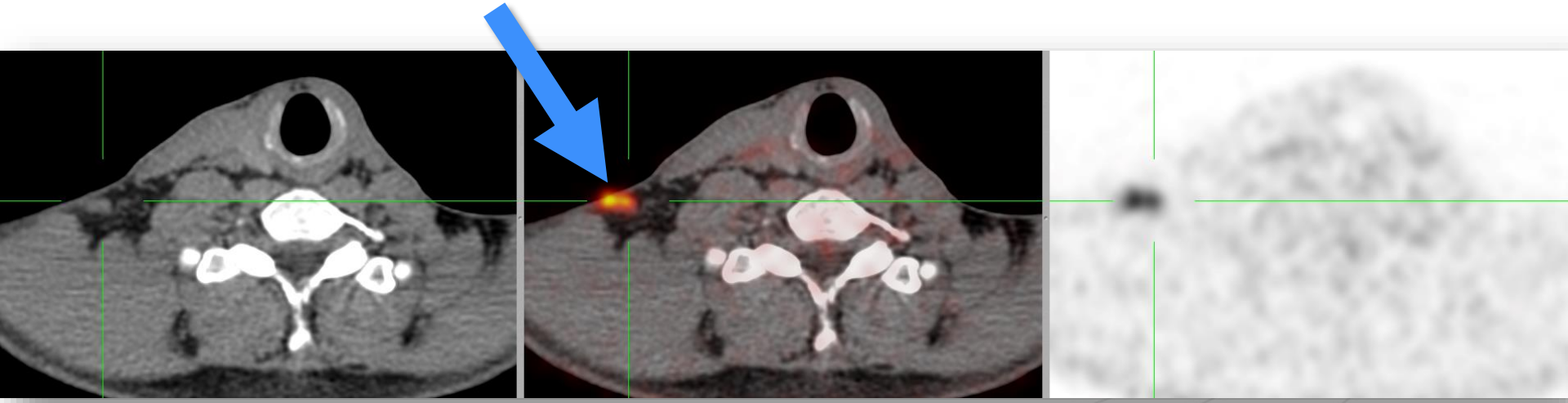
- Guiding panendoscopy
- Local high dose treatment

Lymph node metastases



Small nodal metastases

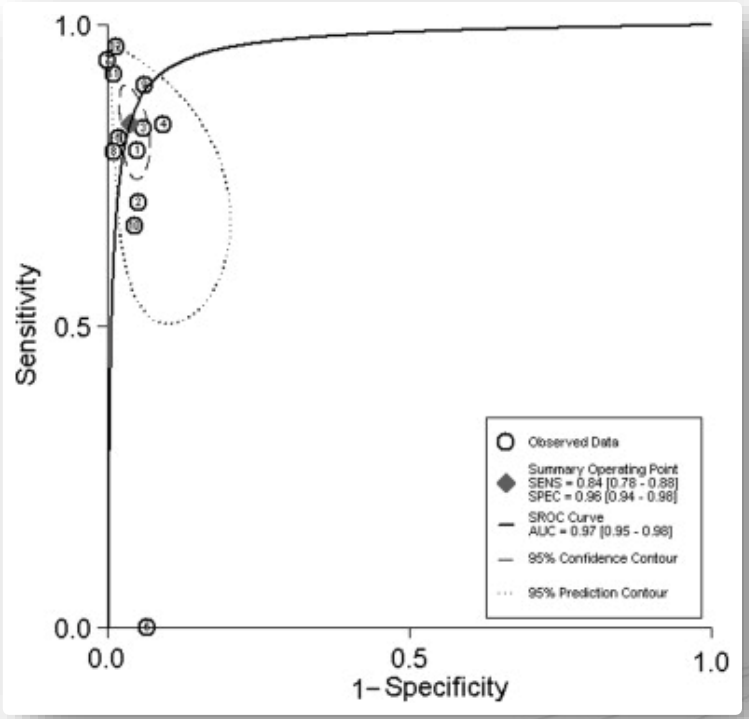
- Increasing sensitivity of scanners
- Overview of the whole neck



Diagnostic value by node level

- Sensitivity 84%
- Specificity 96 %

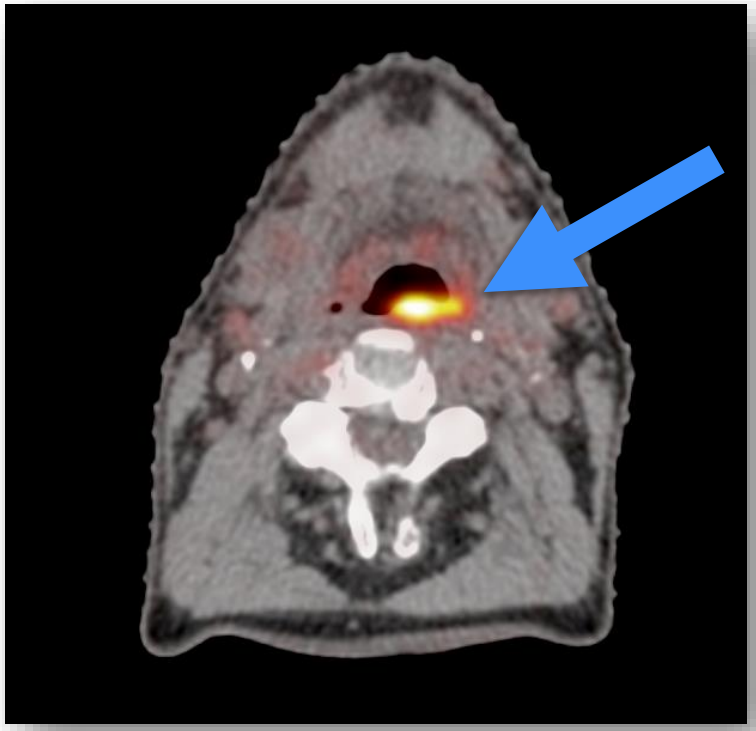
Yongkui et al. Surg Oncol. 2013 Mar 25.

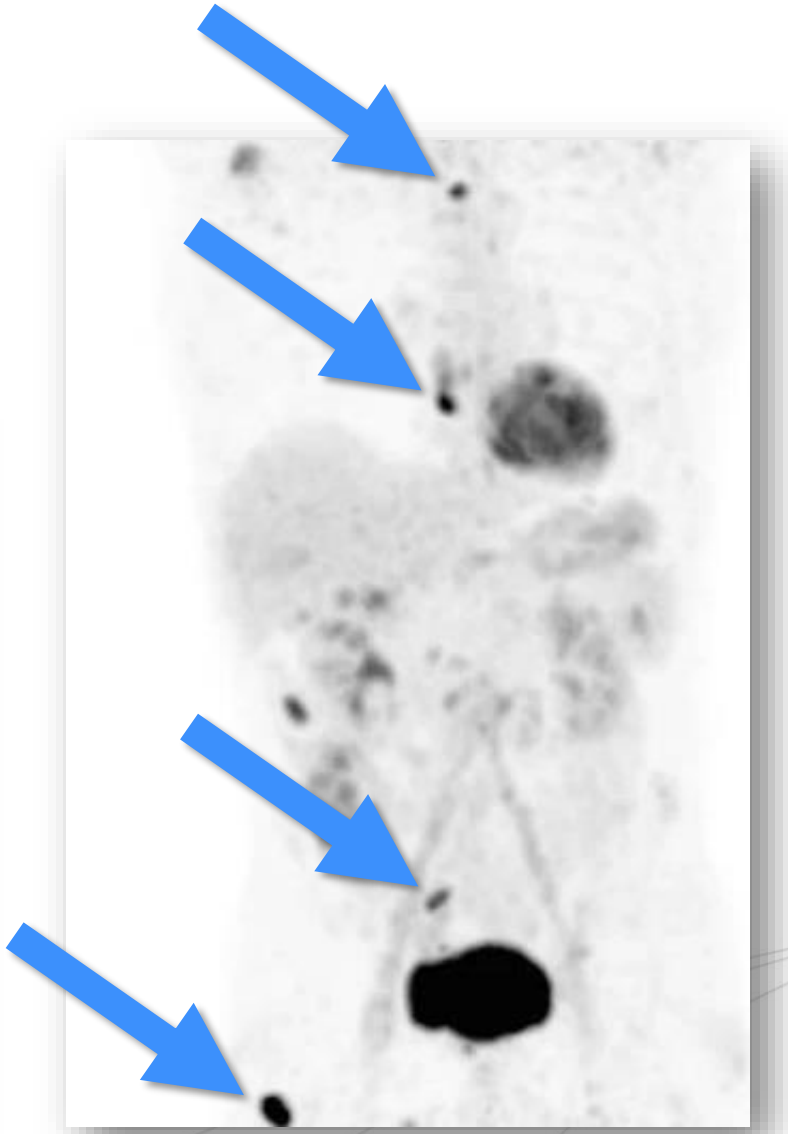


Impact on radiotherapy

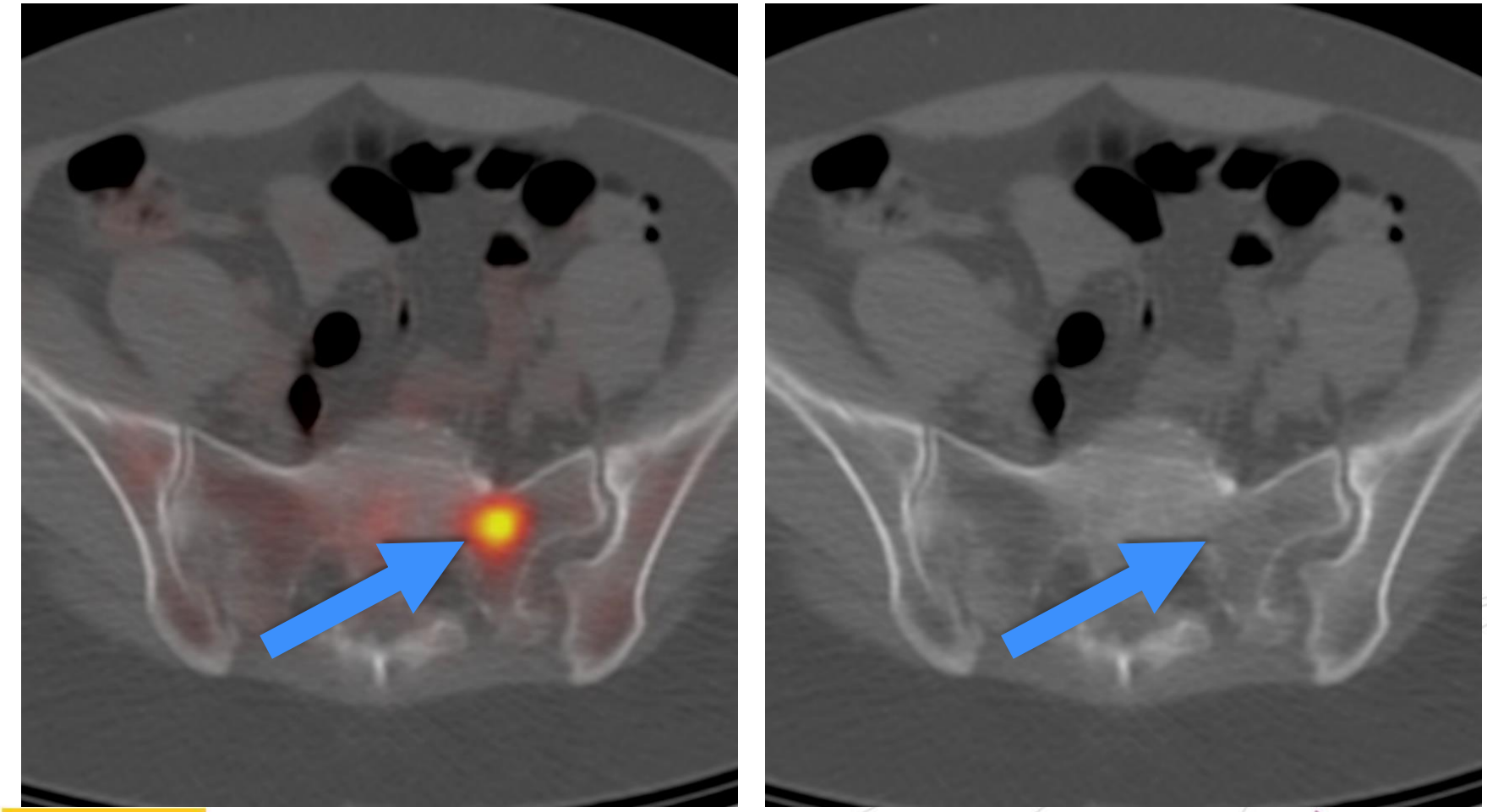
- Nodal boost fields
- Elective nodal fields

Distant metastases





Example M1 negative on CT



Diagnostic value

- **About 12% unexpected M1**

Kim, Ann.Onc, 2007
Fleming, Laryngoscope, 2007
Regeling, EJNMMI, 2002
Kitagawa, OSOMOPORE, 2002

Impact on radiotherapy

- Curative -> palliative intent RT
- Adequate palliation of metastases

Value of diagnostic FDG PET/CT

Prior to the start of radiotherapy

- Staging
- Patient selection

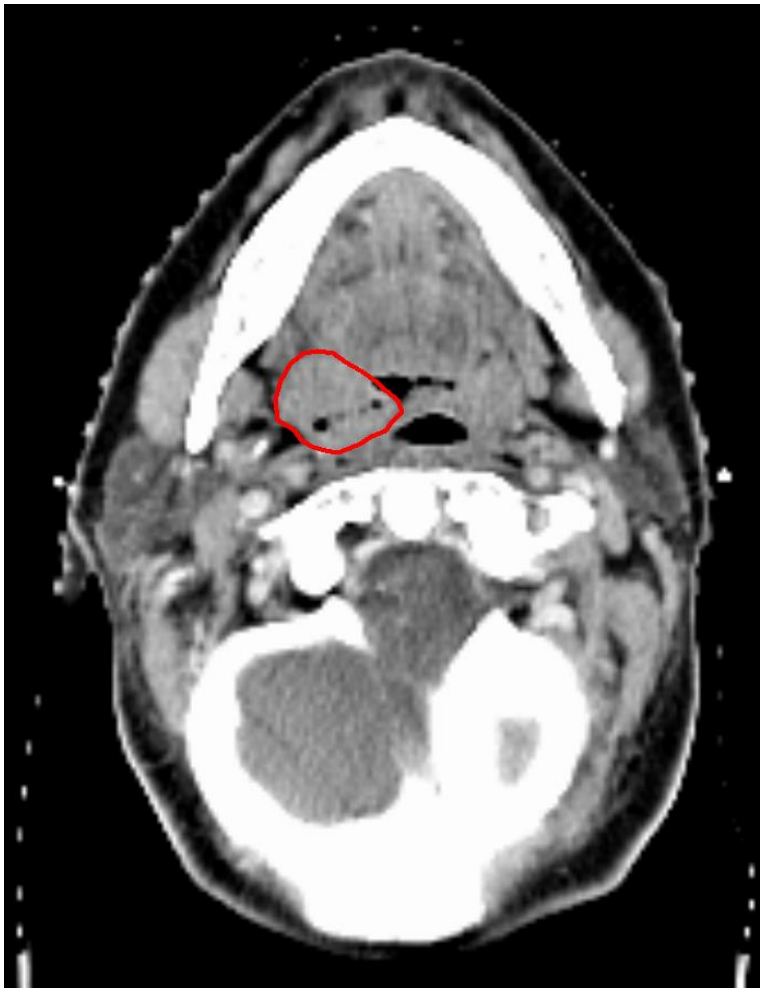
How can we apply this diagnostic value in the radiotherapy treatment planning process ?

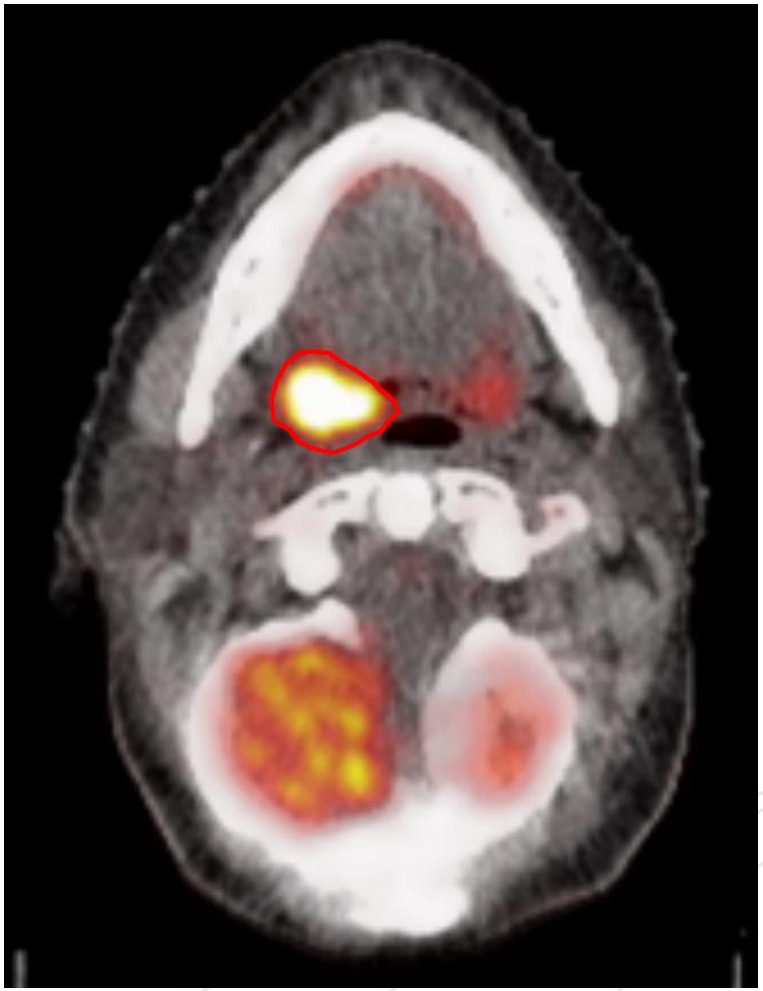
Primary tumour delineation

Potential benefits

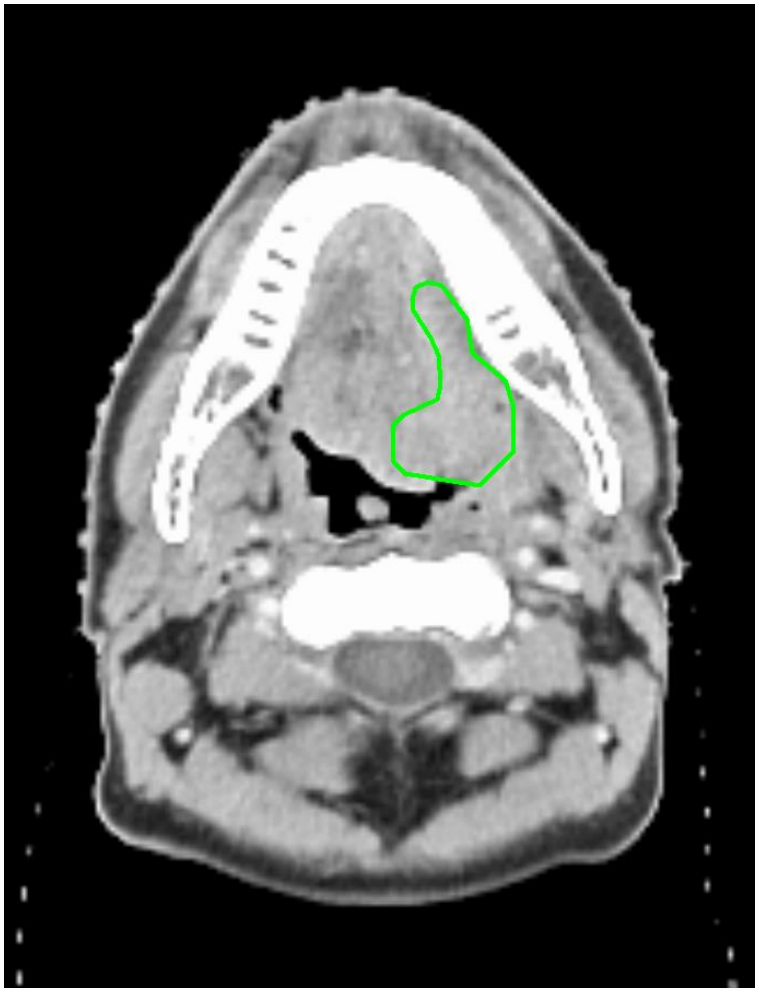
- Avoid tumour miss
- Sparing normal tissues
- Operator agreement

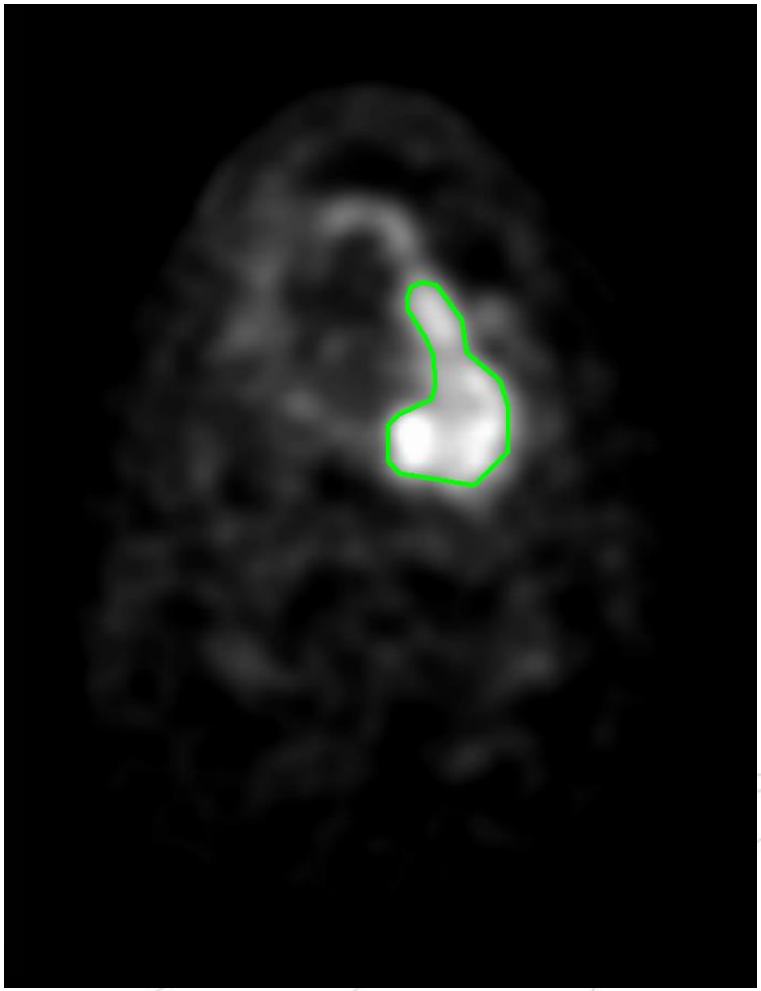
Improve confidence



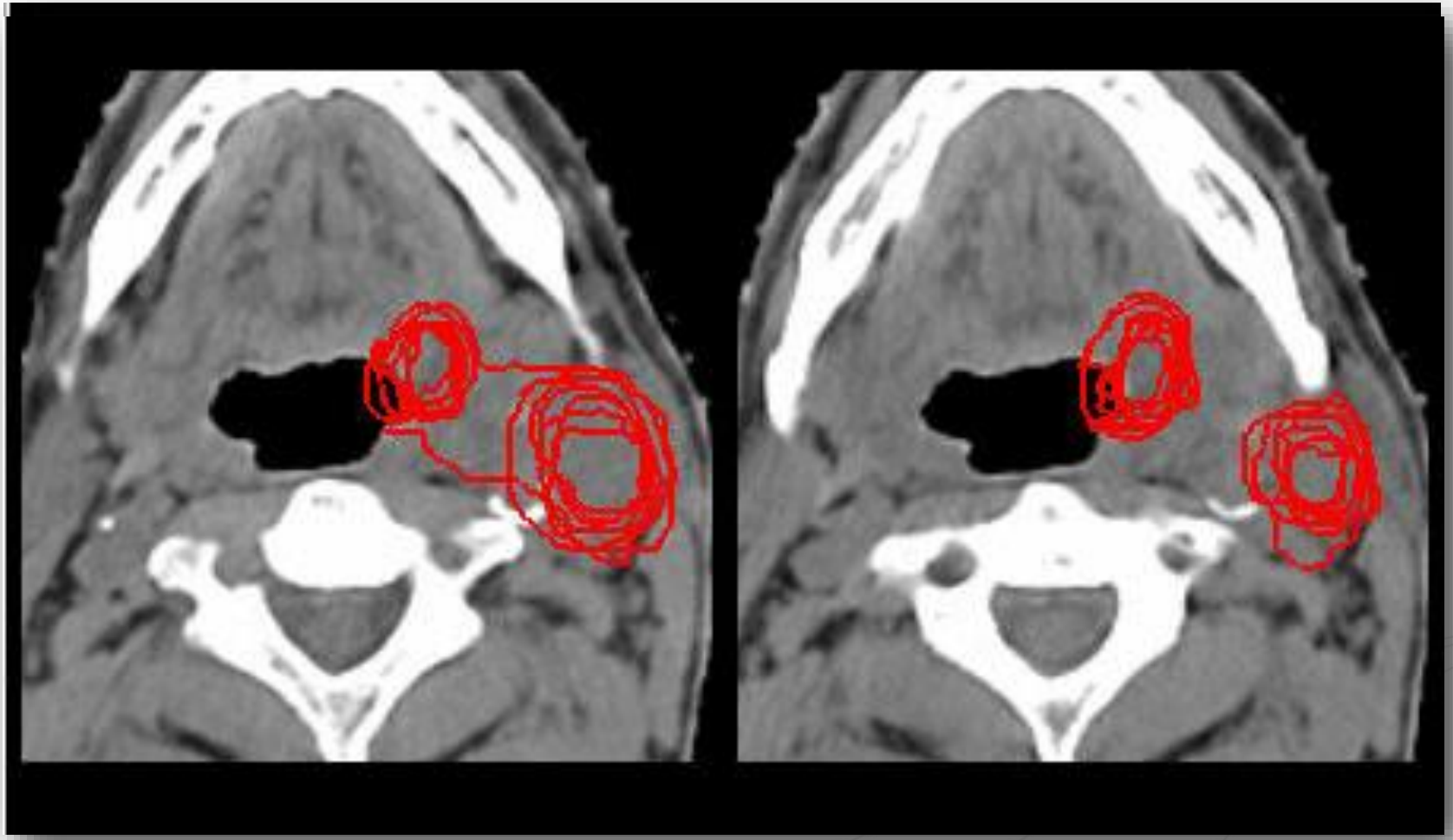


Example of tumour delineation





PET/CT based delineation

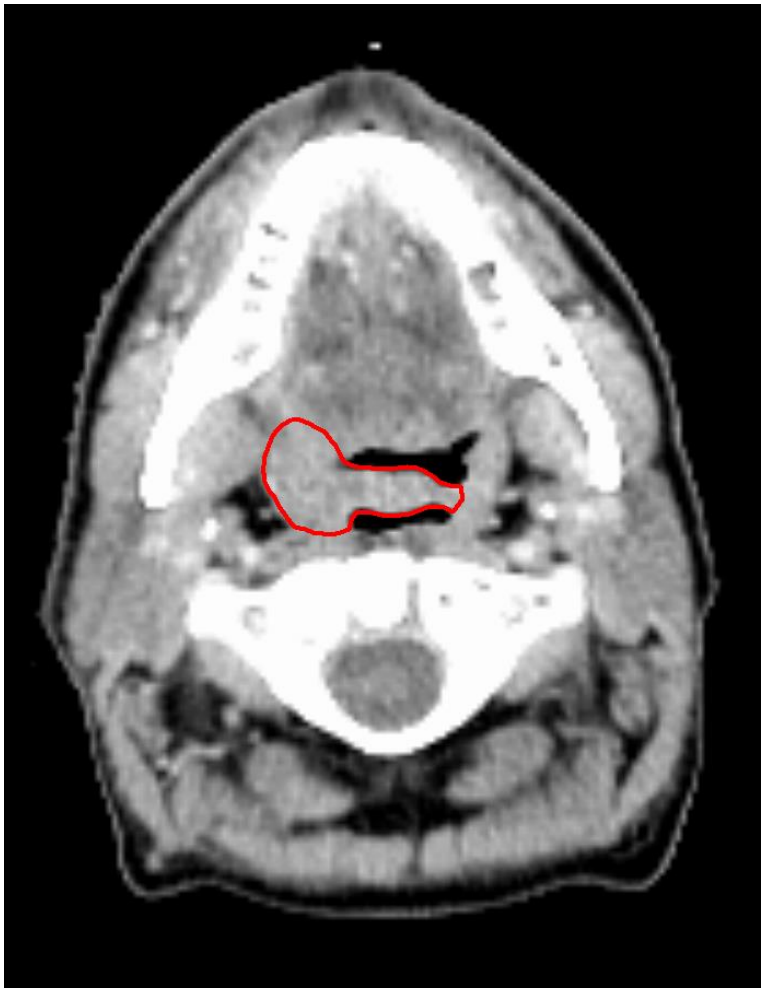


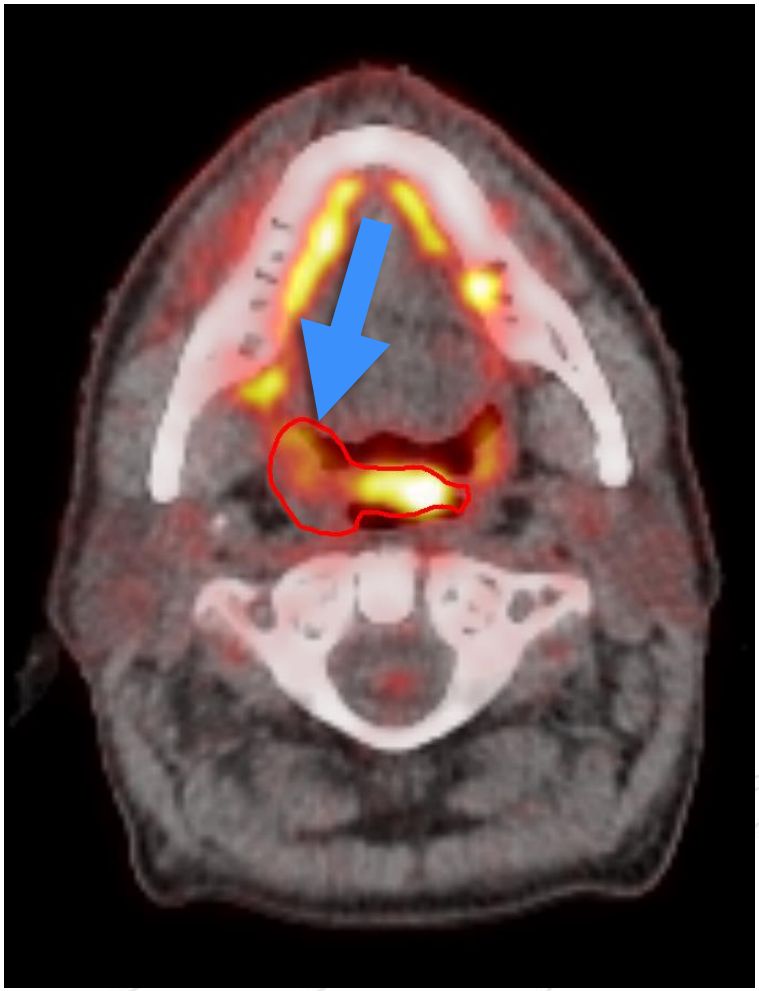
Value for radiotherapy

- Avoid tumour miss
- Avoid unnecessary toxicity
- Operator agreement
- Compare with other centres
- Compare with existing literature
- Facilitate new research

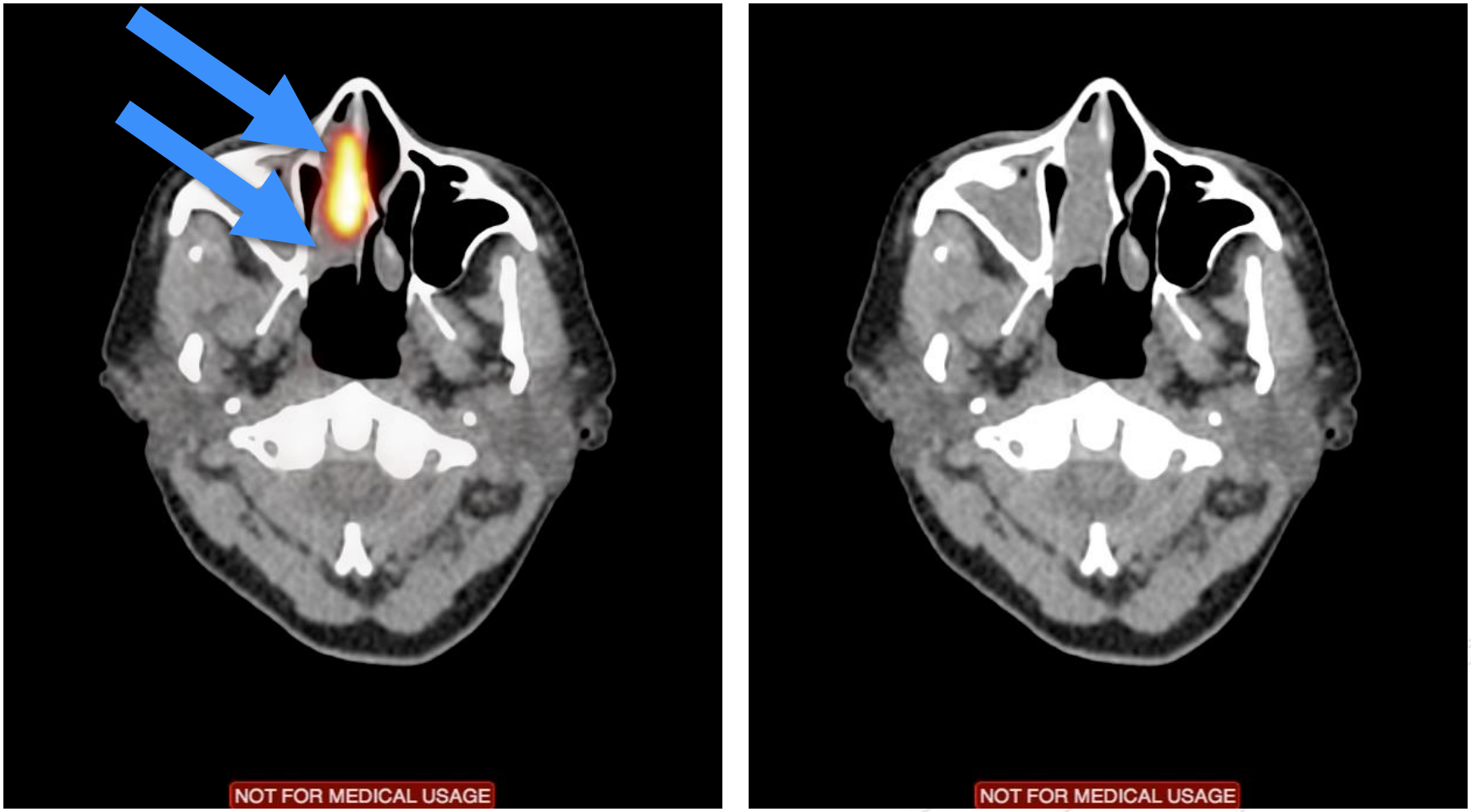
Impact on patient survival needs to be shown

Example: difference BTV - GTV

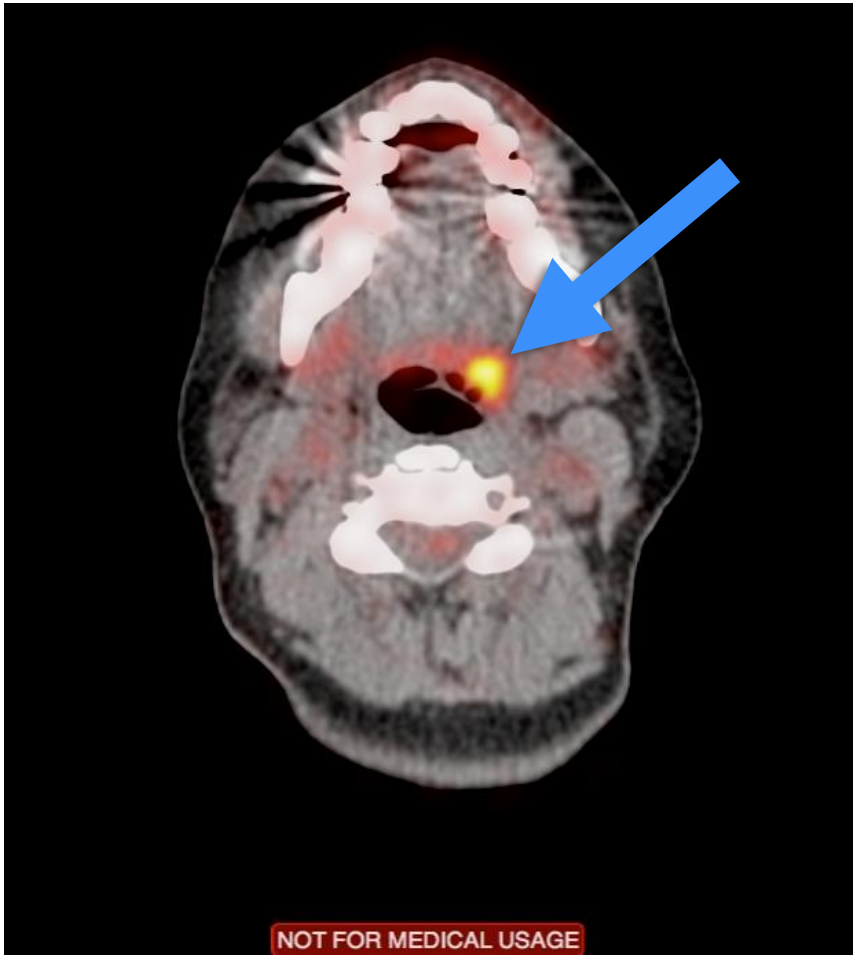


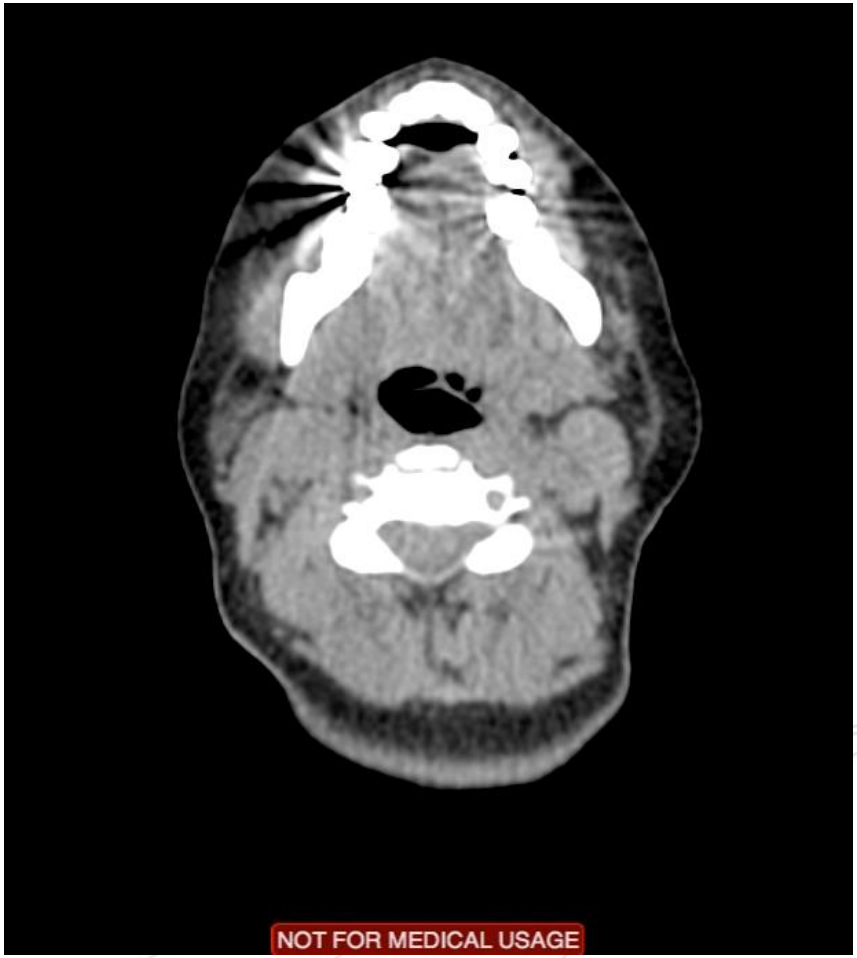


Example: Second primary tumour



Example: Second primary tumour





Selection of lymph nodes for high dose irradiation

Clinical questions

Which nodes need high dose irradiation?

- All macroscopic metastases

Which node levels need elective irradiation?

- Containing metastatic disease
- Draining from other positive levels
- Draining from the primary tumour site

Impact of nodes and verification strategy

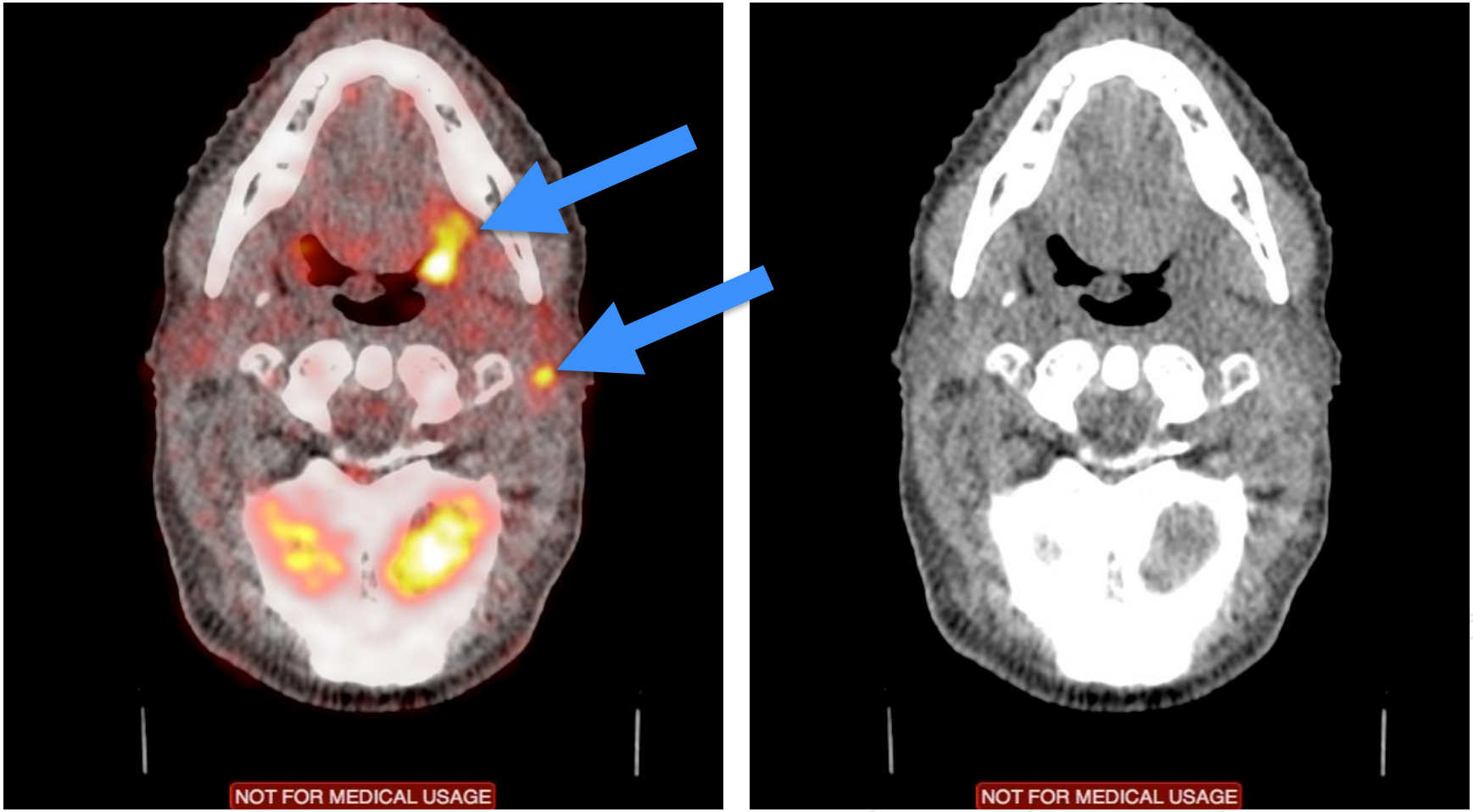
impact

	Solitary ipsilateral node	Additional ipsilateral node	Additional contralateral node
Ignore			
Follow-up			
Verify with imaging			
Verify with biopsy	**43 %**	**12 %**	**62 %**
Change treatment	**57 %**	**88 %**	**38 %**

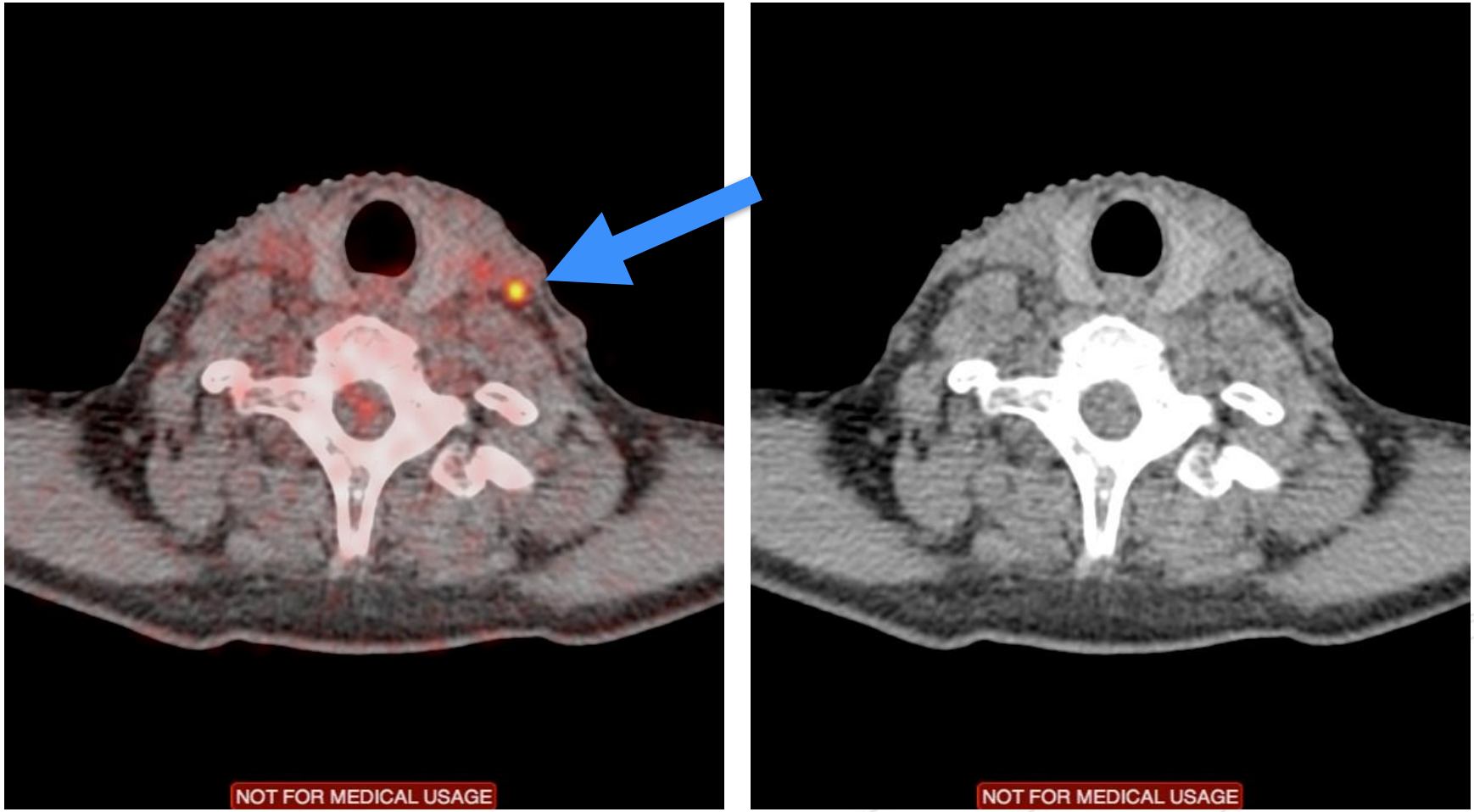
Very high confidence

Especically in a confirmed N+ neck

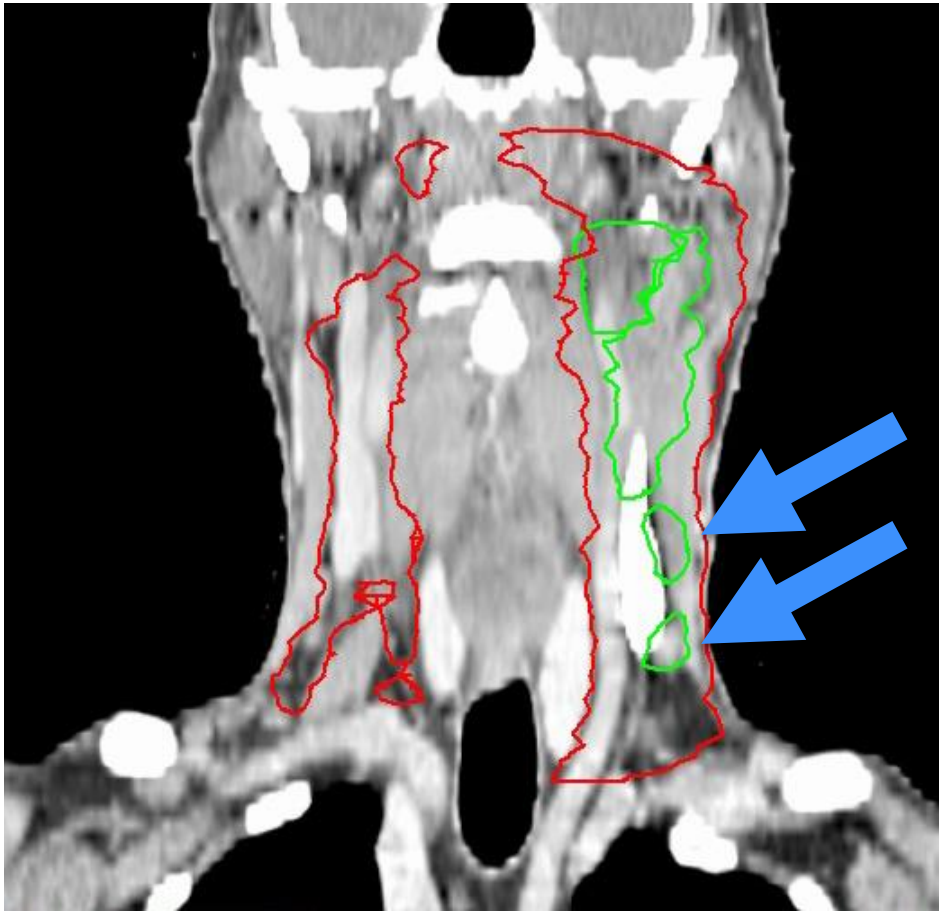
Example: Low neck node



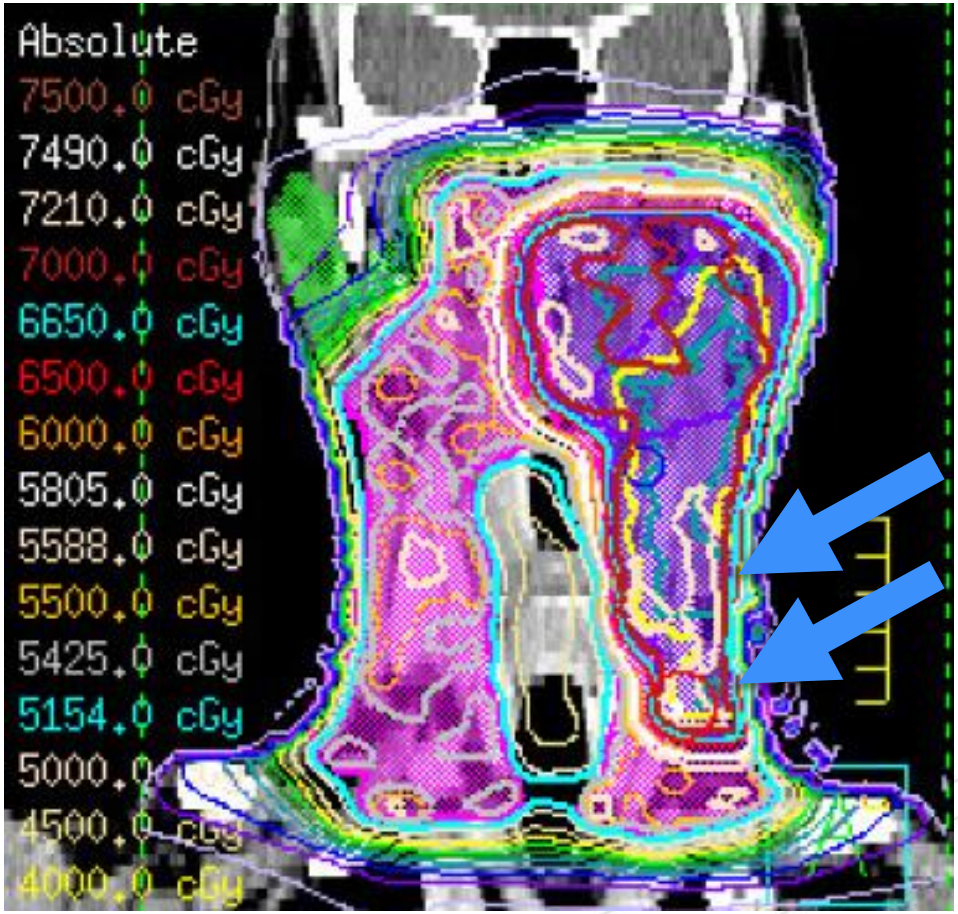
Example: Low neck node



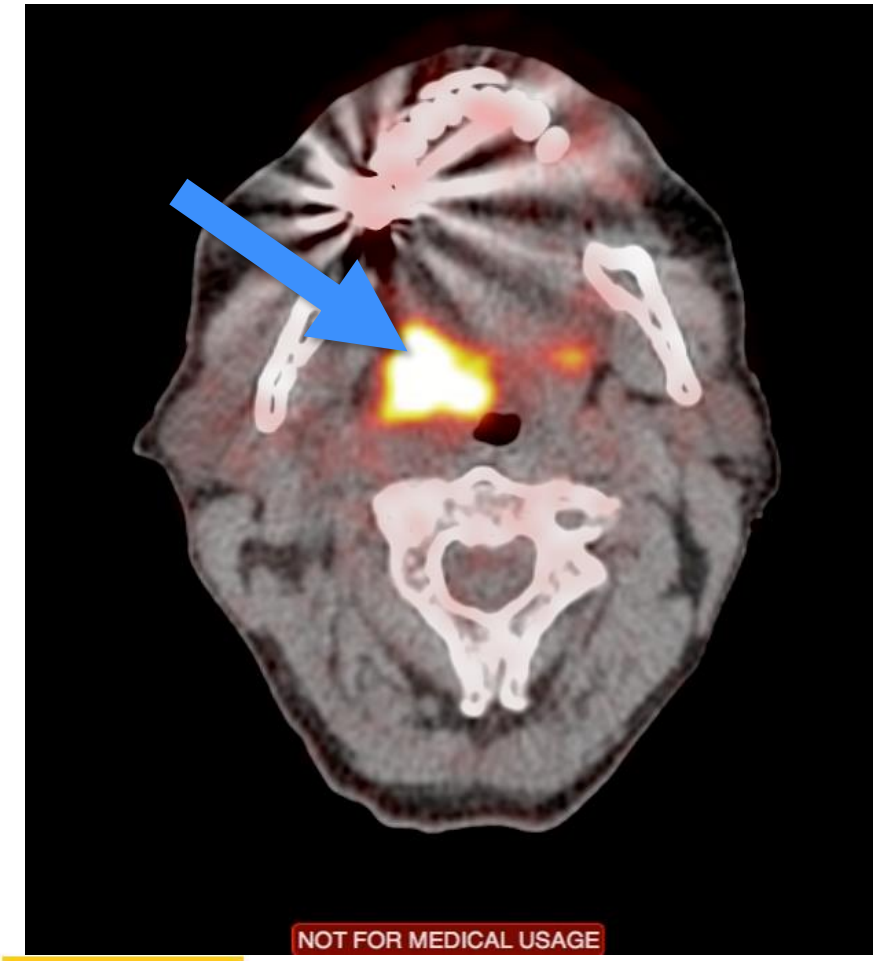
Resulting treatment field

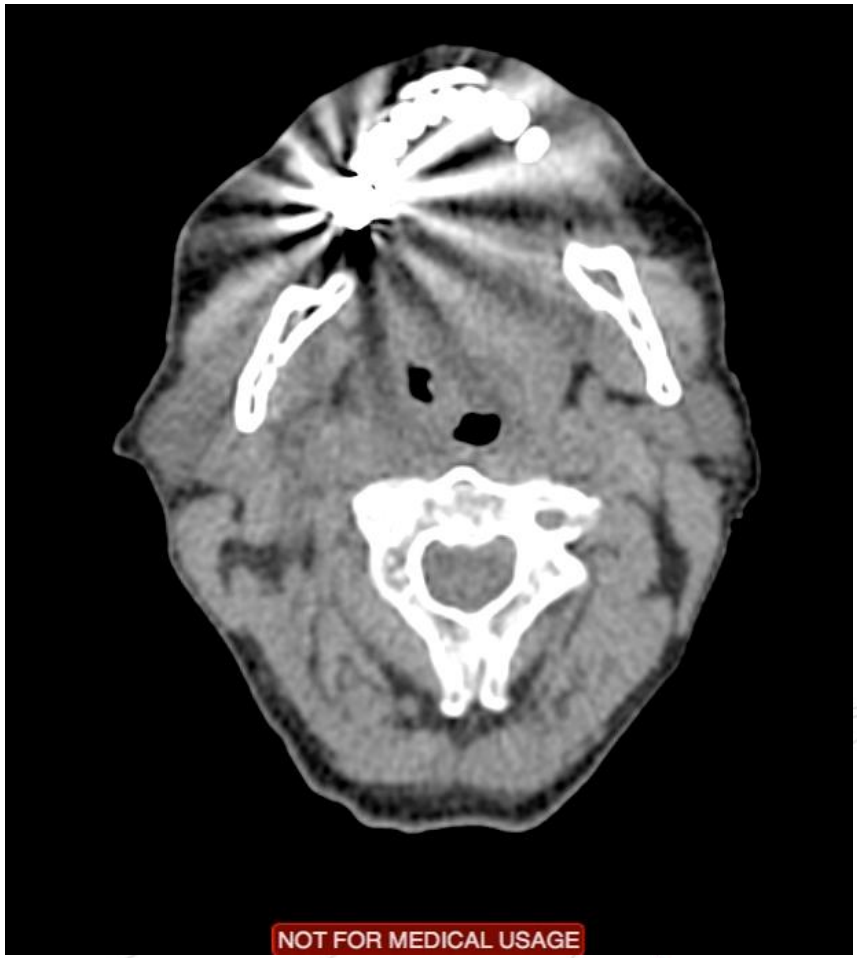


Resulting treatment field

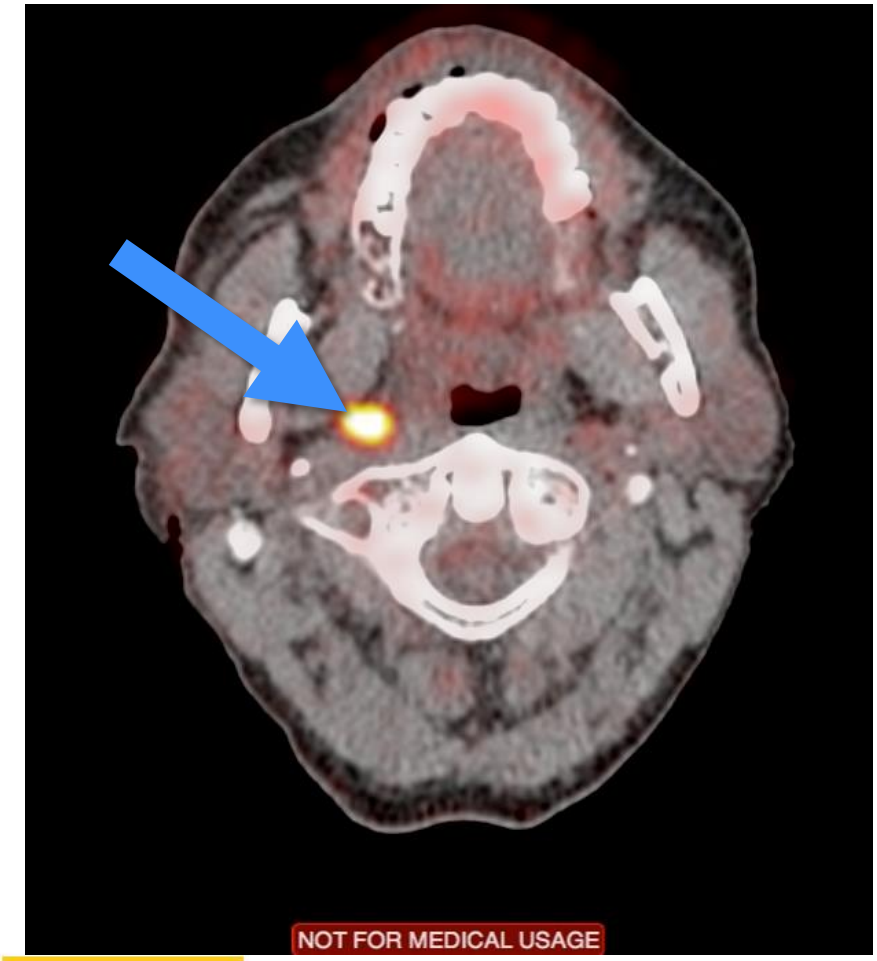


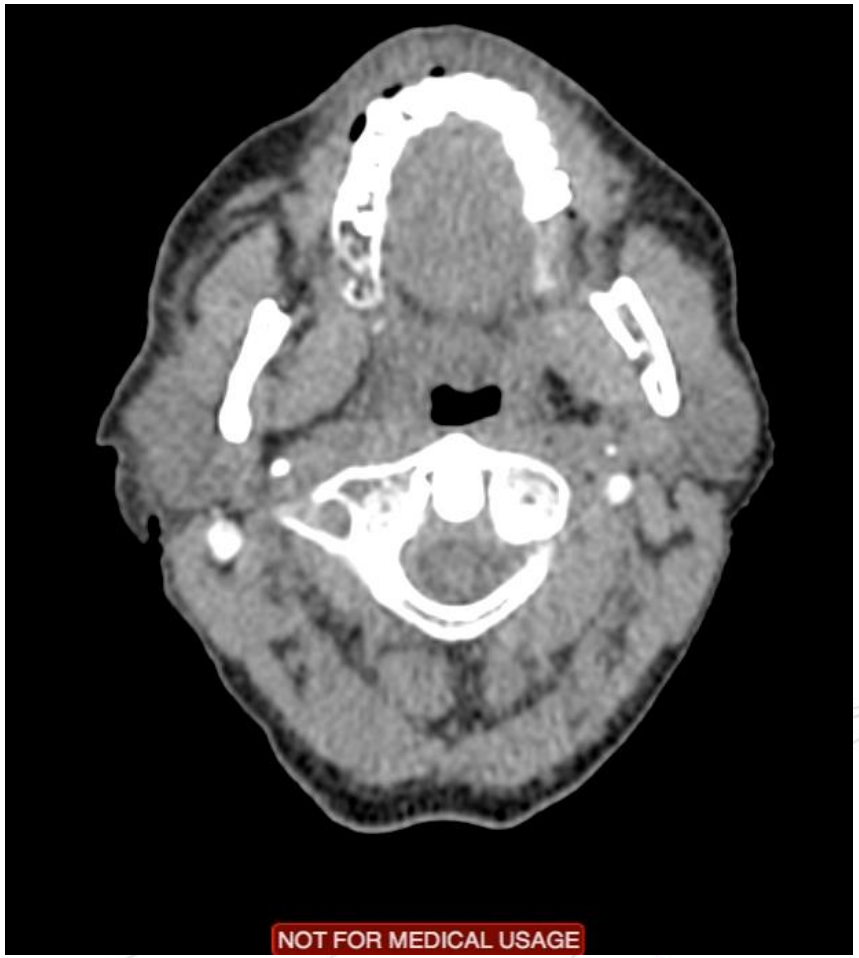
Example: high level 2 nodes



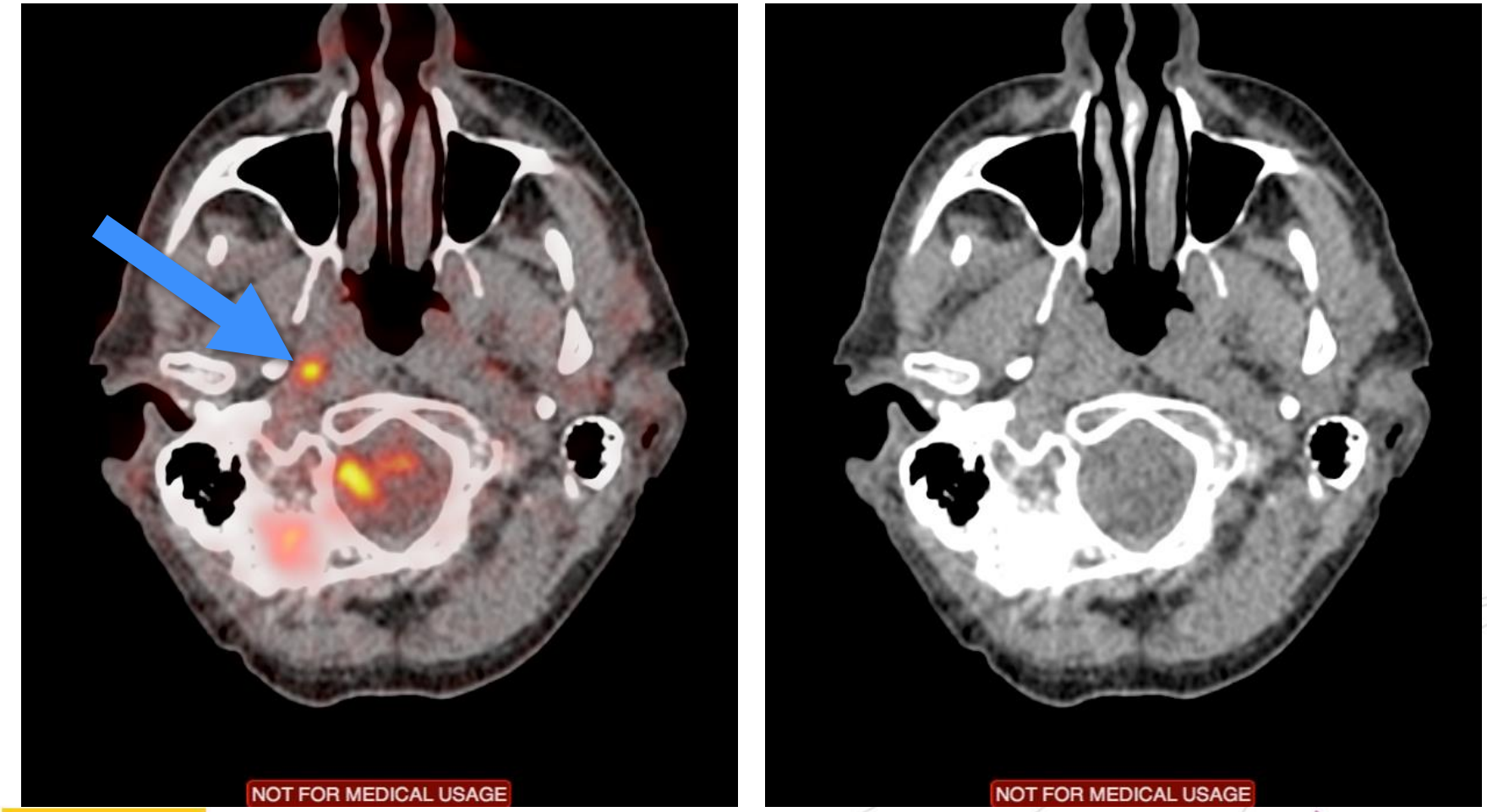


Example: high retropharyngeal nodes

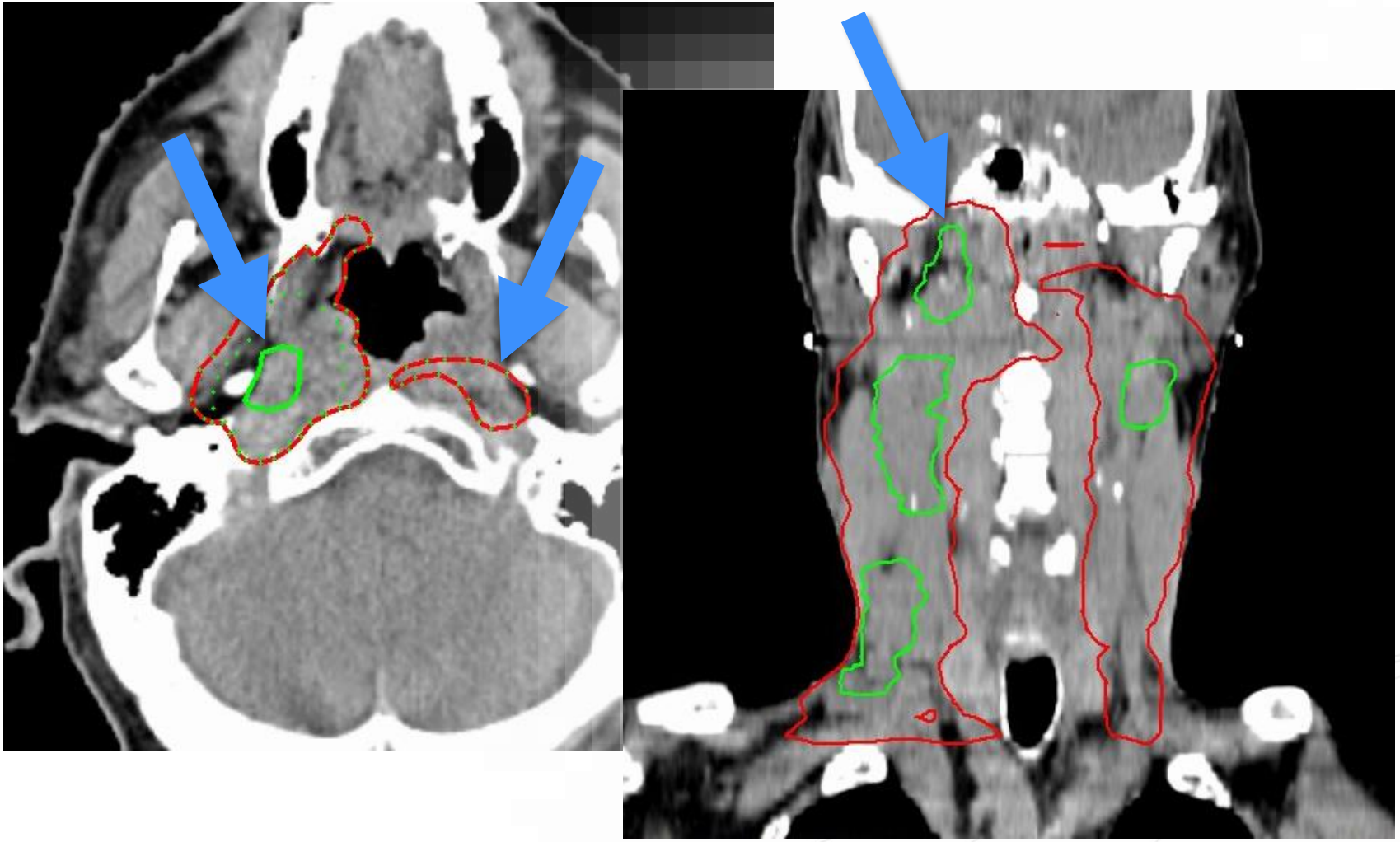




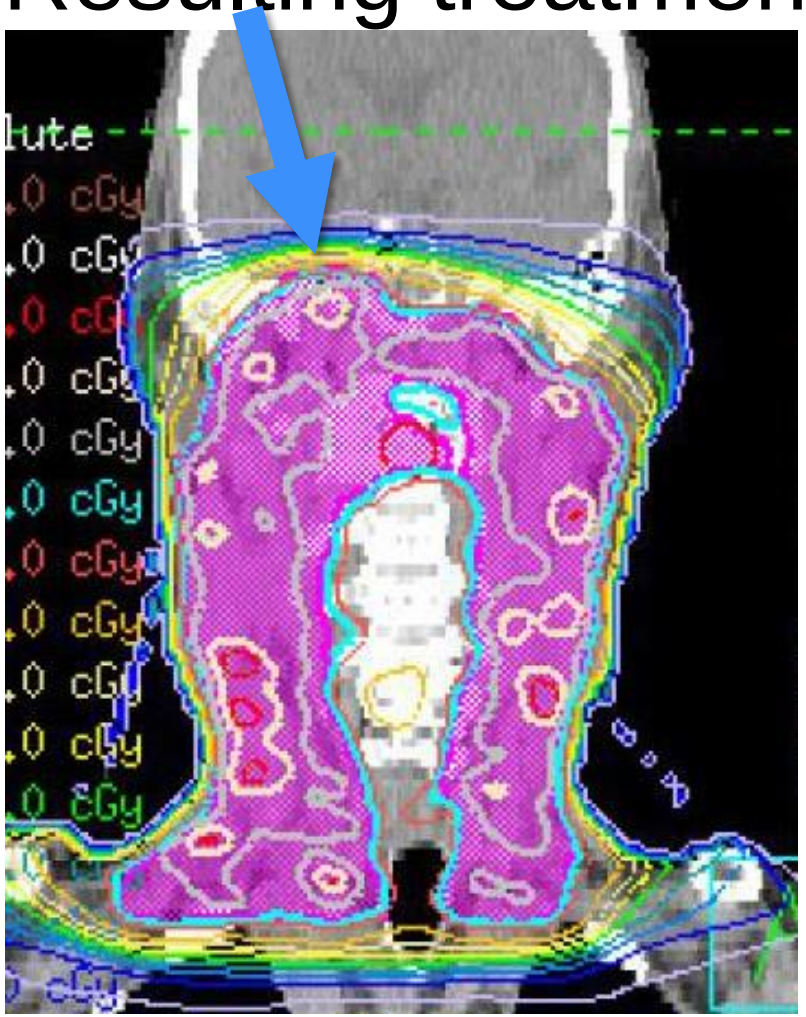
Example: high retropharyngeal nodes

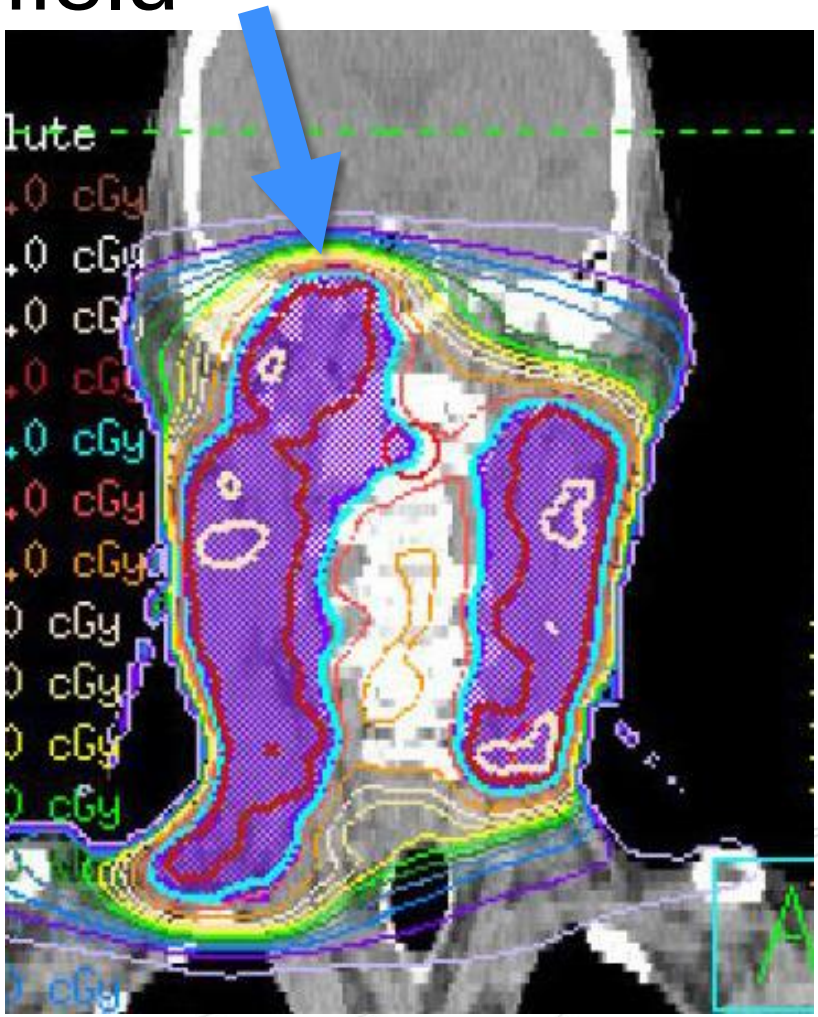


Resulting treatment field



Resulting treatment field



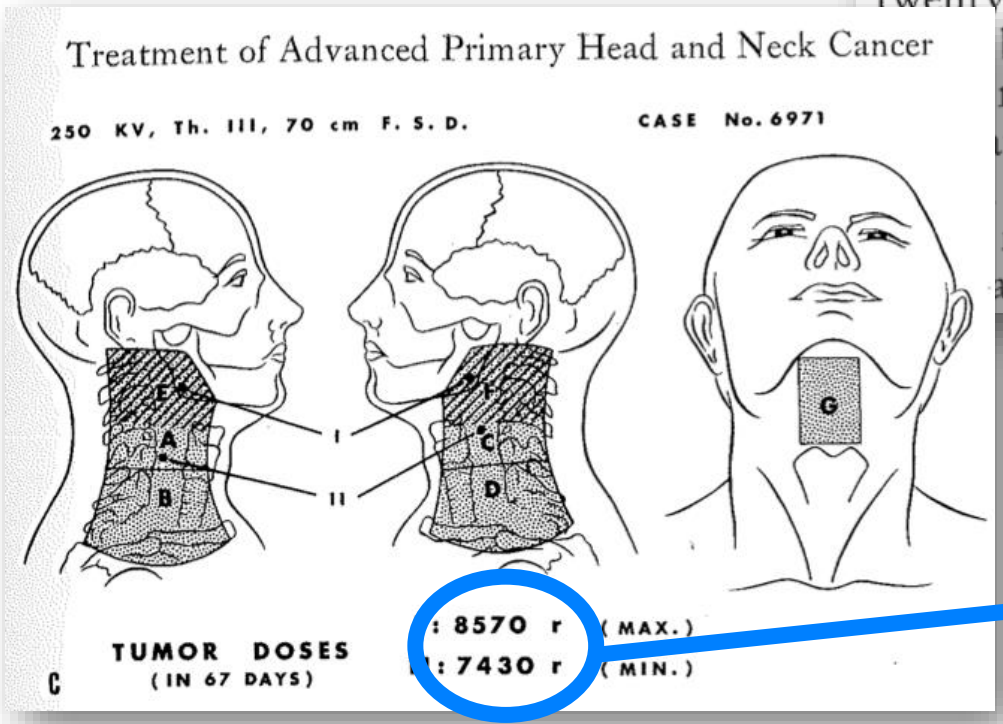


Future perspective

Management based on palpation era

RT dose levels defined in the 1950's

Although surgical removal will not be curative in many instances, it extirpates bulky and infiltrating lesions. As soon as the wound is healed, usually within ten to twenty days, postoperative radiation ther- begun with external irradiation. The neck region, from the mastoid tip to vicle, is irradiated through opposing fields. A tumor dose of 6,000 to roentgens is delivered to the mid- al region within seven to eight weeks



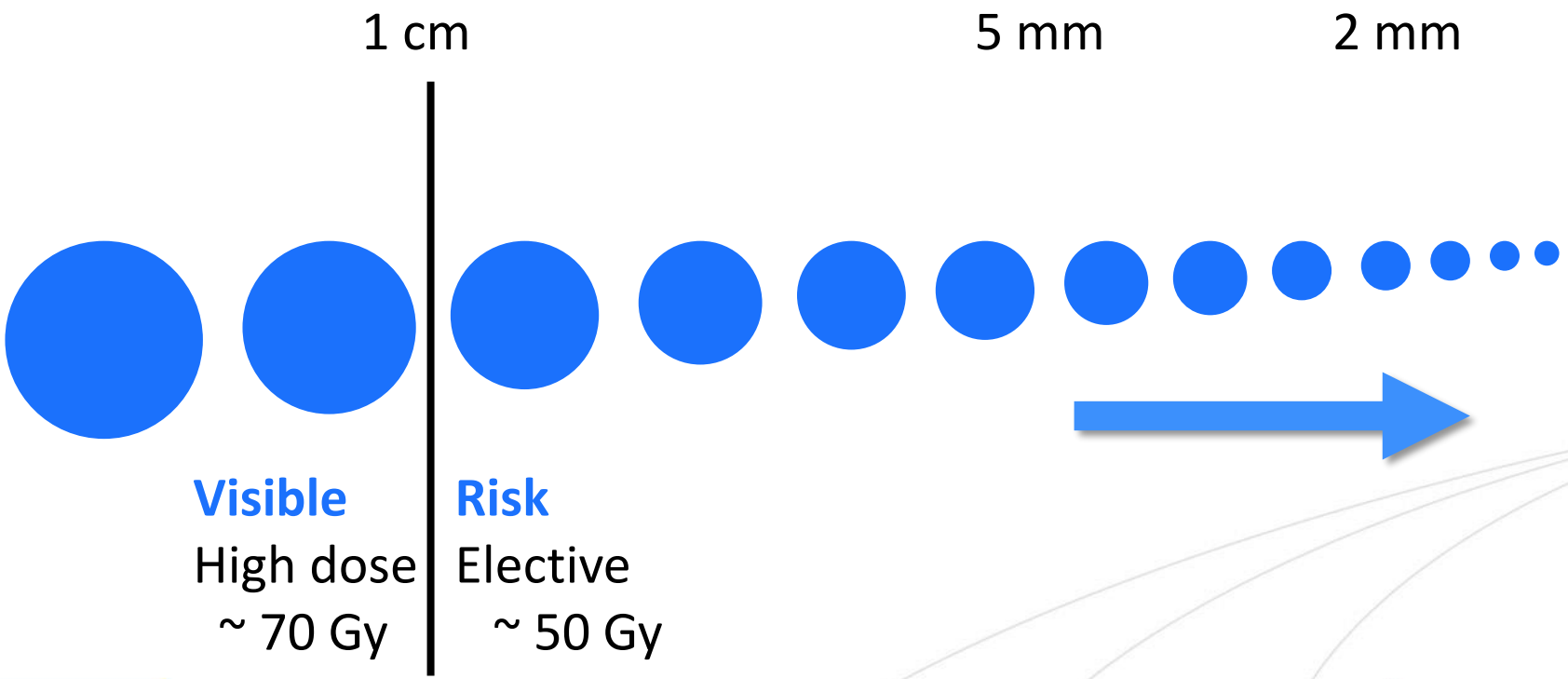
Elective: ~ 50 Gy

Bulk: ~ 70 Gy

Fletcher G.H. et al., Planned combination of surgery and radiation in treatment of advanced primary head and neck cancers. Am J Roentgenol Radium Ther Nucl Med. 1957 Mar;77(3):397-414.

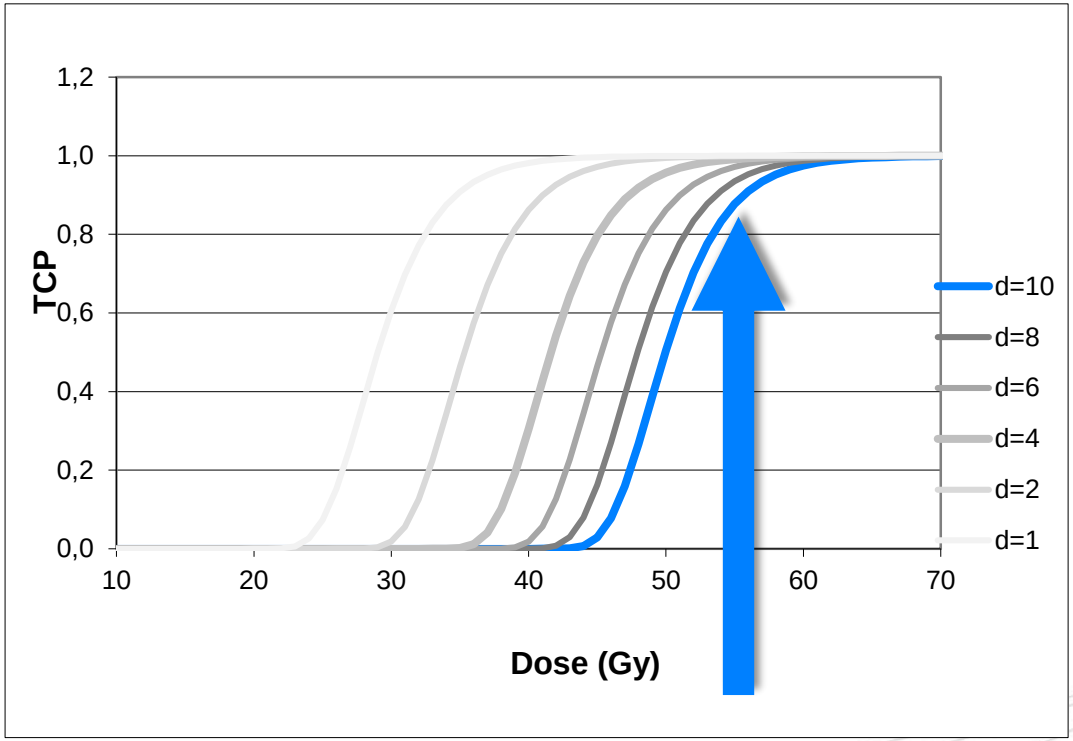
Improving diagnostic procedures

- Increasing sensitivity for lymph node metastases
- Missed nodes will be smaller



Relation TCP and dose

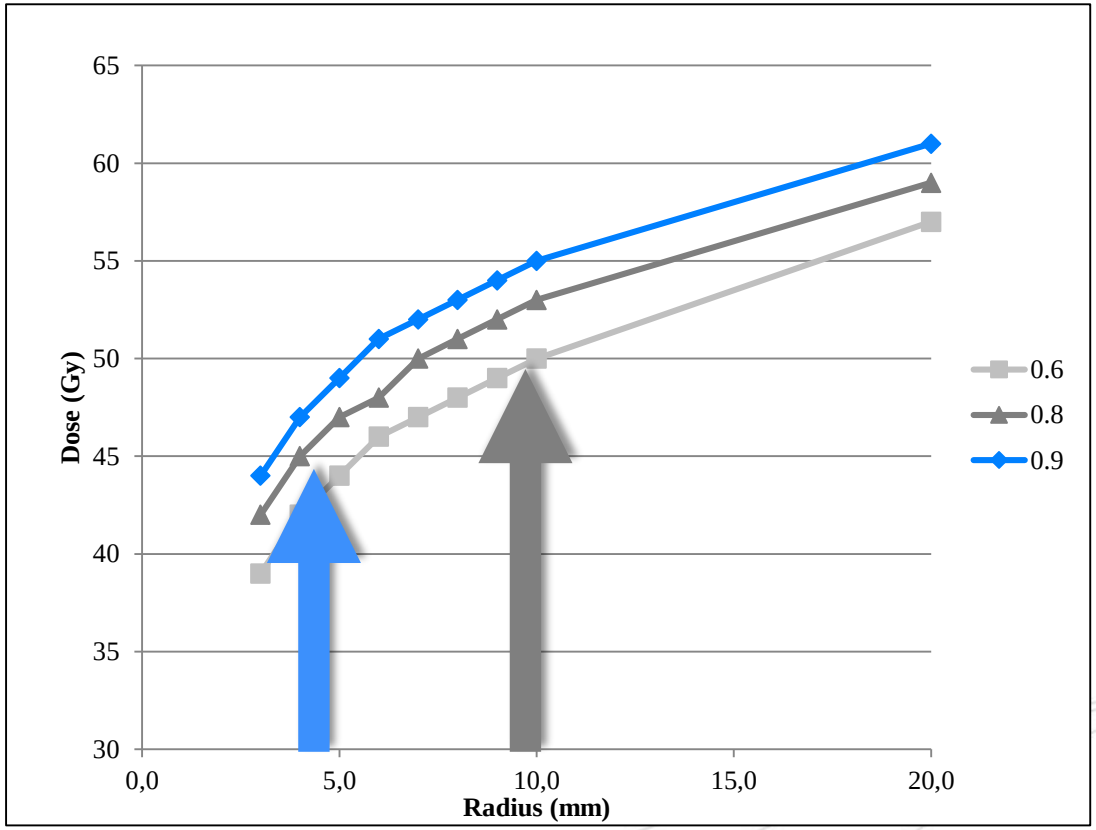
Depends strongly on lesion size



Relation diameter / dose

Regardless of the selected TCP,

1 mm improvement in lesion detection limit = dose reduction **~ 1 Gy** for elective treatment



Implications for treatment

- Increasing use of
  - FDG PET/CT
  - Multiparametric MRI
  - Image-guided US-FNA

- Will lead to changes in RT
  - High-dose: Target definition and tumor load
  - Elective dose: Target definition and tumor load
  - Dose levels: Dose reductions and new levels
  - Chemotherapy: Changing patient selection

- Will lead to changes in surgery
  - Lower chances on positive nodal dissections
  - Lower chances on positive SN procedures

Thank you for your attention

Questions ?

Brain MRI for brain tumors focus on high grade gliomas

Pr Anne Laprie MD PhD
Toulouse France
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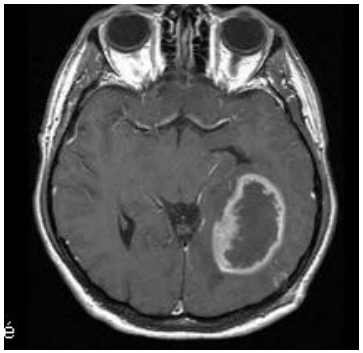
INSTITUT UNIVERSITAIRE
DU CANCER DE TOULOUSE
Oncopole

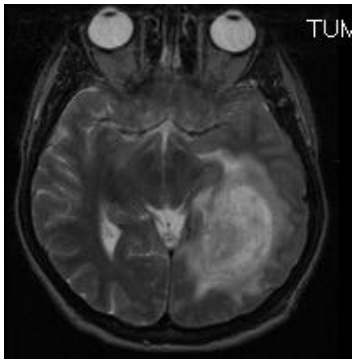
Use of brain MRI for brain tumors RT

- **Low Grade Glioma**
  - Registration for volume definition
    - T2/FLAIR
    - Check the fusion before contouring
  - Contouring
    - 0,5 cm around T2/FLAIR abnormality

- **High grade glioma**
  - Registration for volume definition
    - T1 gadolinium : 3D sequences are recommended for better coregistration (axial or sagittal)
    - T2/FLAIR
    - Check the fusion before contouring
  - Contouring
    - 2 cm around T1 CE
    - Enlarge it to FLAIR/T2 abnormalities if necessary

Standard Brain MRI





T1 gado reflects the rupture of hematomeningeal barrier and underestimates tumoral volume

T2/FLAIR reflects edema and micoscopic invasion and overestimates tumoral volume

Tumor with complex infiltration

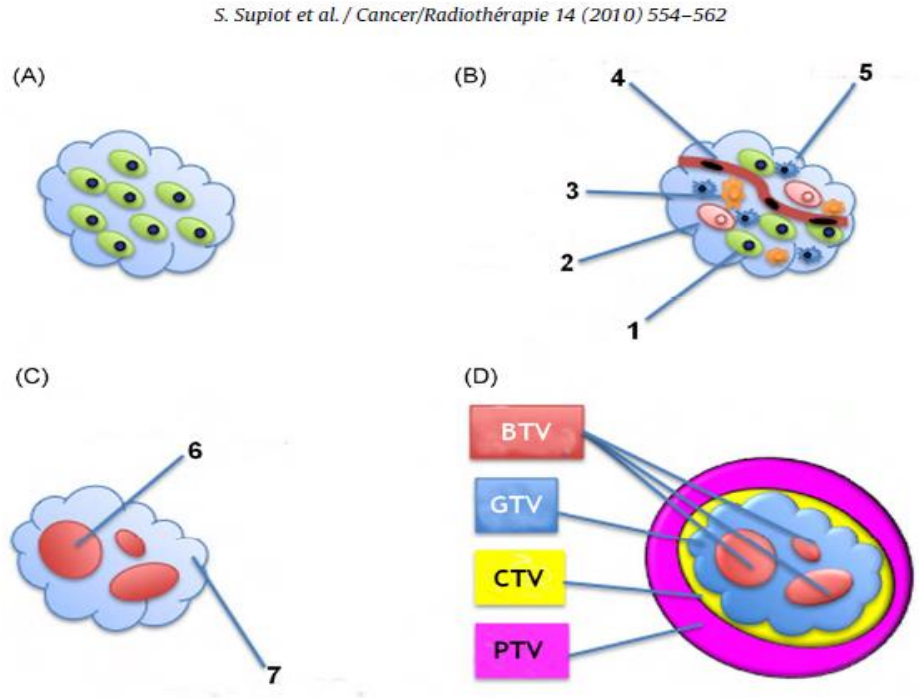
Histological series : tumors 2 cm around CE

CTV = CE + 2cm

What is the real tumor extension ?

95% relapse within the fields : how can we define resistant regions ?

Depicting the Biological Target Volume= BTV



Local relapses can be due to cellular or micro-environment clusters that resist to standard homogeneous dose.

Metabolic imaging can help define radioresistant clusters → **Biological Target Volume**

New radiotherapy techniques allow a precise targeting of BTV

Optimisation of radiotherapy can be performed with **Dose-painting** : delivering heterogenous dose guided by metabolic imaging

Seminal work

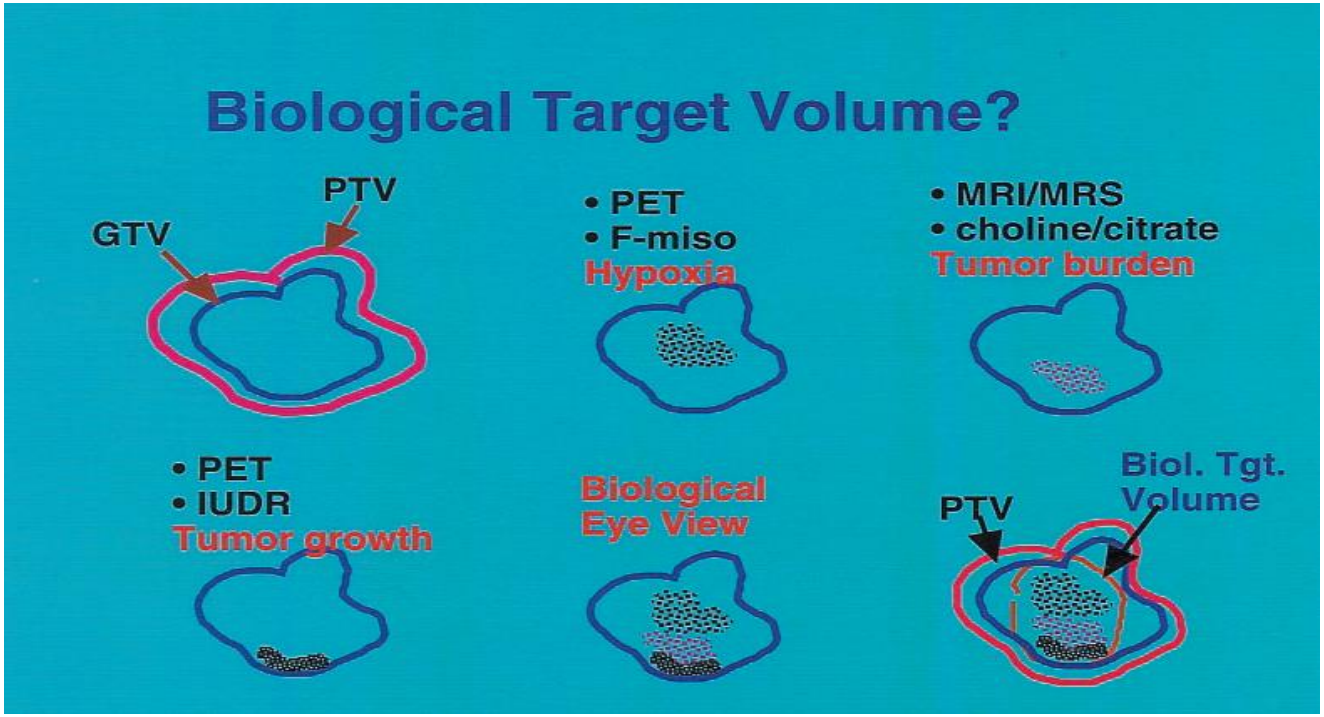
CRITICAL REVIEW

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 3, pp. 551–560, 2000

TOWARDS MULTIDIMENSIONAL RADIOTHERAPY (MD-CRT): BIOLOGICAL IMAGING AND BIOLOGICAL CONFORMALITY

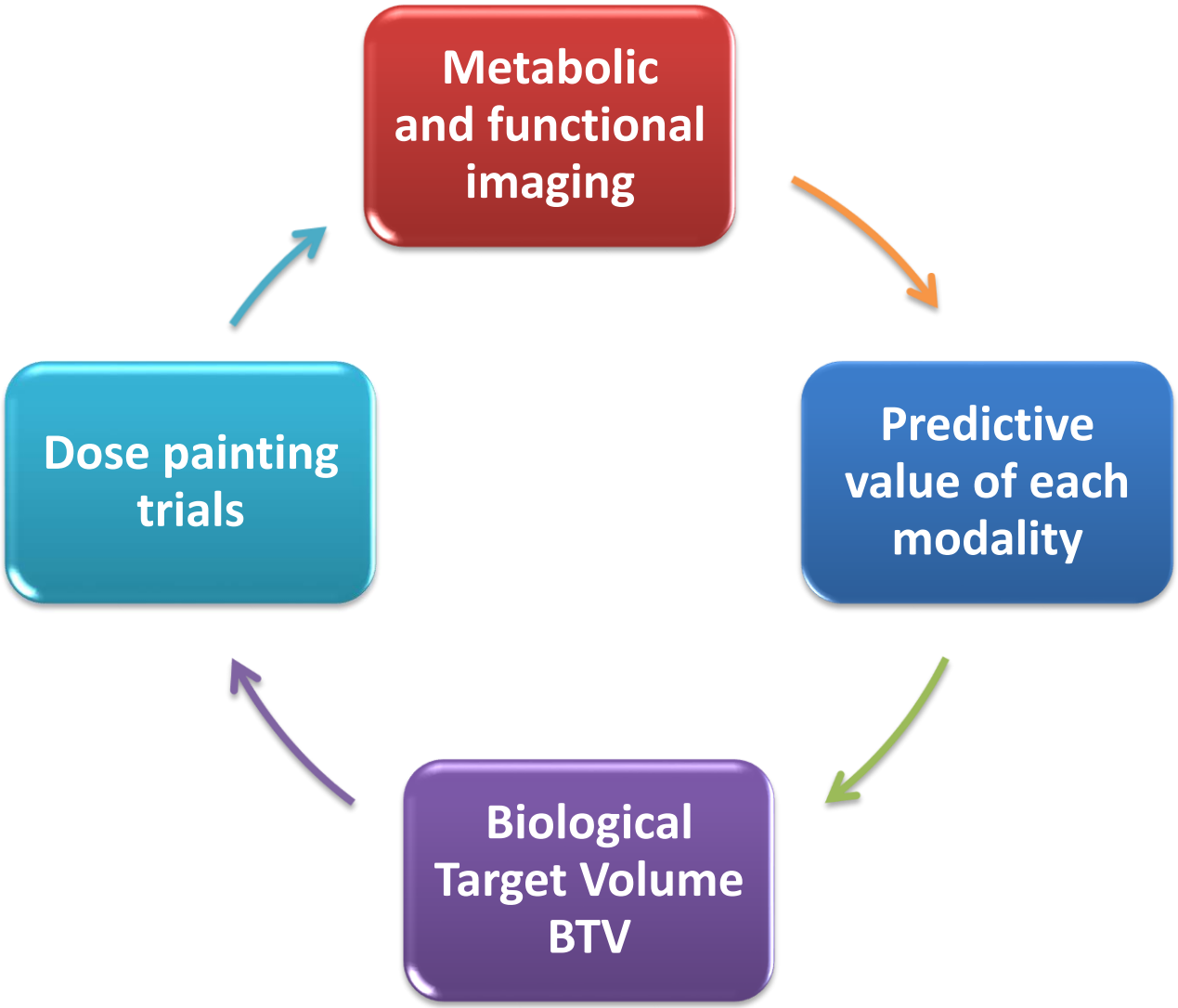
C. CLIFTON LING, PH.D.,* JOHN HUMM, PH.D.,* STEVEN LARSON, M.D.,† HOWARD AMOLS, PH.D.,* ZVI FUKS, M.D.,‡ STEVEN LEIBEL, M.D.,‡ AND JASON A. KOUTCHER, M.D., PH.D.*

Departments of *Medical Physics, †Radiology, and ‡Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY



« most patients treated with biological imaging by 2010 »

Virtuous circle of dose-painting



Three main MR metabolic and functional imaging modalities for High grade brain tumors

- MR spectroscopy → lecture on thursday
- Diffusion MRI
- Perfusion MRI

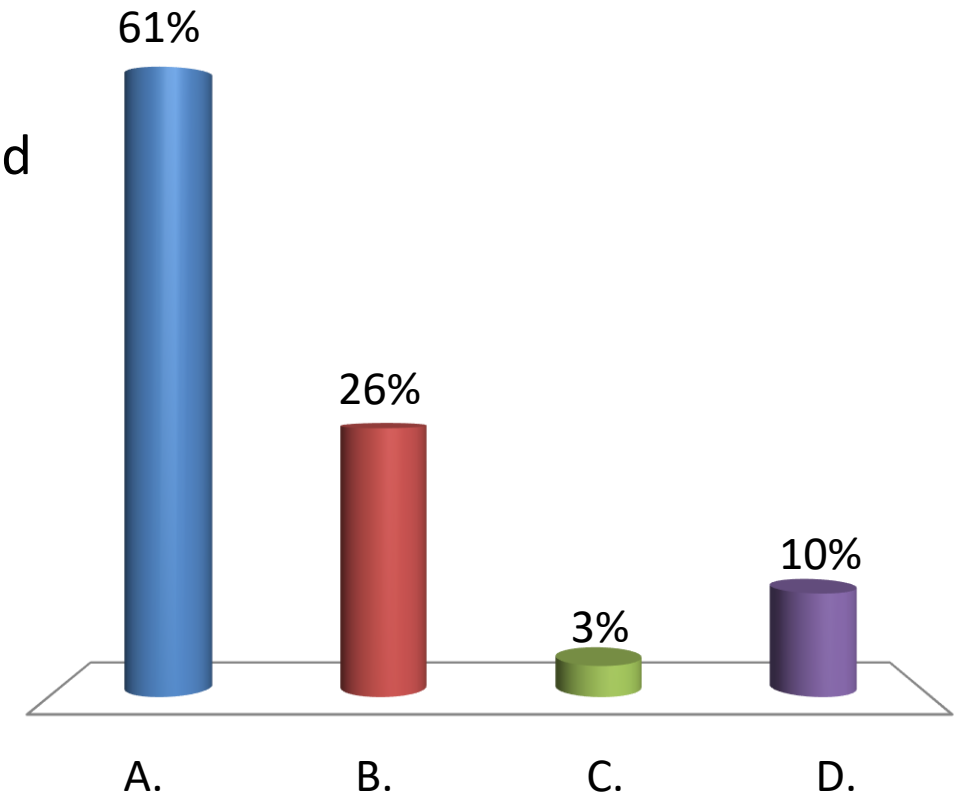
Question 1: Imaging for glioblastoma RT

A. T1 gadolinium and FLAIR should be systematically used to define GTV and CTV.

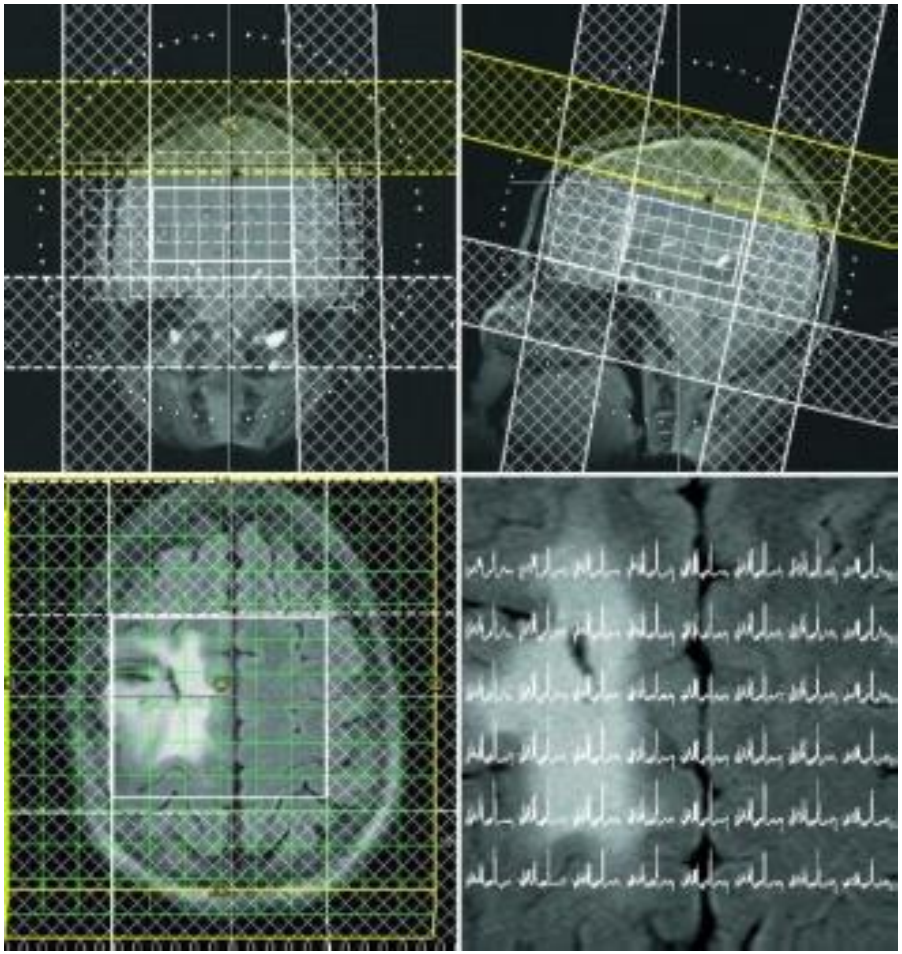
B. Perfusion and diffusion sequences provide reliable and reproducible abnormalities map that can be coregistered with planning CT

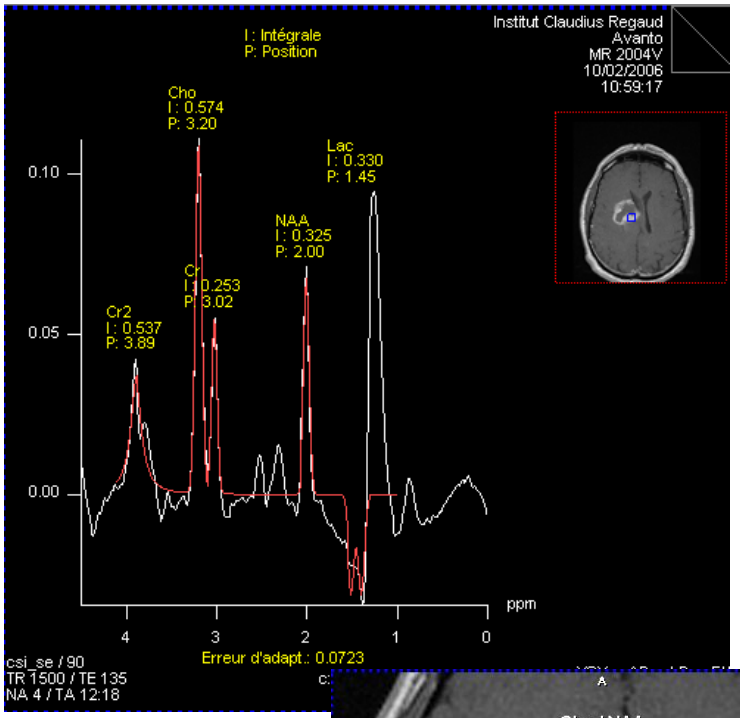
C. Spectroscopy , diffusion and perfusion should be used routinely to define target volumes.

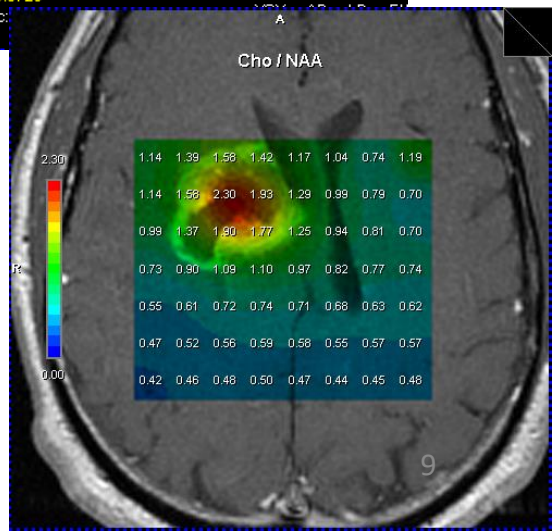
D. Only did MR spectroscopic imaging provide predictive value for the site of relapse



High grade brain tumors 3D MR spectroscopy



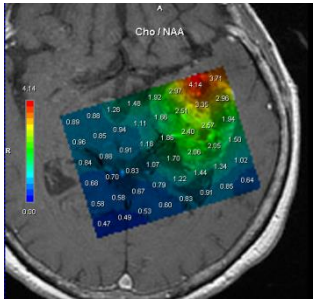




7 minutes exams added to standard MRI examination

MR spectroscopy and glioblastoma RT

MR Spectroscopy abnormality regions represent a minority of MRI anatomical abnormalities regions.



Predictive value of Cho/NAA >2 for the site of post RT relapse

Pirzkall et al, IJROBP 2004

Laprie et al, IJROBP 2008

Regions of radioresistance

Dose-increase guided by MR spectroscopy?

Prospective clinical trial SPECTRO-GLIO financed by French national Institute of Cancer

SPECTRO GLIO

Newly Diagnosed Glioblastoma

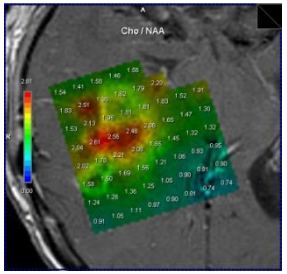
Prospective multicentric phase III trial- Coordination Anne Laprie

Promoted by Institut Claudius Regaud– financed by French national cancer institute

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

220 patients – 9 institutions

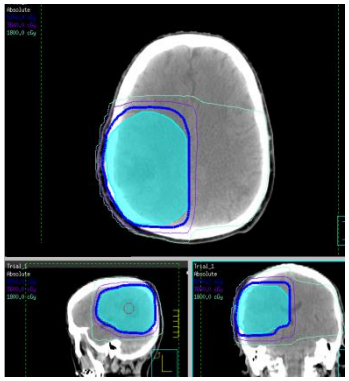
MRI T1, Flair, diff, Perf + spectro



Randomization

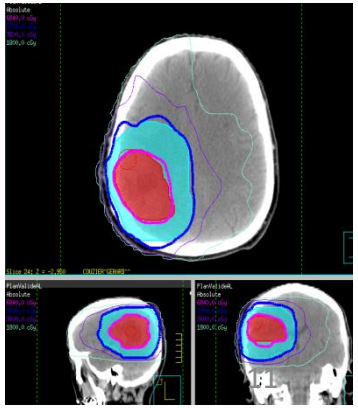
60 Gy + TMZ

60 Gy + TMZ + 72 Gy/2,4 Gy
IMRT SIB guided by MR spectroscopy



MRI T1, Flair, diff, Perf + spectro
/2months

Global survival



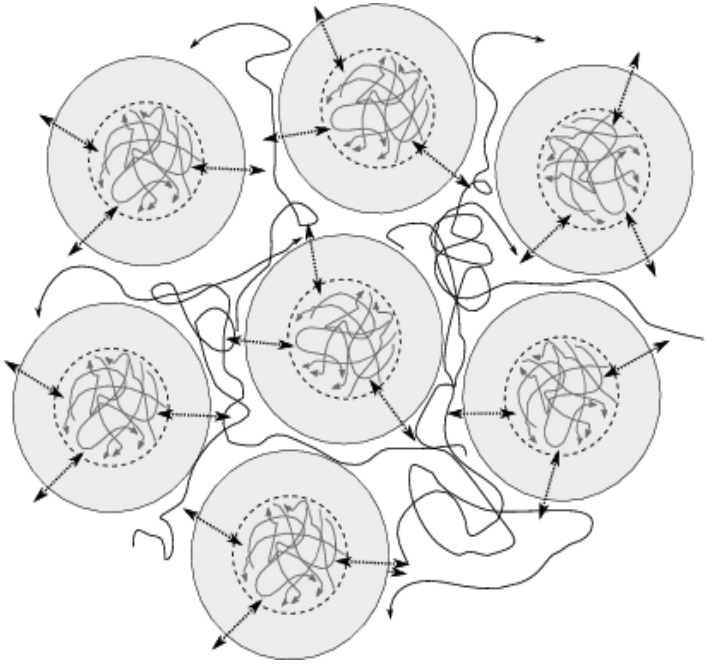
Three main MR metabolic and functional imaging modalities for High grade brain tumors

- MR spectroscopy
- Diffusion MRI
- Perfusion MRI

Diffusion weighted imaging

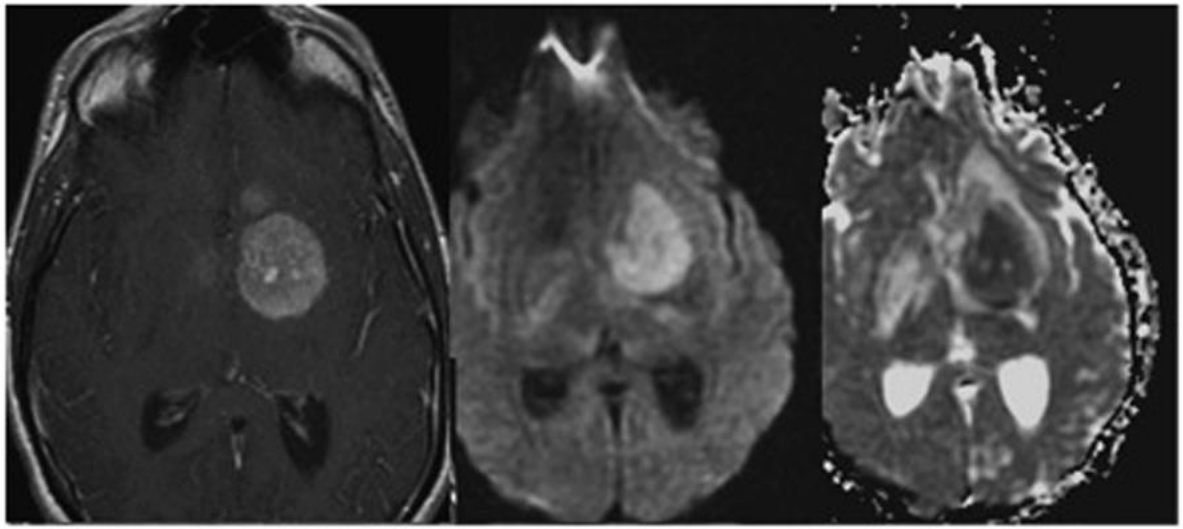
Diffusion-weighted imaging(DWI) characterizes tissues by probing differences in the random mobility of water molecules (brownian motion) related to tissue cellularity and cellular membrane integrity.

3 contributions to the diffusion signal :
intracellular diffusion,
extracellular diffusion
exchange between intracellular and extracellular space



Diffusion weighted MRI DWI

- DWI can generate apparent diffusion coefficient (ADC) maps which characterize the diffusion environnement on a voxelwise basis.
- Regions of diffusion restriction result from tumor hypercellularity : sequestration of fluid into the intracellular compartment and decreased extracellular space.
- Based on biopsys and resection sample : cellularity, nuclear-cytoplasmic ratio and tumor grade are inversely propotional to ADC.



T1 gado DW MRI ADC

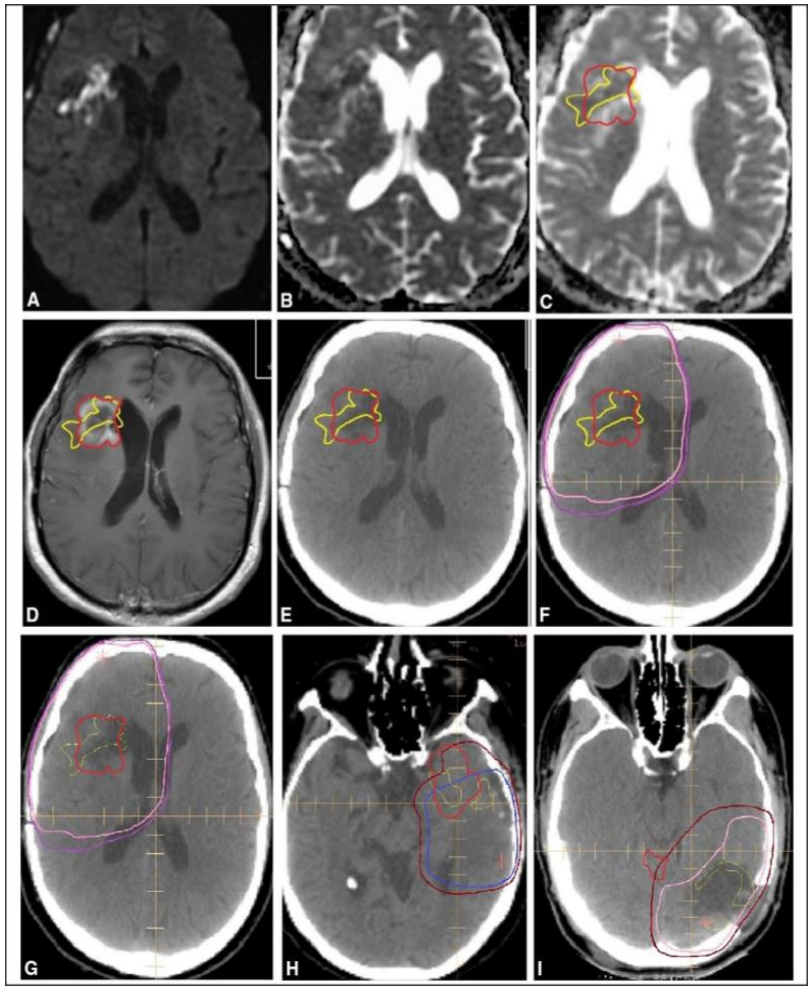
DWI and treatment response of GBM

- Most studies evaluate ADC values within regions of abnormal T2/FLAIR or contrast enhancmeent
  - Increase in normalized ADC post RT : consistent with treatment response *Li et al, neurooncol 2011*
  - Tumor progression exhibits lower ADC values post RT compared with stable disease *Lutz et al JMRI 2013*
  - ADC changes may have prognostic impliations in patients treated with bevacizumab (significant alterations in CE) *Pope AJN2011*

- Study in 27 patients of isolated ADC hypointensity without corresponding CE -> in 85% of the cases CE developed at the site of ADC hypointensity

Gupta et al AJN 2011

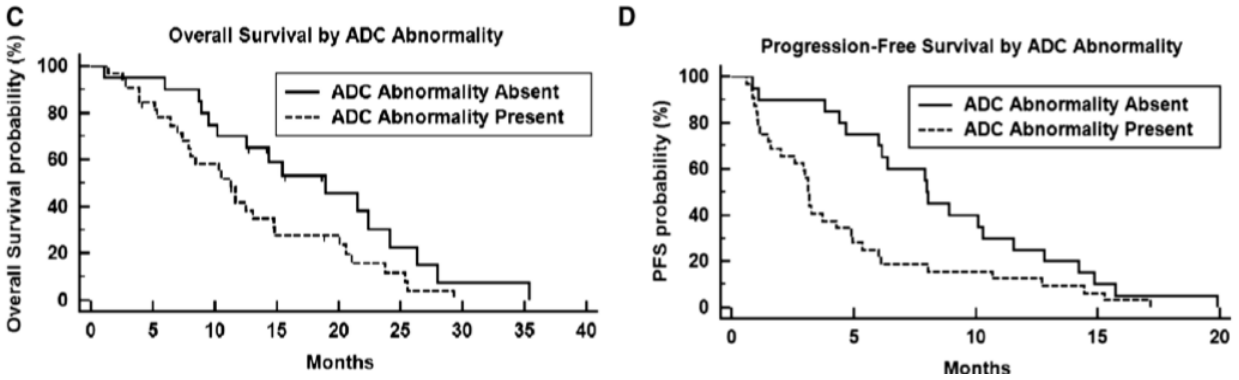
Predictive value of diffusion for relapse ?



- 52 patients
- Correlation of ADC with relapse site
- 32 patients exhibited ADC hypointensity outside of CE or resection cavity.
- Study of overlap of ADC hypointensity with CE at recurrence and correlation with RT dose.
- ADC abnormality=regions of DWI hyperintensity corresponding to an area of ADC hypointensity
- 84% relapse central, 13% marginal.

Elson et al, J neurooncol 2015

Predictive value of diffusion for relapse ?



- ADC abnormalities overlap with the eventual recurrence in 88 % of cases and the proportion of overlap is 60 %
- The ADC hypointensity itself volumetrically is much smaller than the recurrence volume
- Patients with a region of diffusion restriction exhibited a significantly reduced median progression free survival of 3.2 versus 8.0 months

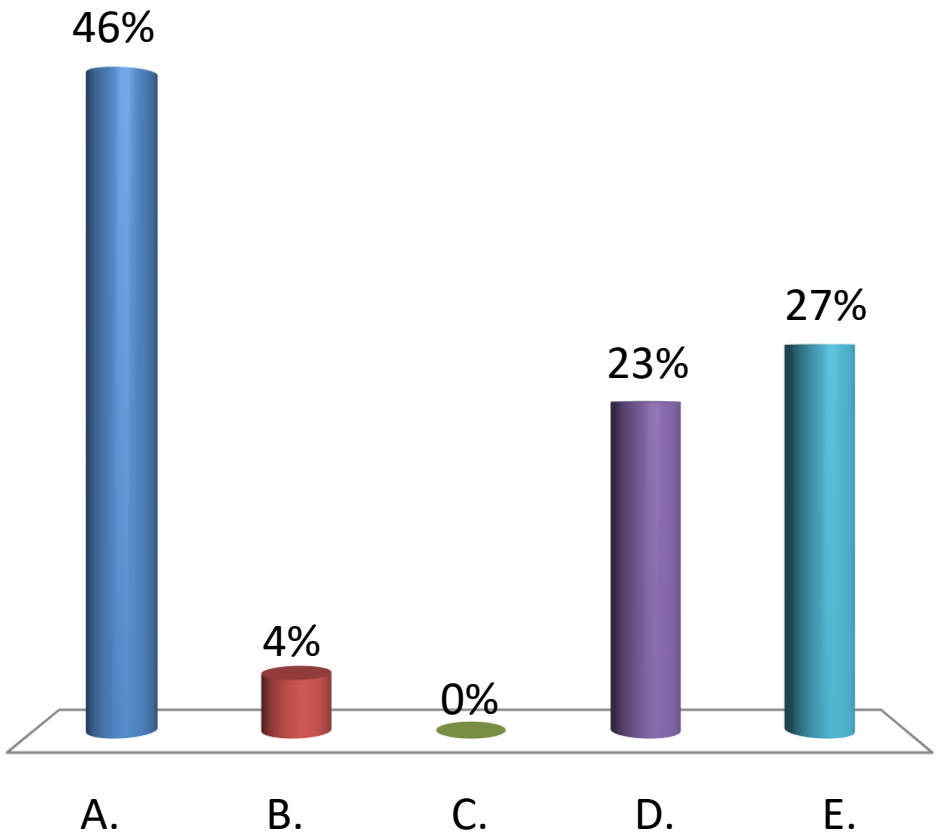
Elson et al, J neurooncol 2015

Three main MR metabolic and functional imaging modalities for High grade brain tumors

- MR spectroscopy
- Diffusion MRI
- Perfusion MRI

Question 2:Among perfusion imaging for brain tumors there is

A. 2 different techniques
B. There are all easy to implement and reproducible
C. They all take the same examination time
D. From Dynamic Susceptibility Contrast (DSC) imaging is obtained cerebral blood volume. (CBV)
E. From Dynamic contrast enhancement (DCE) technique is obtained K Trans.



Perfusion Weighted Imaging : *PWI : basic principles*

- Two major approaches 3 techniques
  - Gadolinium
    - DSC : dynamic susceptibility contrast imaging : CBV, CBF, TTM
    - DCE : dynamic contrast enhanced imaging : K trans
  - No gadolinium
    - ASL Arterial Spin Labelling imaging
- Use of perfusion MRI
  - Study tumor behavior
    - Vascular normalisation
    - Prediction for relapse ?

PWI : basic principles

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  - Gadolinium
    - **DSC : dynamic susceptibility contrast imaging : CBV, CBF, TTM**
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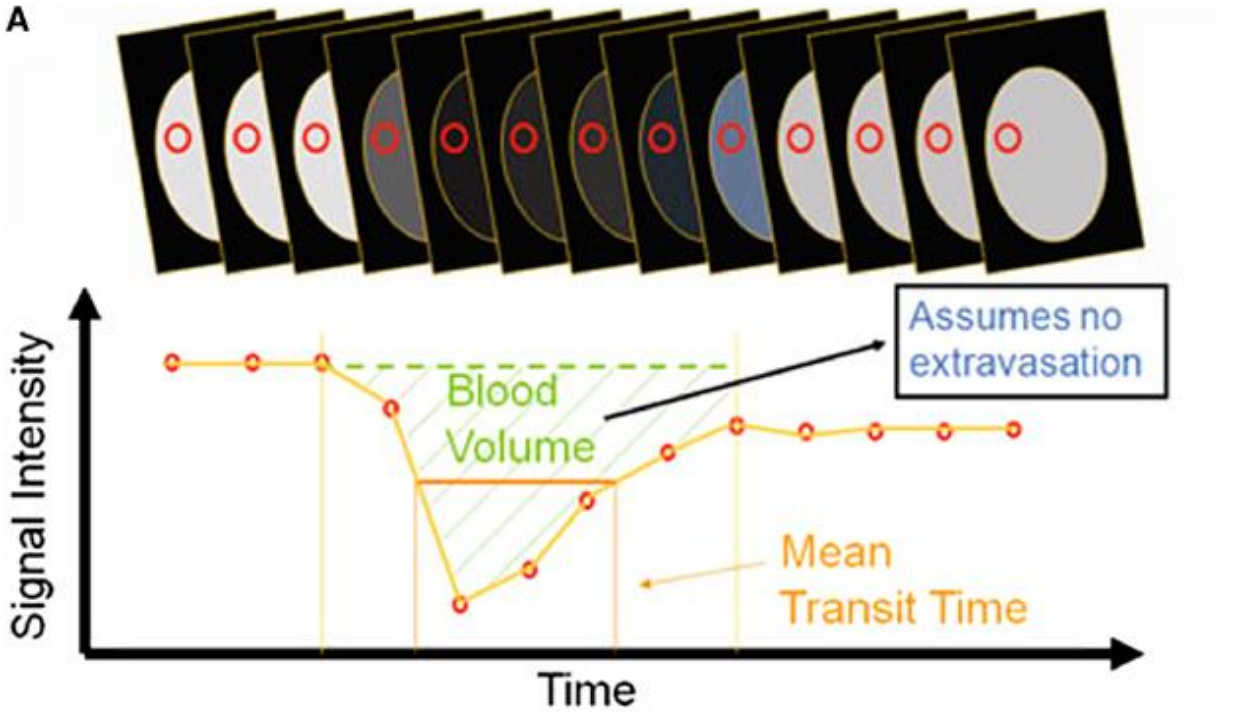
    - Vascular normalisation
    - Prediction for pseudoprogression

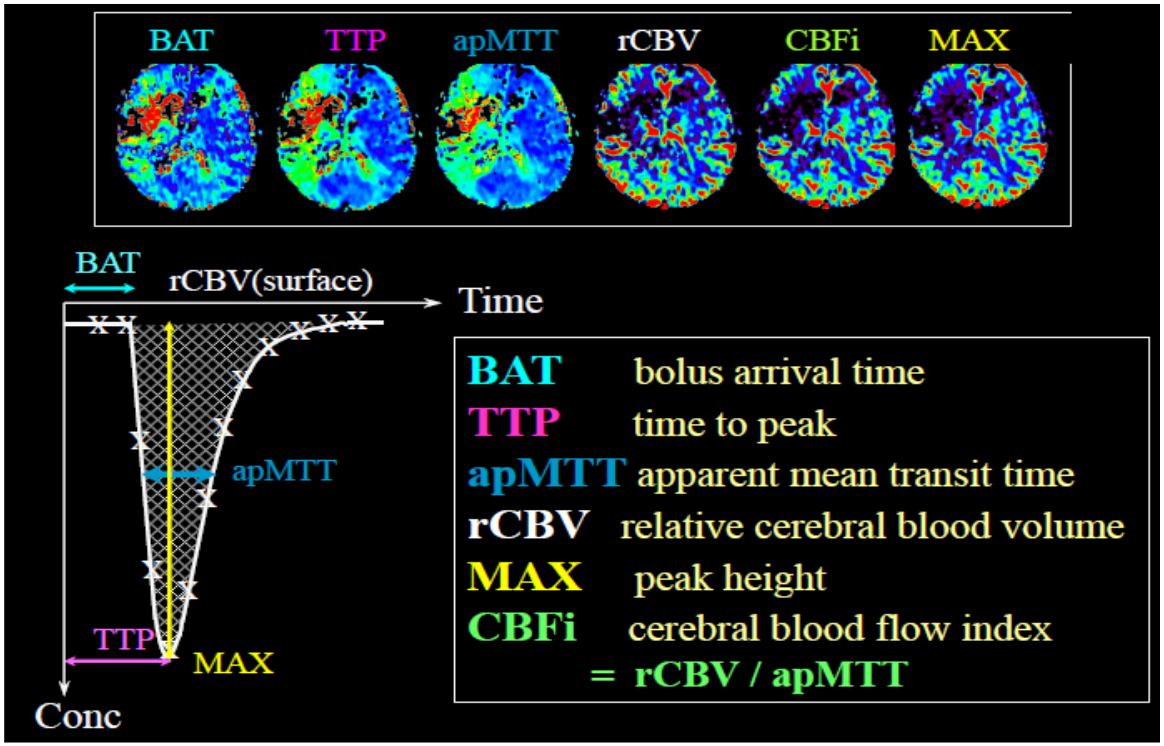
DSC MR perfusion, or bolus-tracking MRI or perfusion-weighted imaging, *PWI : basic principles*

- The first pass of a bolus of gadolinium-based contrast agent through brain tissue is monitored by a series of T2- or T2*-weighted MR images



PWI : basic principles

- From these data, parametric maps can be derived :
  - Cerebral blood **volume** (CBV) is the most widely used parameter



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    - ASL Arterial Spin Labelling imaging
- Use of perfusion MRI
  - Study tumor behavior
    - Vascular normalisation
    - Prediction for progression

DCE : dynamic contrast enhancement or permeability MRI

- **based on the acquisition of serial T1-weighted images before, during, and after administration of gadolinium-based contrast agent.**
- **DCE MR perfusion imaging depicts the wash-in, plateau, and washout contrast kinetics of the tissue → insight into the nature of the bulk tissue properties at the microvascular level.**
- **Most often, DCE MR perfusion imaging is based on a two-compartmental (plasma space and extravascular-extracellular space) pharmacokinetic model.**
- **The general steps are (in order):**
  - **perform baseline T1 mapping,**
  - **acquire DCE MR perfusion images,**
  - **convert signal intensity data to gadolinium concentration,**
  - **determine the vascular input function, and perform pharmacokinetic modeling.**
- **The most frequently used metric in DCE MR perfusion is k trans . It can have different interpretations depending on blood flow and permeability.**

PWI : basic principles

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- Use of perfusion MRI
  - Study tumor behavior
    - Vascular normalisation
    - Prediction for progression

ASL Arterial Spin-labelling

- ASL is a perfusion method that uses magnetically labeled blood as an endogenous tracer.
- two main types of ASL technique:
  - continuous ASL

  prolonged radiofrequency pulse that continuously labels arterial blood water below the imaging slab until a steady state of tissue magnetization is reached
  - pulsed ASL

Comparison of perfusion techniques

- **DSC**
  - **Advantages :**
    - **the most widely used method to measure brain perfusion with MRI.**
    - **The software to postprocess these data is widely available and relatively straightforward to use.**
    - **DSC-derived relative CBV is the most widely used and robust method to evaluate brain tumors.**
    - **High SNR : whole brain < 1mn**
  - **disadvantages**
    - **difficulty in determining absolute quantification,**
    - **susceptibility artifacts (i.e., blood product, calcification, metal, air, and bone)**
- **DCE**
- **ASL**

Comparison of perfusion techniques

- **DSC**
- **DCE**
  - **Advantages :**
    - **ability to examine the brain microvasculature ≠ from DSC**
    - **quantitative assessment of the blood-brain barrier and microvascular permeability.**
    - **more complete assessment of brain tumor angiogenesis.**
    - **High SNR**
  - **Disadvantages**
    - **complexity in image acquisition and pharmacokinetic model postprocessing,**
    - **user-dependence,**
    - **lack of widely available and easy-to-use postprocessing software.**
- **ASL**

Comparison of perfusion techniques

- **DCE**
- **DSC**
- **ASL**
  - **Advantages**
    - **No CE**
  - **Disadvantages**
    - **overall SNR is still limited,→ much longer scanning times, e.g., 8–10 minutes at 1.5 T or 4–5 minutes at 3 T. →sensitivity to potential motion artifacts,.**

Limits to perfusion implementation

- Lack of awareness of physicians
- Lack of standardized and optimized perfusion MRI protocols
- Lack of simple and standardized perfusion postprocessing softwares and lack of straight forward guidelines on how to interpret the results
- Lack of reimbursement
- Most used technique for high-grade brain tumors is DSC → CBV

PWI : basic principles

- Two major approaches
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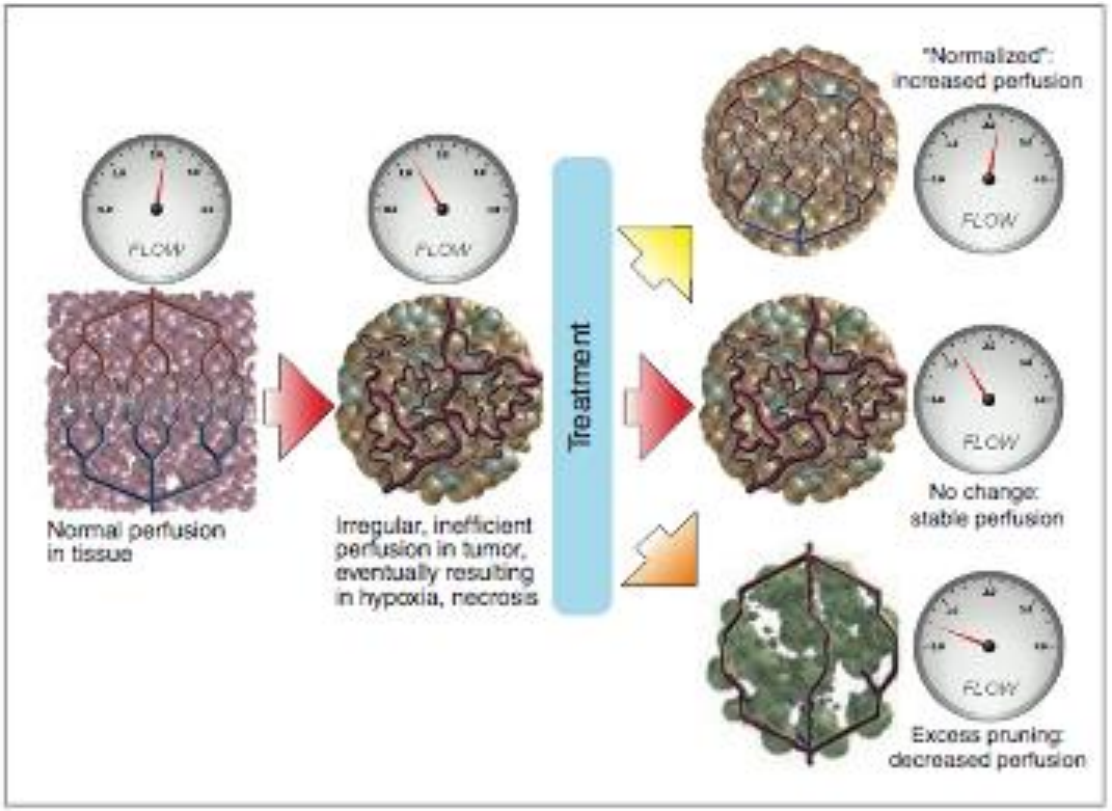
- Use of perfusion MRI
  - Study tumor behavior
    - Vascular normalisation
    - Prediction for pseudoprogression

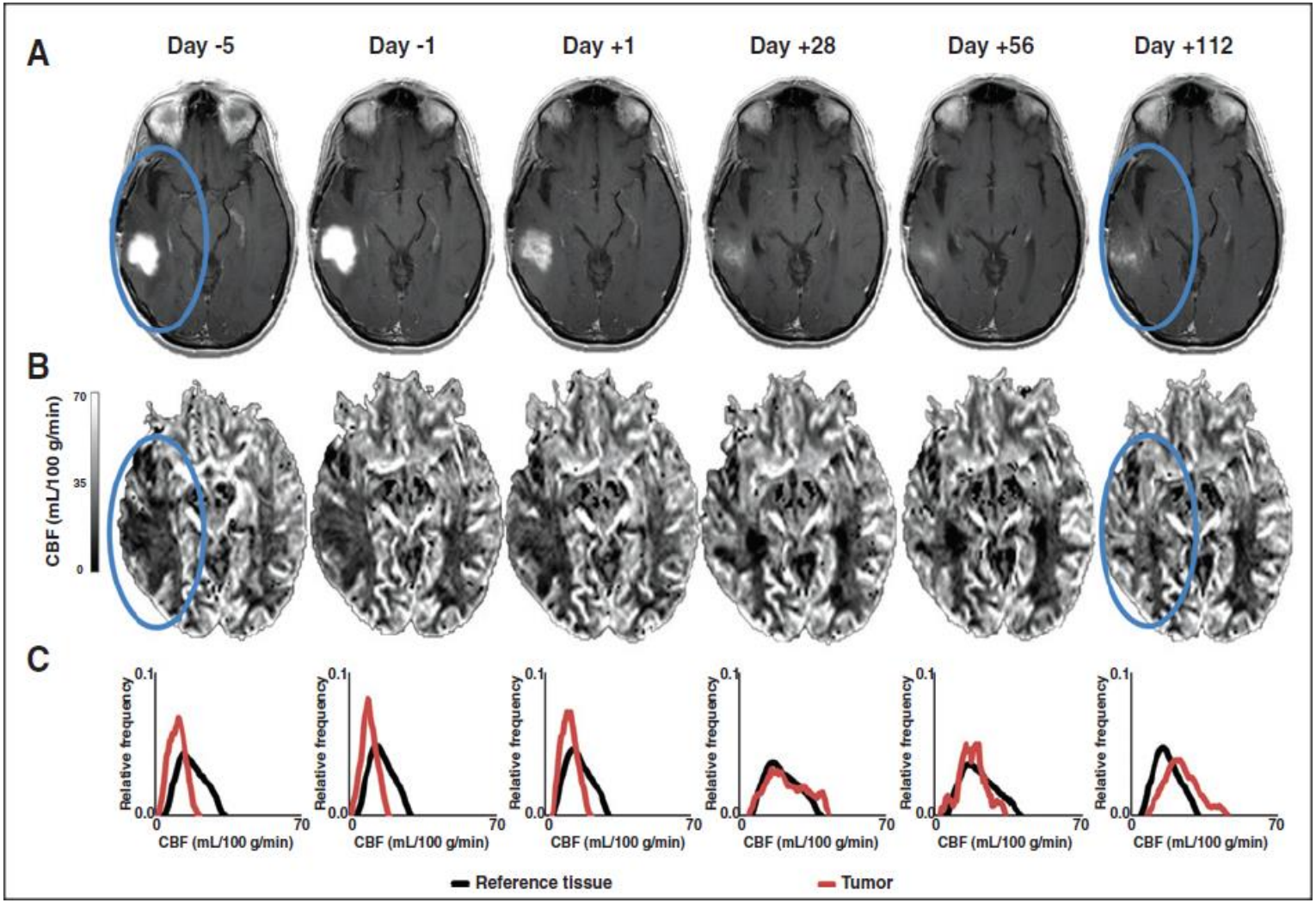
Hypothesis of vascular normalization

- Main studies for MRI perfusion



Jain et al, Nat Med 2001
Sorensen et al, Cancer Research 2011

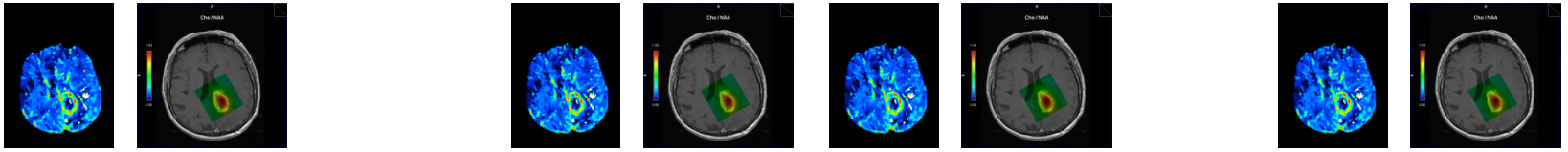
Normalization with bevacizumab in relapsing patients



Sorensen Cancer Res 2011

DSC predictive value for response to treatment ? Data from a prospective trial on newly diagnosed GBM

23 2D- spectros , 1207 voxels



Biopsy or surgery

RT+Tipifanib

2mois

4mois

Relapse

MRI + DSC

MRI + DSC

MRI + DSC

MRI + DSC

Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–6, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.02.043

CLINICAL INVESTIGATION

PHASE I TRIAL OF TIPIFARNIB (R115777) CONCURRENT WITH RADIOTHERAPY IN PATIENTS WITH GLIOBLASTOMA MULTIFORME

Elizabeth Cohen-Jonathan Moyal, M.D., Ph.D.,*† Anne Laprie, M.D.,* Martine Delannes, M.D.,* Muriel Poublanc,‡ Isabelle Catalaa, M.D., Ph.D.,§ Florence Dalenc, M.D., Ph.D.,‖ Delphine Berchery, M.D.,¶ Jean Sabatier, M.D., Ph.D.,# Philippe Bousquet, M.D.,# Peter De Porre, M.D.,** Béatrice Alaux, M.D.,‡ and Christine Toulas, Ph.D.†

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 773–781, 2008

0360-3016/08/$–see front matter

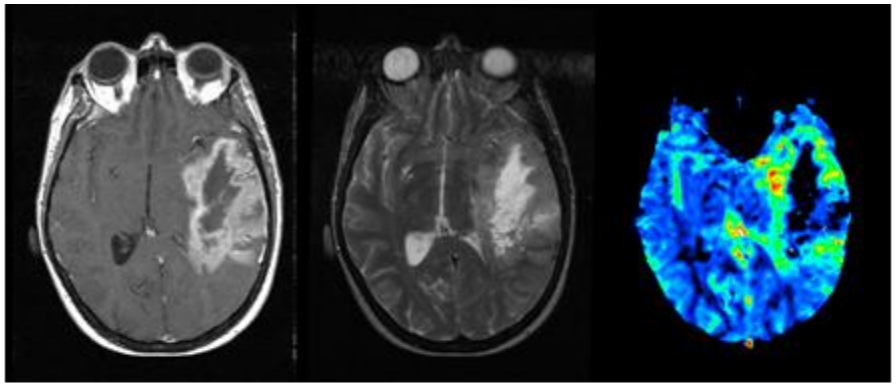
ELSEVIER

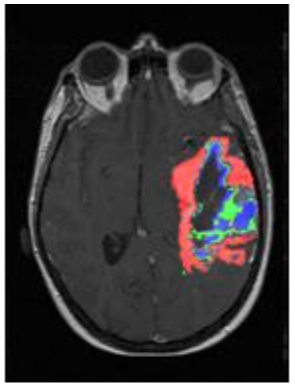
doi:10.1016/j.ijrobp.2007.10.039

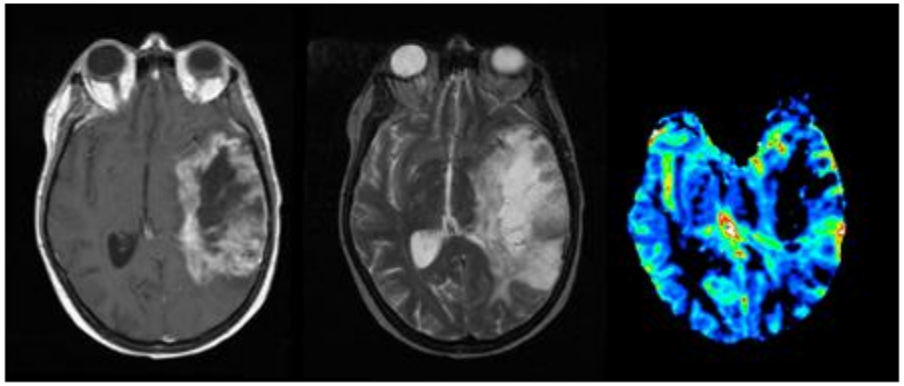
CLINICAL INVESTIGATION **Brain**

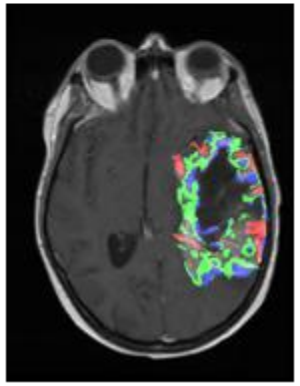
PROTON MAGNETIC RESONANCE SPECTROSCOPIC IMAGING IN NEWLY DIAGNOSED GLIOBLASTOMA: PREDICTIVE VALUE FOR THE SITE OF POSTRADIOTHERAPY RELAPSE IN A PROSPECTIVE LONGITUDINAL STUDY

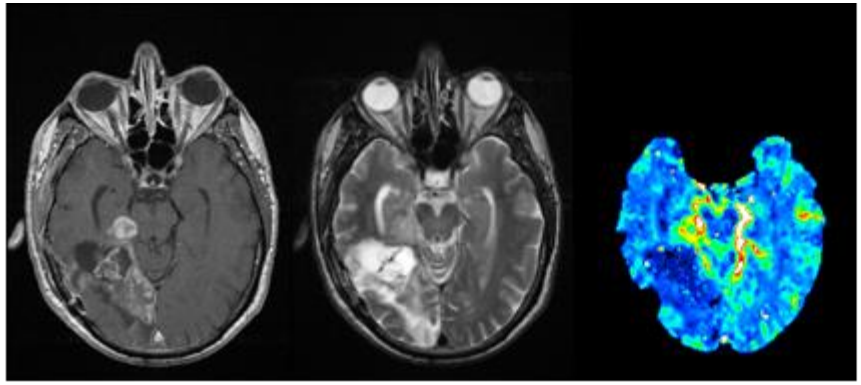
Anne Laprie, M.D., Ph.D,*† Isabelle Catalaa, M.D., Ph.D,†§ Emmanuelle Cassol, Ph.D.,† Tracy R. McKnight, Ph.D.,¶ Delphine Berchery, M.D.,‖ Delphine Marre, Ph.D.,* Jean-Marc Bachaud, M.D.,* Isabelle Berry, M.D., Ph.D,† and Elizabeth Cohen-Jonathan Moyal, M.D., Ph.D*‡

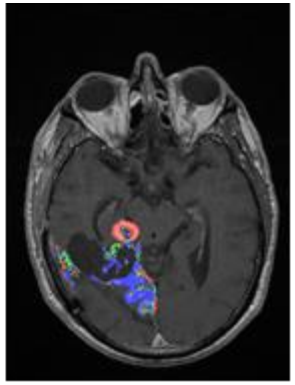


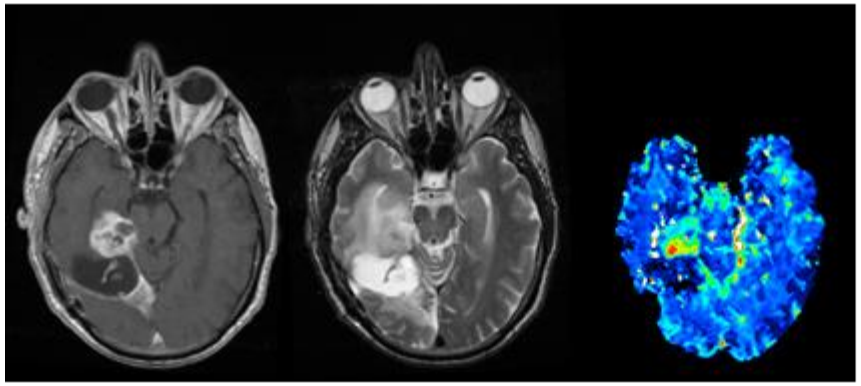


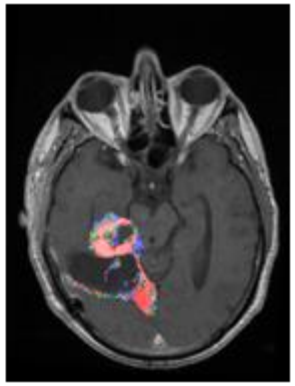












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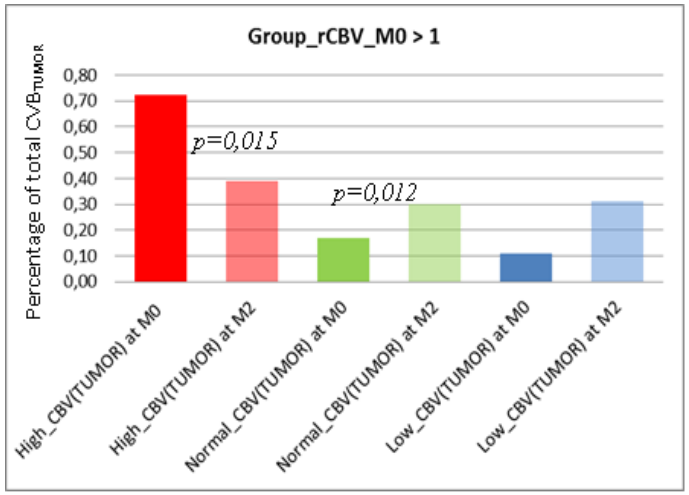
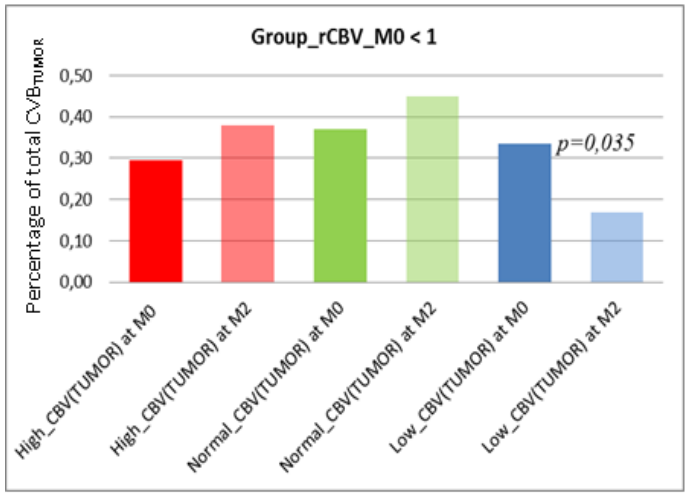
Results





Pre and post-treatment CBV measurements with DSC-MRI characterized tumor perfusion variations in favour of normalization

(in agreement with our pre-clinical results of vascular normalization).

Ken et al, J Neurooncol 2015

Perfusion and diffusion data from the ongoing Spectro Glio Trial

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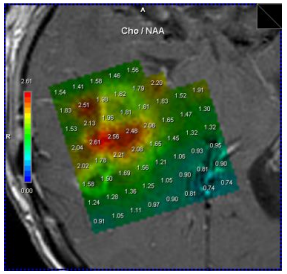
220 patients – 9 institutions

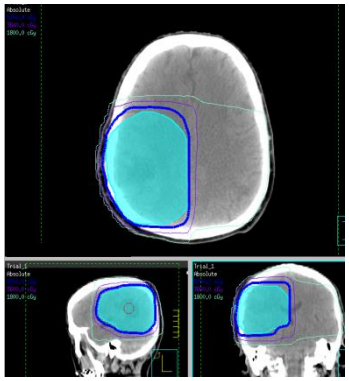


MRI T1, Flair, diff, Perf + spectro

Randomization

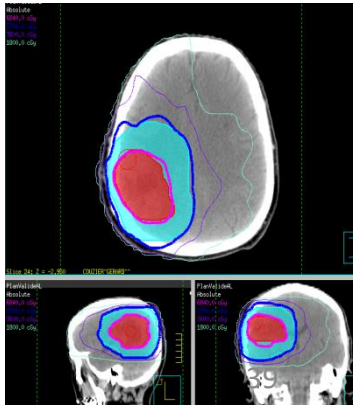
60 Gy + TMZ

60 Gy + TMZ + 72 Gy/2,4 Gy
IMRT SIB guided by MR spectroscopy



MRI T1, Flair, diff, Perf + spectro
/2months

Global survival



PWI : basic principles

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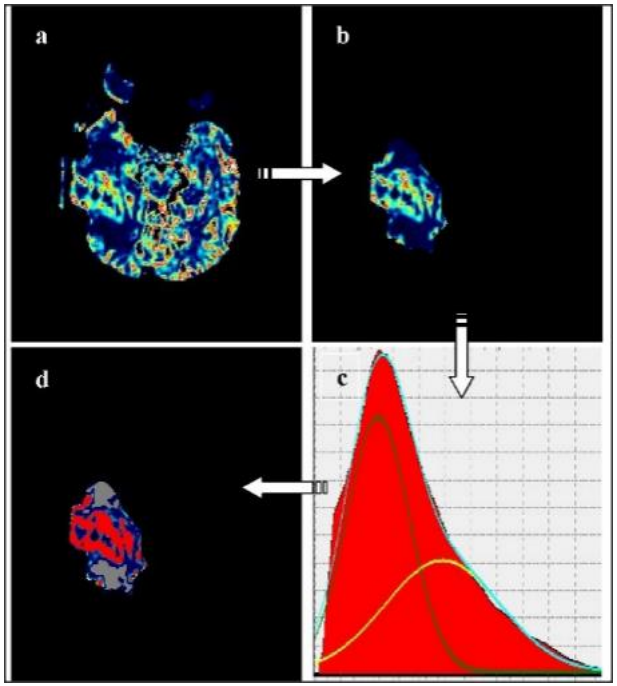
    - Prediction for progression? Anticipation or site ?

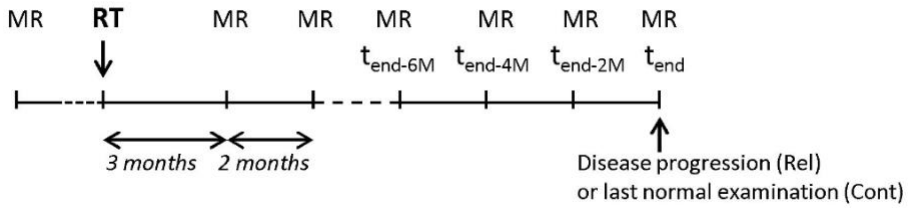
Identification of a MRI perfusion biomarker to anticipate progression of glioblastoma after radio-chemotherapy

- **25 patients of spectro glio trial , follow up** > 6 months
- Analysis of 11 perfusion biomarkers

2 months , 4 months and 6 months before the last MR acquisition with confirmed disease status were analyzed, with a total of 100 scans analyzed



Khalifa et al, Eur J Radiology 2016

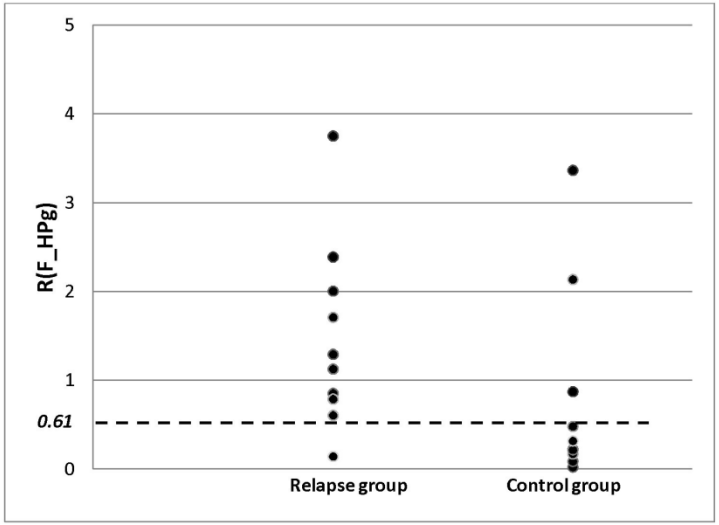


Identification of a MRI perfusion biomarker to anticipate progression of glioblastoma after radio-chemotherapy

- **25 patients of spectro glio trial , follow up** > 6 months
- Analysis of 11 perfusion biomarkers

- **The fraction of hypoperfused tumoral volume** ≥ 0.61 could anticipate relapse at the following scan with sensibility/specificity of 92.3%/63.6%

- In the group >0,61 , 75% relapses vs 12.5%, p = 0.008.



Khalifa et al, Eur J Radiology 2016

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PWI : predictive value for sites of relapse

Do perfusion and diffusion MRI predict glioblastoma relapse sites following chemoradiation?

Jonathan Khalifa[1,2] · Fatima Tensaouti[1] · Jean-Albert Lotterie[1,3] · Isabelle Catalaa[1,4] · Leonor Chaltiel[5] · Alexandra Benouaich-Amiel[6] · Carlos Gomez-Roca[7] · Georges Noël[8] · Gilles Truc[9] · Patrice Péran[1,10] · Isabelle Berry[1,3,10] · Marie-Pierre Sunyach[11] · Marie Charissoux[12] · Corinne Johnson[13] · Elizabeth Cohen-Jonathan Moyal[2,14,15] · Anne Laprie[1,2,14]

TONIC TOULOUSE NEURO IMAGING CENTER

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

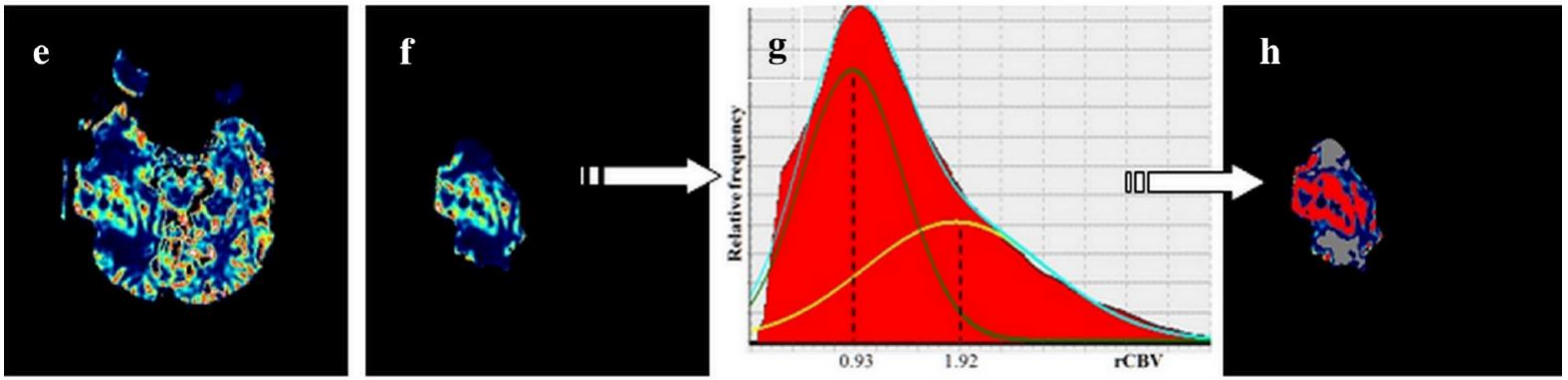
UNIVERSITÉ TOULOUSE III PAUL SABATIER Université de Toulouse

- **44 patients from Spectroglio trial : arm A (standard treatment)**
- **15 relapses assessed**
- **Voxels within sites of relapse (SR) correlated to their pre-RT perfusion and/or diffusion abnormality (PDA) :**
  - PWI : rCBV
  - DWI : ADC

Khalifa et al,, J neuro oncol 2016

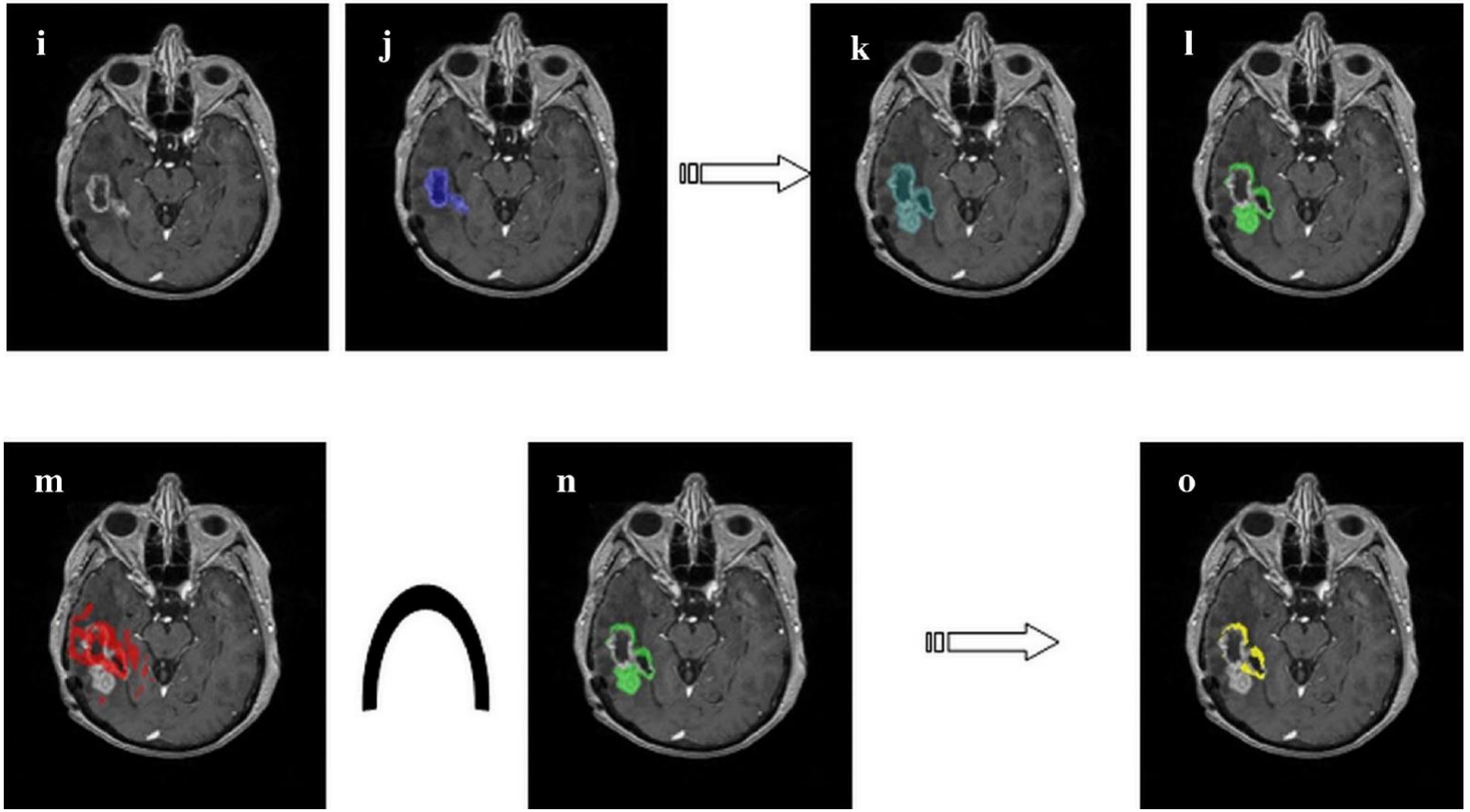
PWI : predictive value for sites of relapse

- **Several PDA thresholding methods :**
  - HPt : hyperperfused voxels using a 1.75 fixed threshold
  - hPg and HPg : hypoperfused and hyperfused voxels using a histogram-based Gaussian method
  - DRg : diffusion-restricted method using a histogram based method
  - HPg&DRg : HPg voxels with diffusion restrictioin



Khalifa et al, J NeuroOncol 2016

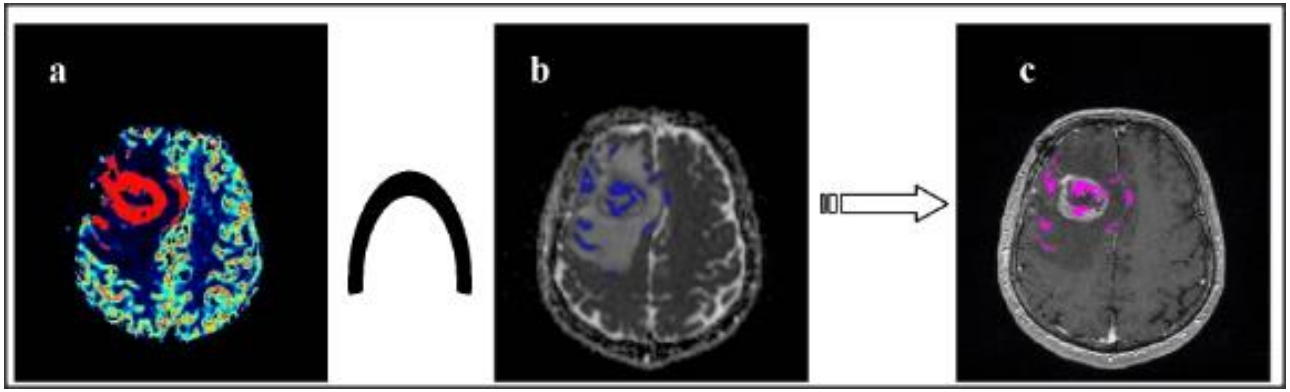
PWI : predictive value for sites of relapse

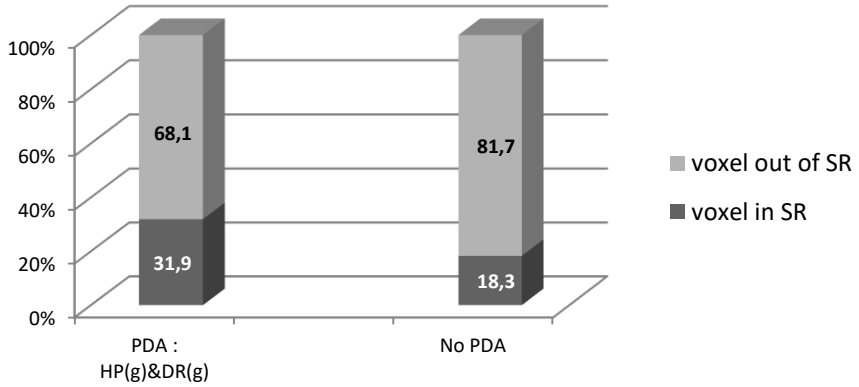


Khalifa et al, J NeuroOncol 2016

PWI : predictive value for sites of relapse

Best results obtained with HPg&DRg voxels : PPV = 31.9%...but <50%!





No local predictive value of diffusion and perfusion for the site of relapse after radio-chemotherapy

Khalifa et al, J NeuroOncol 2016

Question 2: Among perfusion imaging for brain tumors there is

A. 2 different techniques
B. There are all easy to implement and reproducible
C. They all take the same examination time
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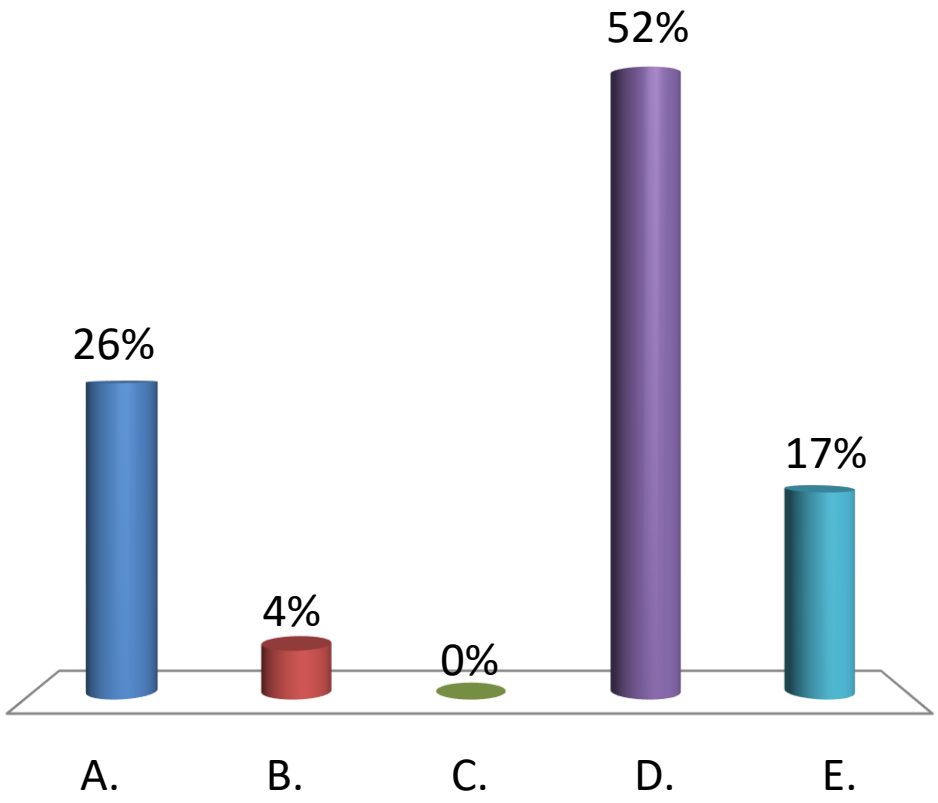


Three main MR metabolic and functional imaging modalities for High grade brain tumors

- MR spectroscopy
- Diffusion MRI
- Perfusion MRI (DSC being the most robust)

Role of imaging in pseudoprogression ?

Question 3: Pseudoprogression

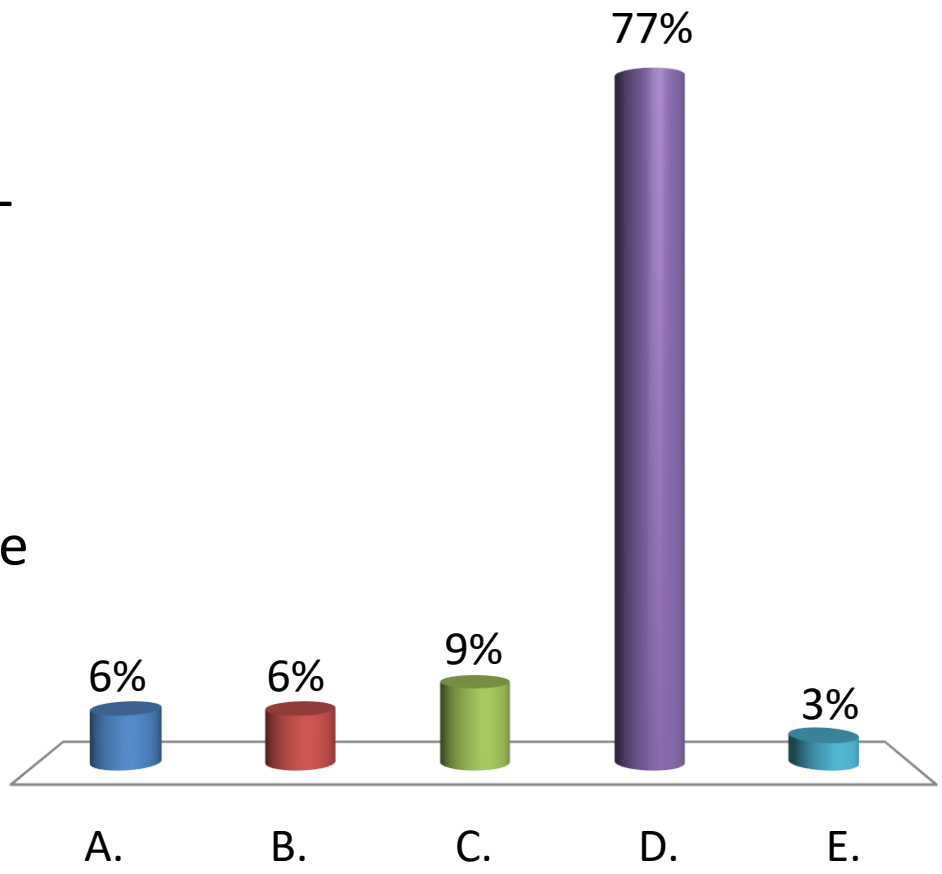
A. Occurs in Glioblastoma after concomittant RT-TMZ in 5% of patients

B. It occurs at 5 months after RT

C. Is more frequent in patients sensitive to TMZ

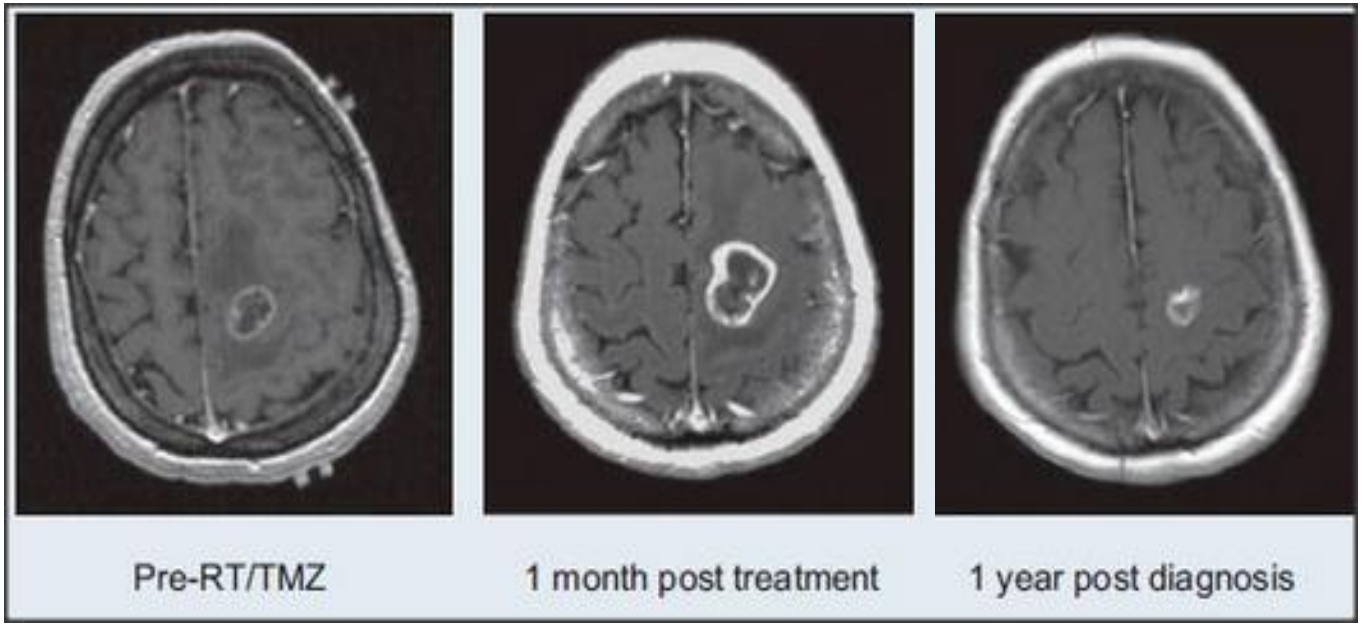
D. Molecular and functional imaging can help differenciate true progression from pseudoprogression

E. It has on impact on response to clinical trials



Pseudoprogression after RT in High Grade Glioma

- Transient worsening
- RT alone : 10% of patients.
- RT + Temozolomide : 20%–30% of patients.



The role of imaging in the management of progressive glioblastoma : a systematic review and evidence-based clinical practice guideline

Which imaging techniques most accurately differentiate true tumor progression from pseudo-progression or treatment related changes in patients with previously diagnosed glioblastoma? Ryken et al, J Neuro Oncol 2014

RECOMMENDATIONS LEVEL II:

Magnetic resonance imaging with and without gadolinium enhancement is recommended as the imaging surveillance method to detect the progression of previously diagnosed glioblastoma.

LEVEL II:

Magnetic resonance spectroscopy is recommended as a diagnostic method to differentiate true tumor progression from treatment-related imaging changes or pseudo-progression in patients with suspected progressive glioblastoma.

LEVEL III:

The routine use of positron emission tomography to identify progression of glioblastoma is not recommended.

LEVEL III:

Single-photon emission computed tomography imaging is recommended as a diagnostic method to differentiate true tumorprogression from treatment-related imaging changes or pseudo-progression in patients with suspected progressive glioblastoma.

IN DOUBT IN THE FIRST 4 MONTHS, A NEW MRI MUST BE REPEATED ONE MONTHS LATER

Question 3

- Pseudoprogression
  A. Occurs in Glioblastoma after concomittant RT-TMZ in 5% of patients
  B. It occurs at 5 months after RT
  C. Is more frequent in patients sensitive to TMZ
  D. Molecular and functional imaging can help differenciate true progression from pseudoprogression
  E. It has on impact on response to clinical trials

  – Answer C, D, E

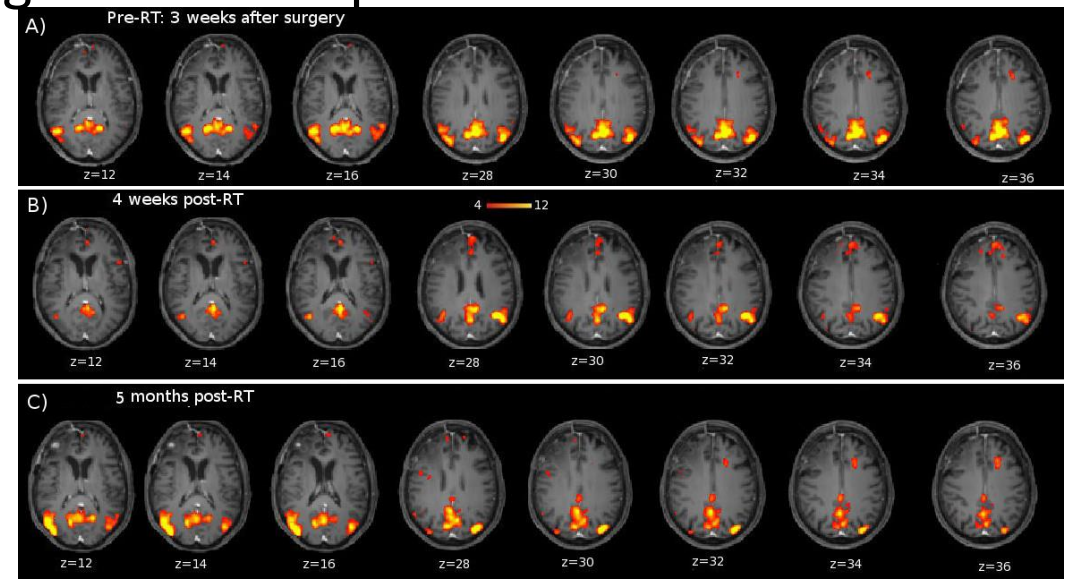
Activation MRI (or functional MRI fMRI) and Glioblastoma RT

- Guiding one day balistic choices in order to avoir the most active regions ?

Functional MRI and Glioblastoma RT ? Guiding one day balistic choices through the less active regions ?

- acquired longitudinal (pre- and post-radiotherapy) resting-state functional magnetic resonance imaging on three selected glioblastoma patients

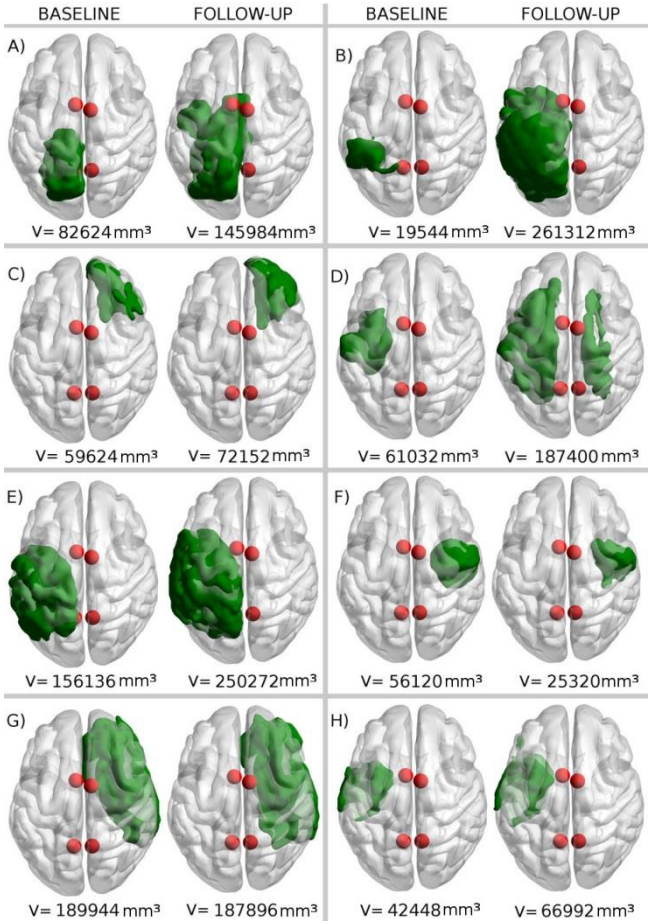
NEW

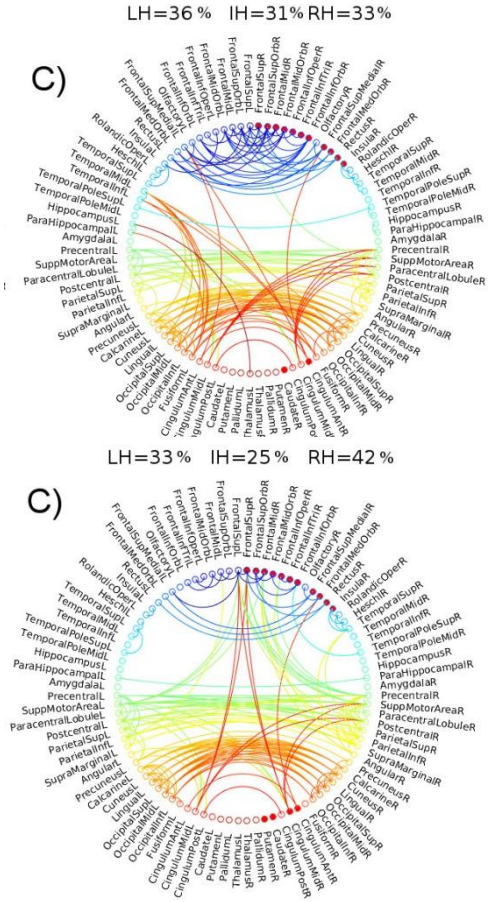


- Transient effects of lesion location on the functional architecture at rest in glioblastoma patients

Tuovinen et al, Radiation Oncology 2016

Functional MRI and Glioblastoma RT ? Guiding one day balistic choices through the less active regions ?





Tuovinen et al, submitted 2017

Question 1

- Imaging for glioblastoma RT
  A. T1 gadolinium and FLAIR should be systematically used to define GTV and CTV.
  B. Perfusion and diffusion sequences provide reliable and reproducible abnormalities map that can be coregistered with planning CT
  C. Spectroscopy , diffusion and perfusion should be used routinely to define target volumes.
  D. Only did MR spectroscopic imaging provide predictive value for the site of relapse

  Answer : AD

Let’s go back to dose painting

Take home message

- Validated metabolic MR imaging for a further dose-painting trial
  - MRSI ✓
  - *DWI : no convincing evidence*
  - *PWI : no convincing evidence*

  Use of fMRI for balistic choices ? work in progress

- **Next step to implement these modalities in the treatment process**
  - Identify a reprodictive BTV based upon the metabolic imaging
  - Dosimetric studies of dose-escalation
  - Clinical trials of dose escalation !

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Radiotherapy Treatment Planning of Brain Tumors with the Guidance of PET

Anca-Ligia Grosu, Ursula Nestle, Oliver Oehlke

Department of Radiation Oncology
University of Freiburg
Germany

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Objectives
Gliomas, Meningiomas

- **Clinical Problem**
- **IMT-SPECT**
- **MET-PET**
- **FET-PET**

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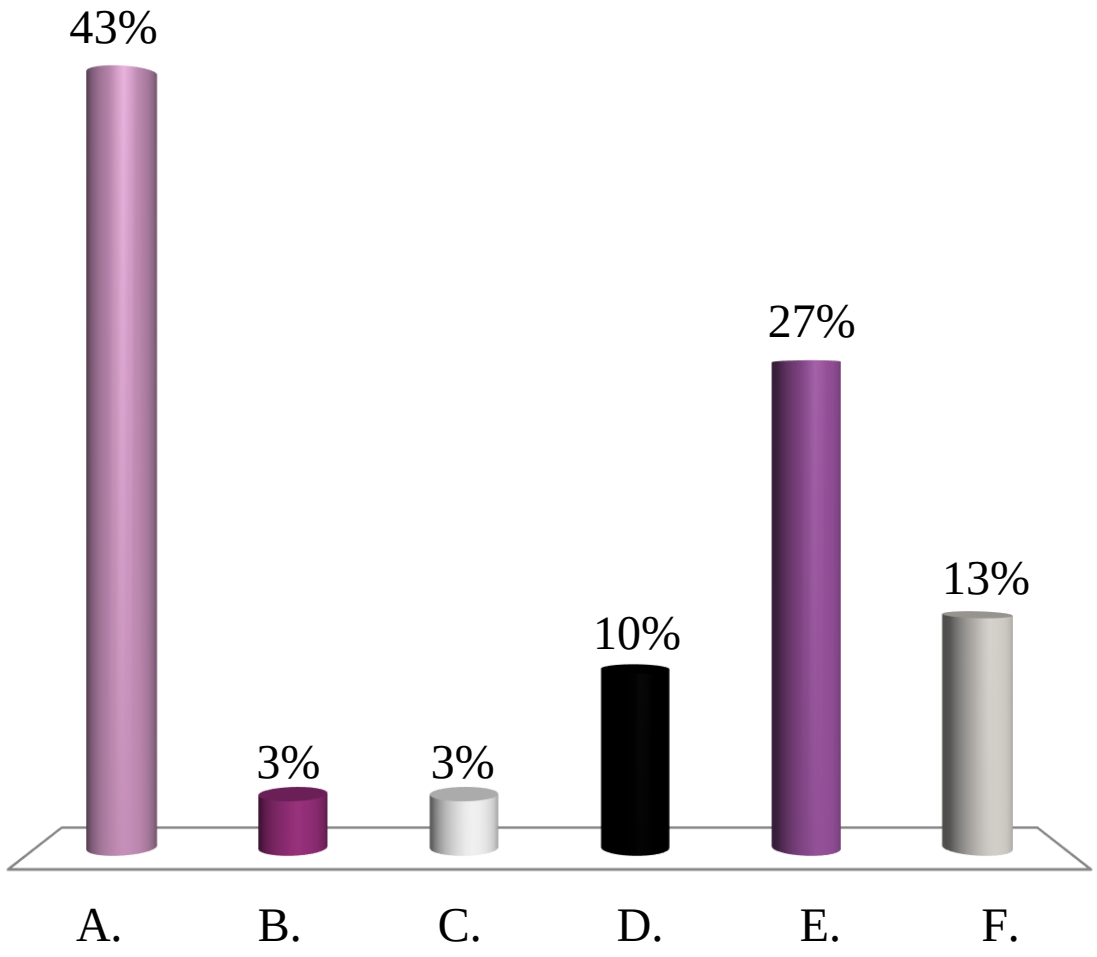
CLINICAL PROBLEM

Limitation of CT and MRI

- Contrast enhancement on CT and MRI and hyperintensity areas MRI are not always real measures of tumor extension. Tumor cells are detected beyond the margins of contrast enhancement, in the surrounding edema, and even in the adjacent normal-appearing tissue.
- After treatment, contrast enhancement and edema can be treatment related and cannot be differentiated from persistent tumor on CT or MRI.
- (Traditional) CT and MRI give no information about the biological properties of the tumor.

In your practice, do you use molecular imaging for brain tumors?

A. No, not available
B. No, don‘t think PET is of help in brain tumors
C. Yes, SPECT Imaging
D. Yes, FDG PET
E. Yes, PET imaging with amino acids (FET, MET, DOPA)
F. Yes: several of the above



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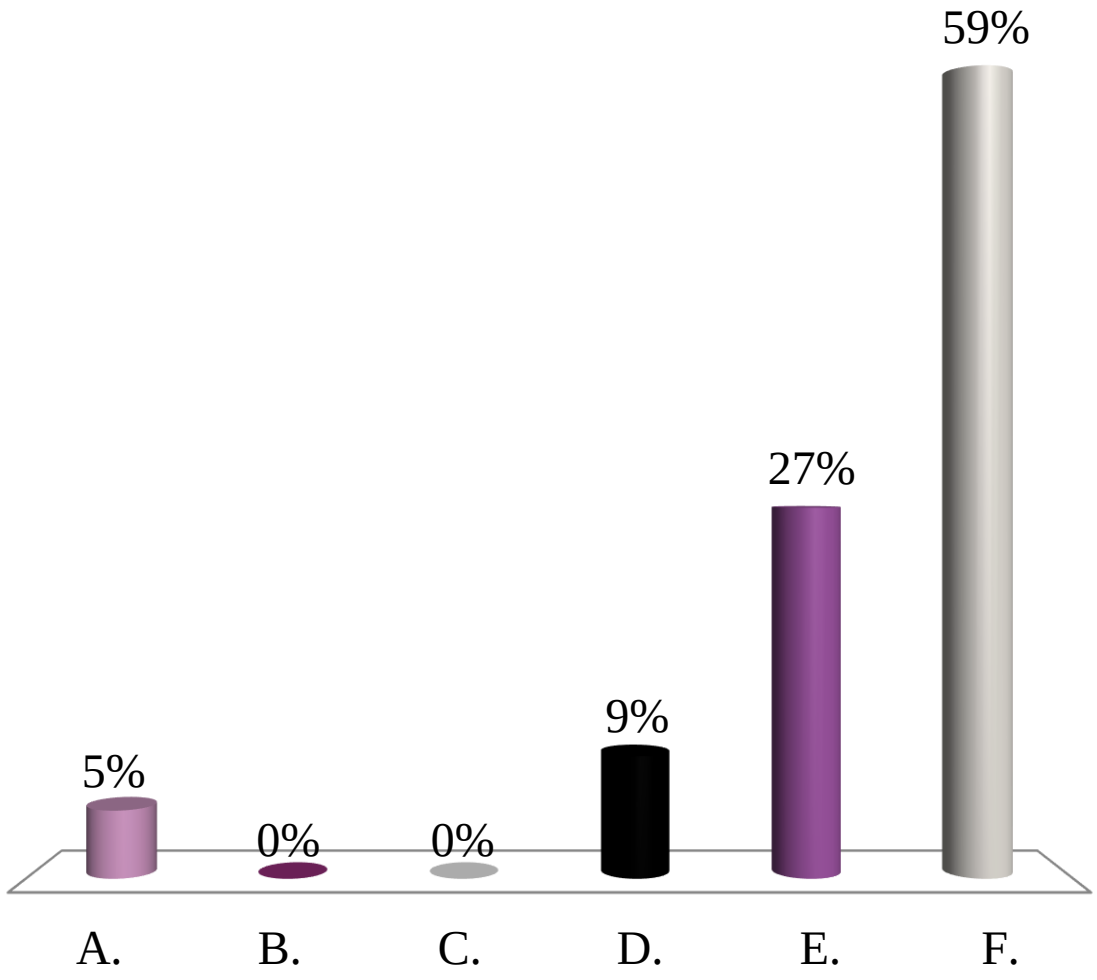
When you use PET for radiotherapy of brain tumors: when?

A. For diagnosis of primary glioma
B. For diagnosis of recurrent glioma
C. for grading of Glioma
D. For RT treatment planning (primary and/or recurrent glioma)
E. For diagnosis of recurrence vs. radionecrosis
F. Yes: several of the above



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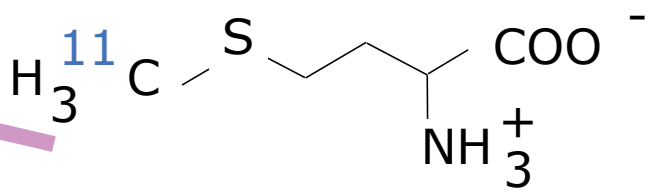
Amino-Acid PET/SPECT in brain tumors

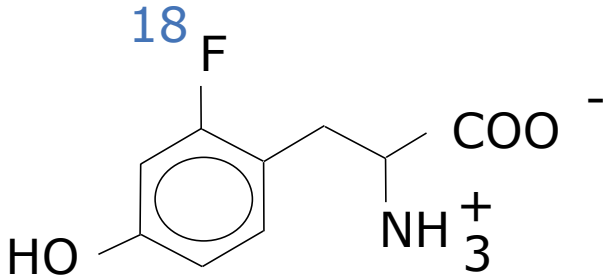
I-123-alpha-Methyl-Tyrosine (IMT) –SPECT

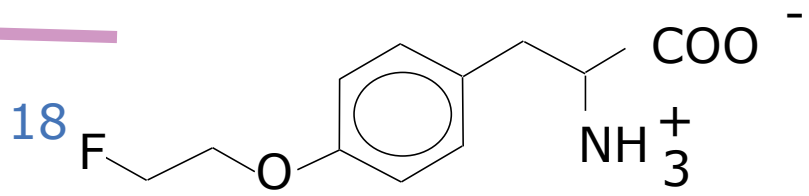
C11-Methionine (MET) - PET

F18-Ethyl-Tyrosine (FET) - PET

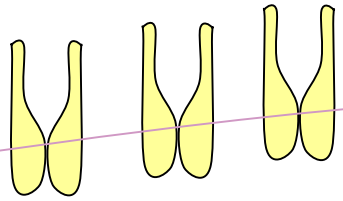
[^{11}C]Methionine / [^{18}F]F-Ethyl-Tyrosine







L and A Amino Acid Transporters



Tumor cell

Transferase
Protein Degradation

X

Protein Synthesis

Proteins

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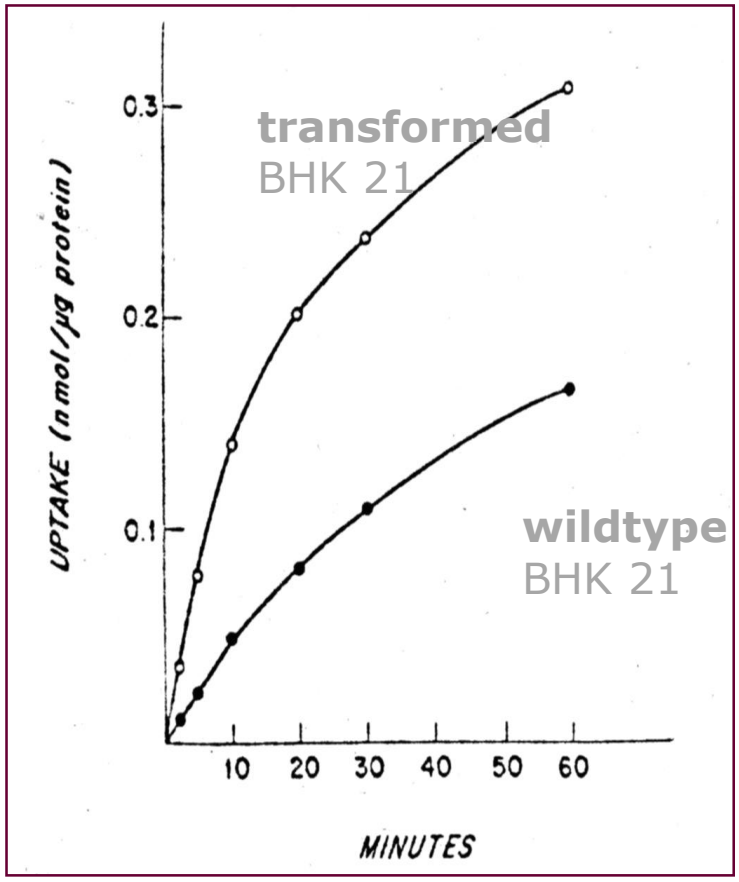
Rationale for Using Amino Acids-PET/SPECT for Tumor Tissue Detection in Gliomas



Accumulation of alpha-amino-isobutyrat (AIB) in-vitro

- High uptake in tumor cells mediated by the L-/A-amino acid transport.
- Amino acids not taken up by normal cortical gray matter.
- Good target-to-background contrast, allowing better characterization and differentiation of tumor from normal cortical tissue.

(Ishiwata 1993; Kanai 1998)

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Amino Acid Imaging (MET/FET)

Principle:

Binding reflects amino acid (i.e. methionine) transport

Disadvantages:

- Limited usefulness outside brain
- Fusion with MRI/CT mandatory
- Very limited availability ([^{11}C]methionine)

Advantages:

- High tumor/background ratio (in brain)
- Independent from BBB disturbance
- Relatively specific for malignancies
- [^{123}I]-IMT SPECT widely available

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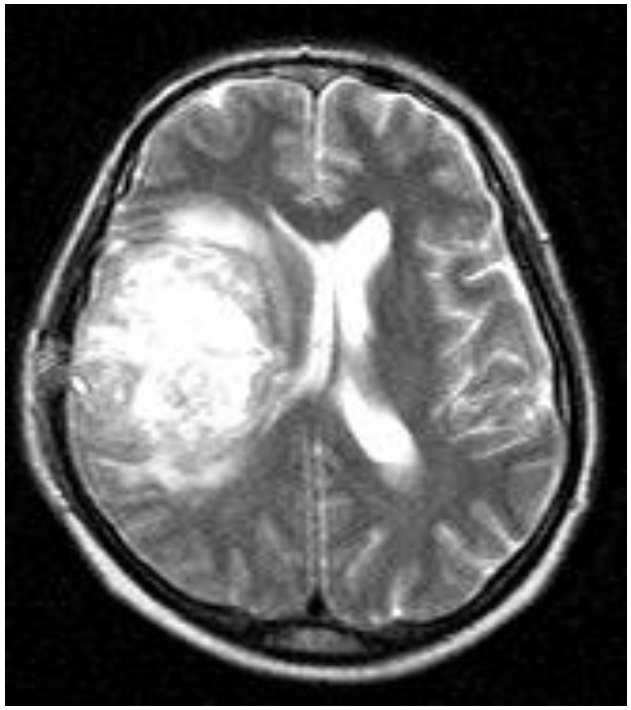
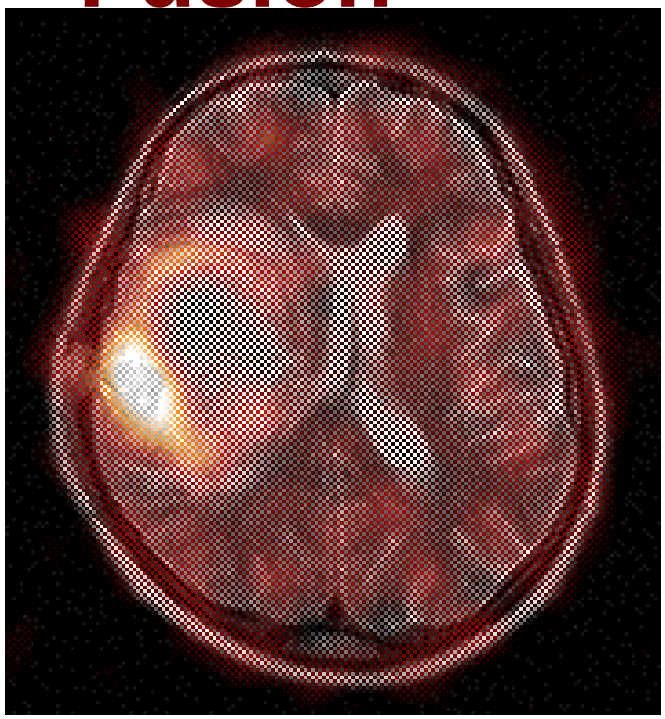
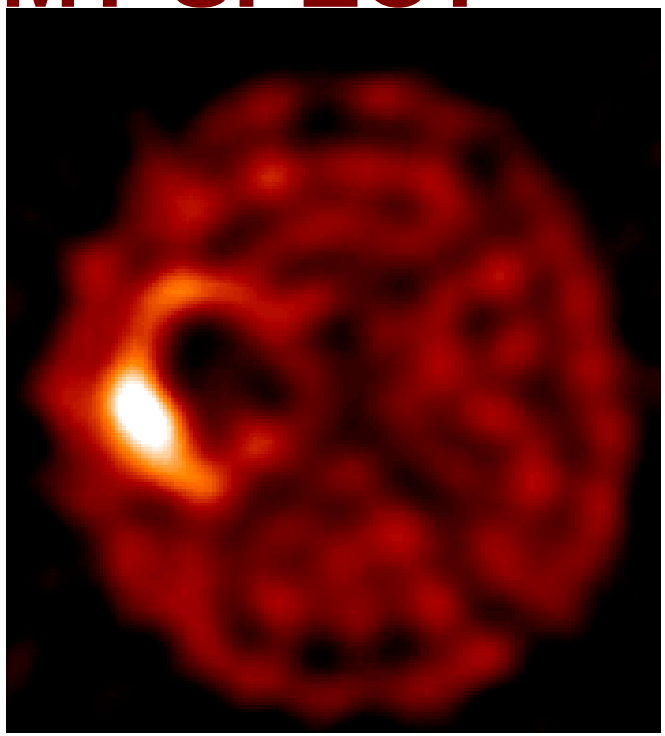
MRI

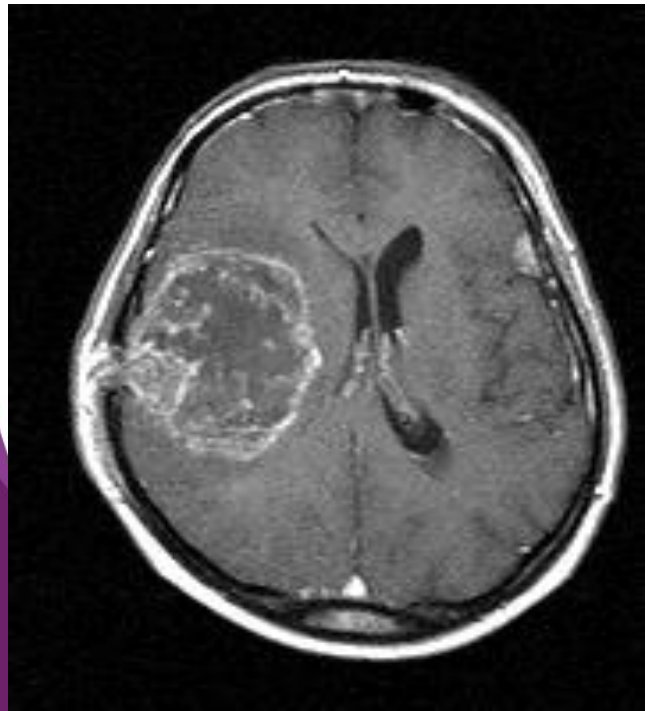
Fusion

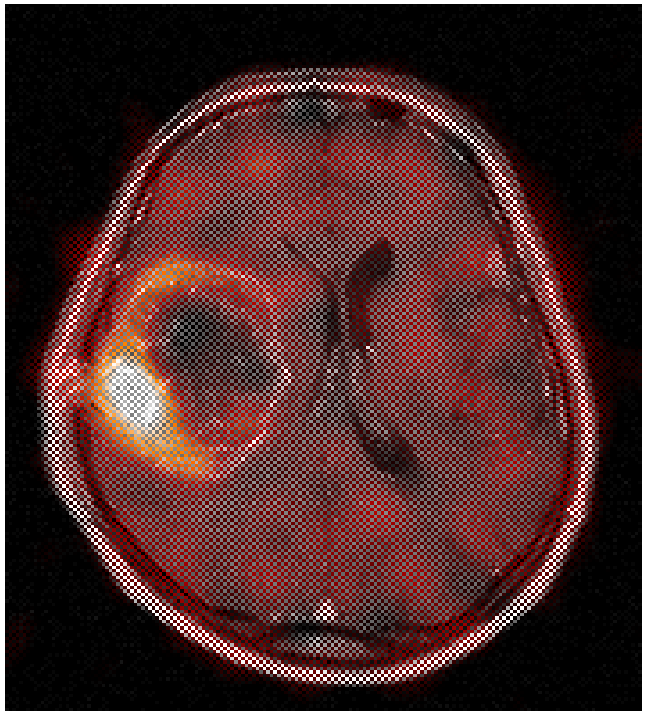
IMT-SPECT

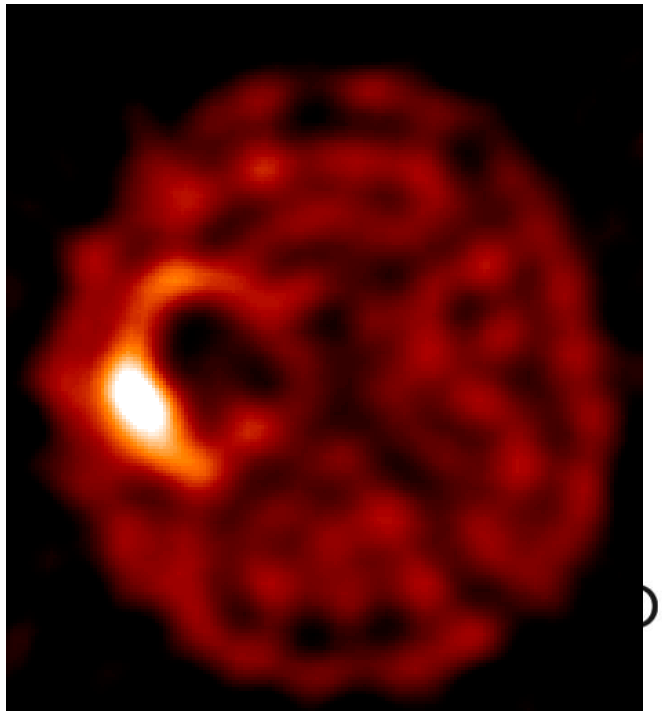




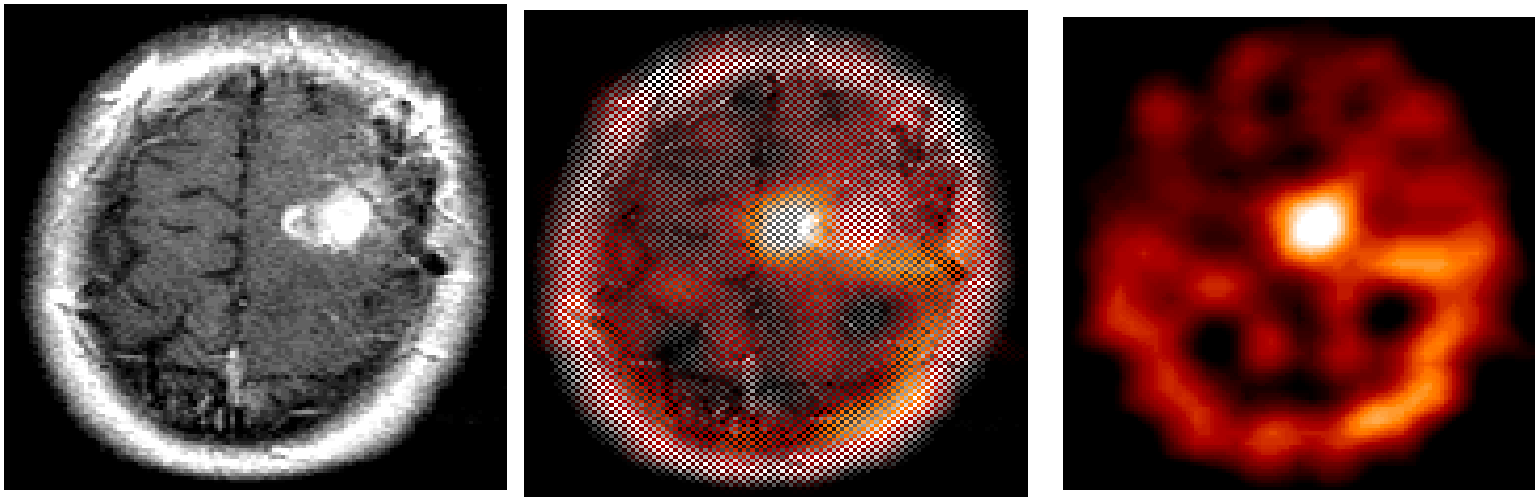




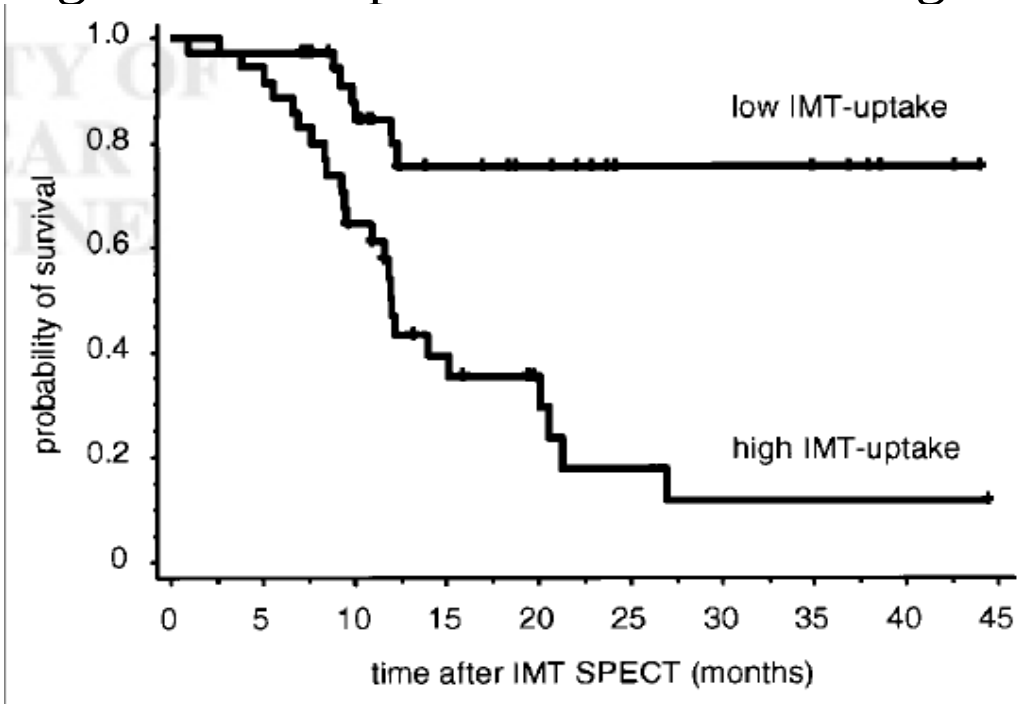




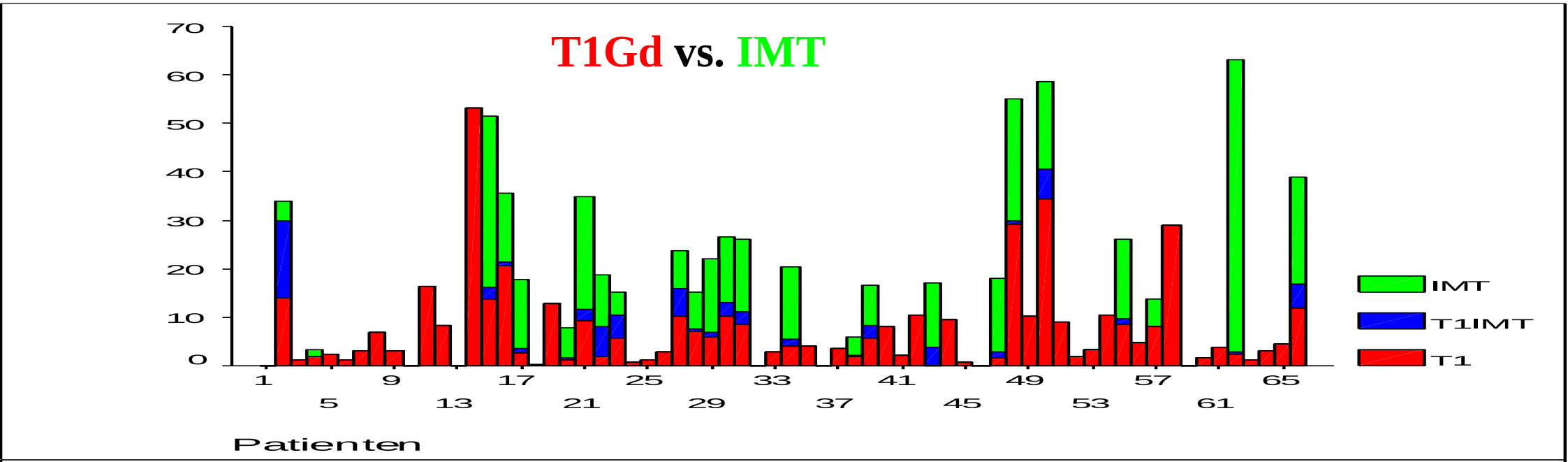
Glio IV

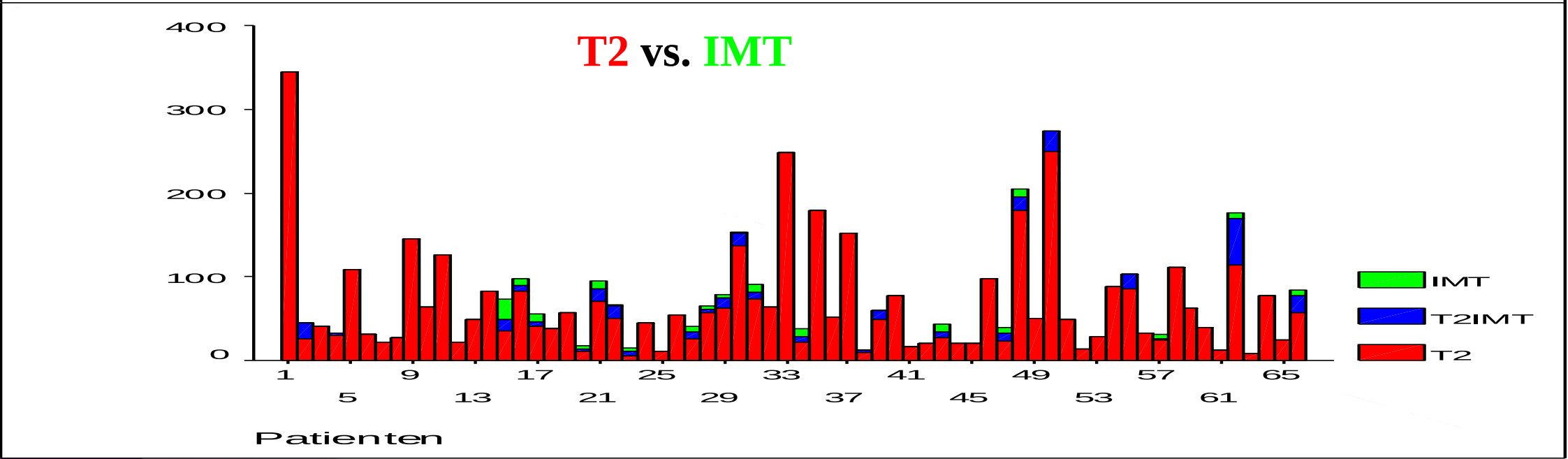


IMT-Uptake in SPECT and prognosis in 76 patients with resected gliomas *(Weber JNM 2001)*

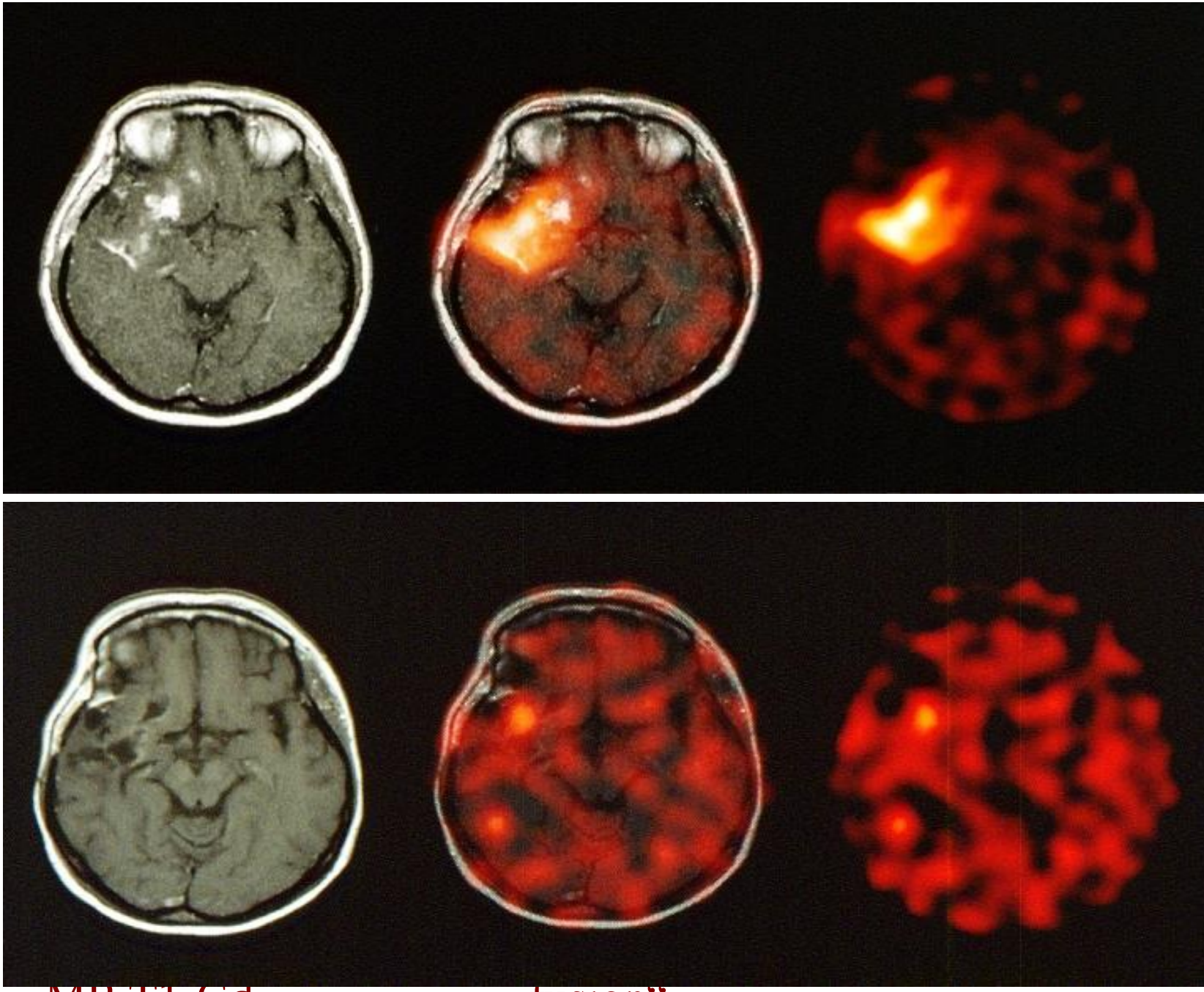


MRI versus IMT-SPECT in 66 Patients with Resected Gliomas Volumetrical Measurements *(Grosu et al IJROBP 2002)*





Astrocytoma III: before and 1 year after radiotherapy



MR T1-Gd „fusion“ IMT-SPECT

IMT-SPECT: conclusions

- Improves lesion detection and delineation in a significant number of patients

- Influences the boost volume in 3D CRT treatment planning and could have important consequences on dose escalation studies

- Intensity of IMT-uptake in operated patients correlates with survival.

- IMT uptake decreases under radiotherapy

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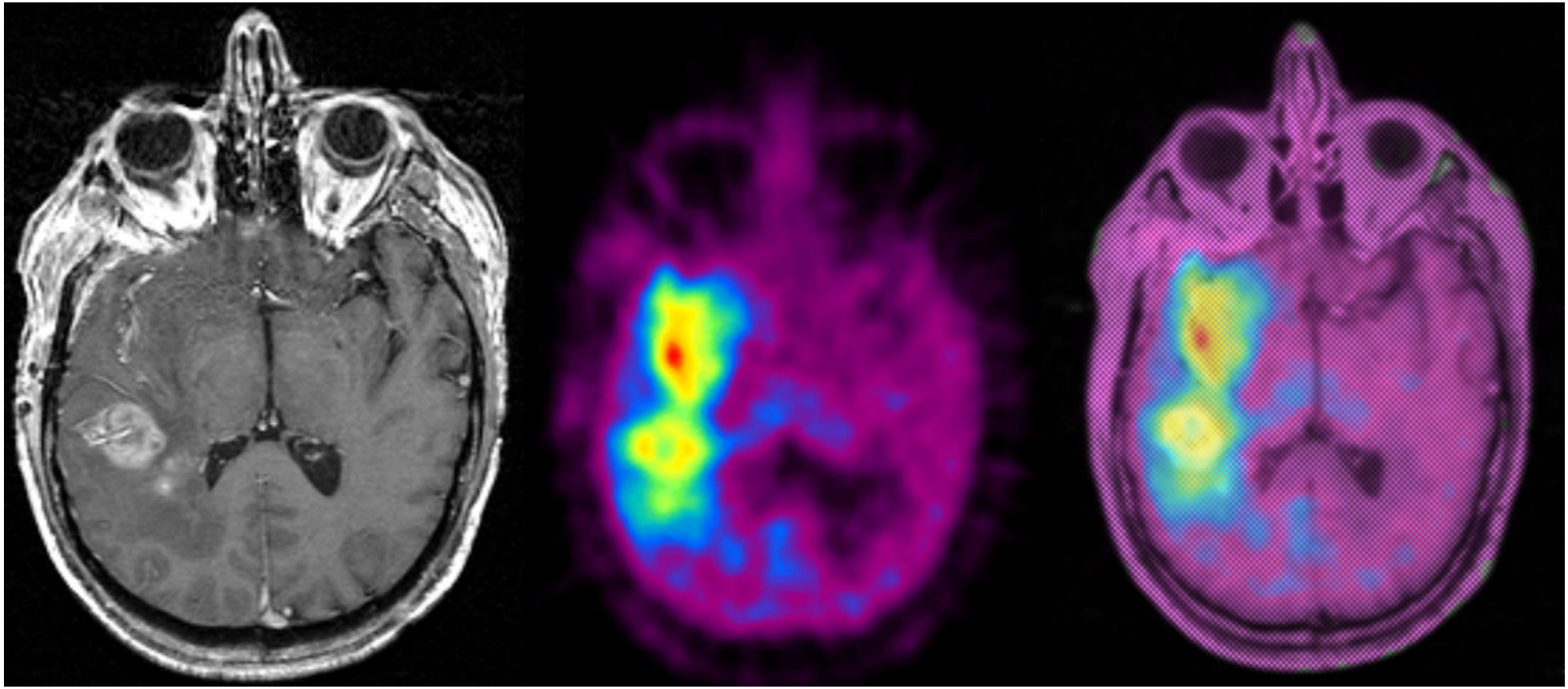
MET-PET for GTV Definition in Gliomas

MRT (T1, Gd-DTPA) Methionine-PET „image fusion“



GTV: 4 ml GTV: 72 ml

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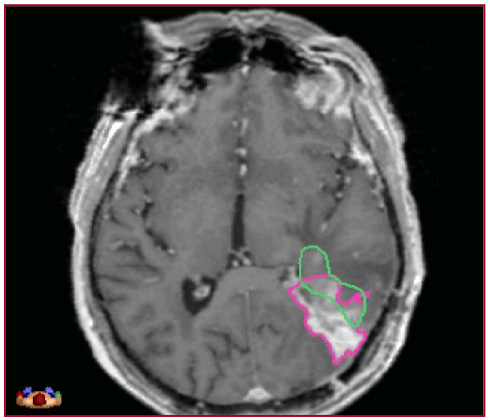
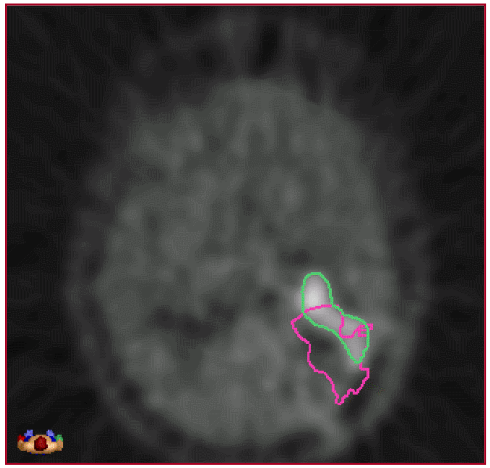
MET-PET / T1Gd-MRI image fusion. Volumetrical evaluation

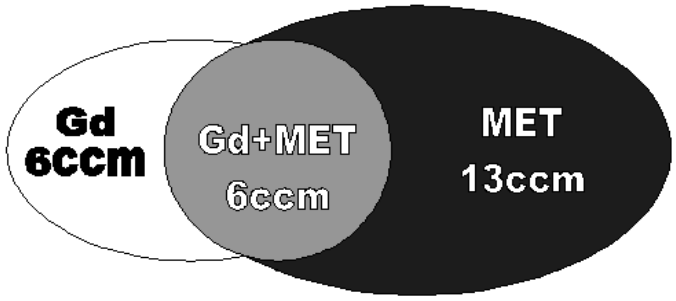
(Grosu IJROBP 2005)





MET uptake corresponds to Gd enhancement	5/39 Patients (13%)
MET uptake located outside of Gd enhancement	29/39 Patients (74%)
Gd enhancement located outside of MET enhancement	27/39 Patients (69%)

MET uptake corresponds to hyperintensity on T2	0/18 Patients (0%)
MET uptake located outside of hyperintensity on T2	9/18 Patients (50%)
hyperintensity on T2 located outside of MET uptake	18/18 Patients (100%)



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Accuracy of amino acid PET for brain tumor delineation in comparison with histologic evaluation

Authors	N[1]	Technique	Sensitivity[2]	Specificity[2]
Braun	32	MET-PET	87% (26/30)	75% (3/4)
Pirotte	32	MET-PET	100% (61/61)	100% (9/9)
Kracht	30	MET-PET	87% (87/100)	89% (16/18)
Pauleit	31	FET-PET	93%[3]	94%[3]
		MRI[4]	96%	53%

[1]number of patients, [2]based on analyzed lesions or biopsies, [3] total of 52 samples, 26 positive for tumor tissue. Sensitivity and specificity were calculated from fitted receiver operator characteristic (ROC) curve. [4]Combined analysis of non-enhanced T1-weighted sequences, Gd-enhanced sequences and FLAIR sequences.(Weber 2008)

(Weber et al., Nature Clin Pract Oncol 2008)

Int. J. Radiation Oncology Biol. Phys., Vol. 73, No. 2, pp. 479–485, 2009
Published by Elsevier Inc.
Printed in the USA.
0360-3016/09/$–see front matter

doi:10.1016/j.ijrobp.2008.04.050

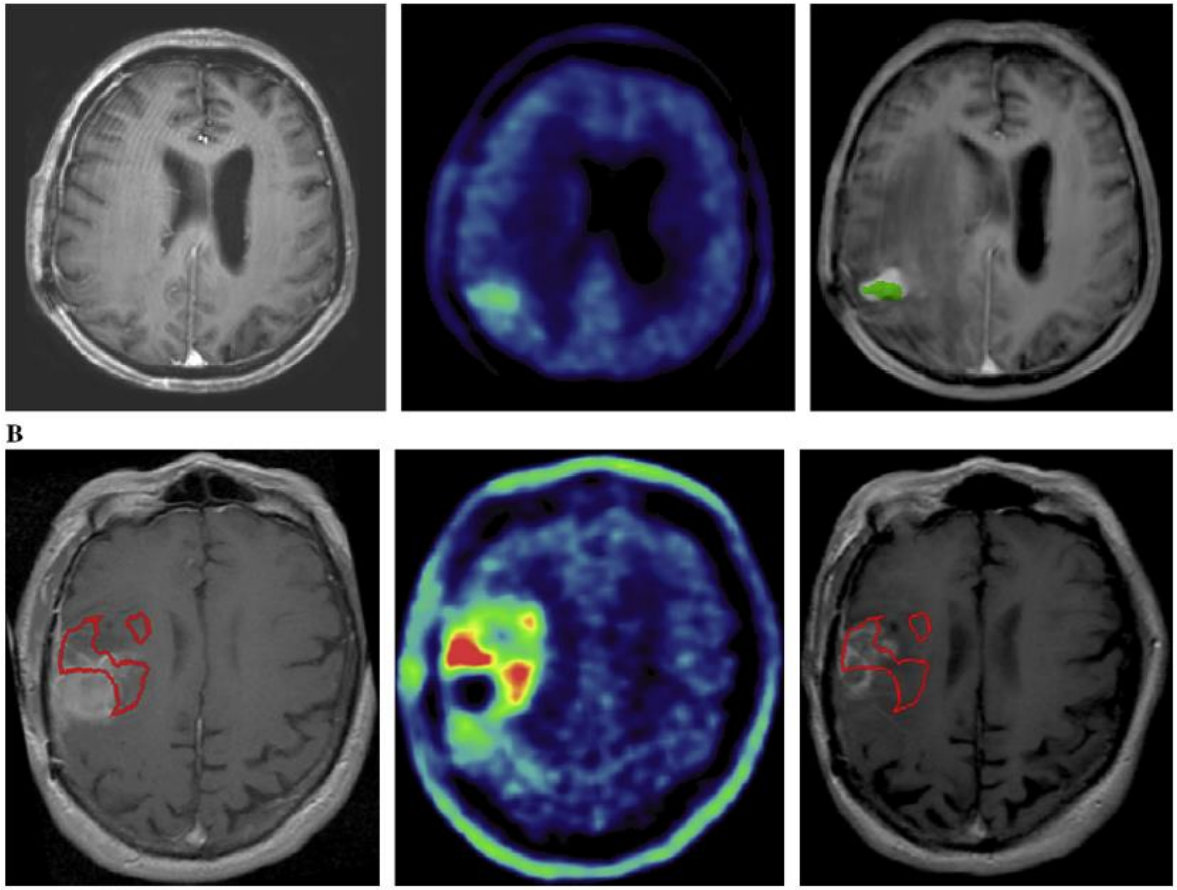
CLINICAL INVESTIGATION **Brain**

ASSOCIATION OF ^{11}C-METHIONINE PET UPTAKE WITH SITE OF FAILURE AFTER CONCURRENT TEMOZOLOMIDE AND RADIATION FOR PRIMARY GLIOBLASTOMA MULTIFORME

Irwin H. Lee, M.D., Ph.D.,* Morand Piert, M.D.,† Diana Gomez-Hassan, M.D., Ph.D.,‡ Larry Junck, M.D.,§ Lisa Rogers, M.D.,§ James Hayman, M.D.,* Randall K. Ten Haken, Ph.D.,* Theodore S. Lawrence, M.D., Ph.D.,* Yue Cao, Ph.D.,* and Christina Tsien, M.D.*

Departments of *Radiation Oncology, †Nuclear Medicine, ‡Radiology, and §Neurology, University of Michigan, Ann Arbor, MI

In five patients, the PET-GTV was not fully encompassed by the 95% IDS, and all of these patients recurred with noncentral failures. In comparison, only 2 of 14 patients whose PET-GTV was fully encompassed by the 95% IDS had noncentral failures. This included 3 patients who have not yet failed with more than 12 months of follow-up. Using the Fisher exact test, this apparent association between suboptimal coverage of the PET-GTV and subsequent noncentral failure was statistically significant ($p < 0.01$).



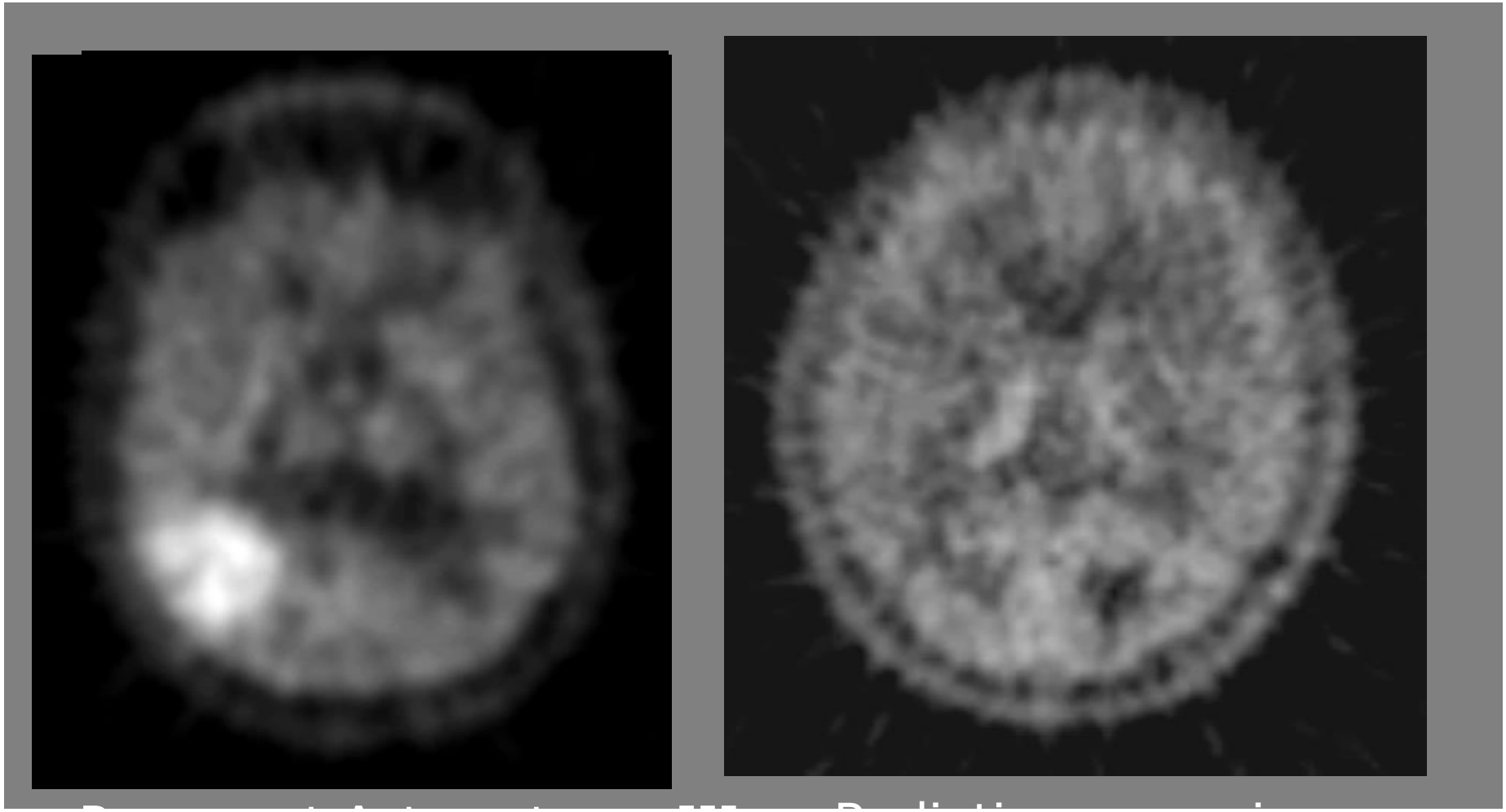
Differentiation of radiation necrosis and tumor recurrence by amino acid PET or SPECT

Authors	N	Technique	Sensitivity	Specificity
Rachinger	45	FET-PET	94% (29/31)	93% (13/14)
		MRI[1]	97%(30/31)	50% (7/14)
Tsuyuguch	21	MET-PET	78% (7/9)	100% (12/12)
Samnick	78	IMT-SPECT	94% (62/66)	100% (12/12)

[1]contrast enhancement in T1-weighted images after administration of Gadolinium-DTPA (Weber 2008)

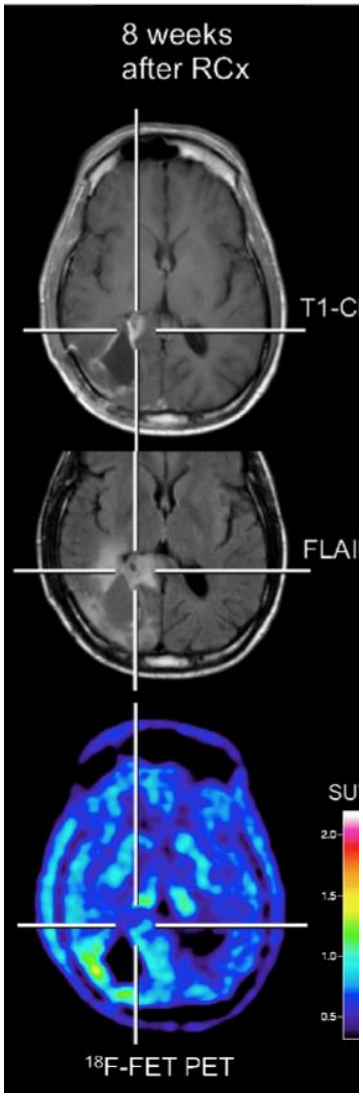
(Weber et al., Nature Clin Pract Oncol 2008)

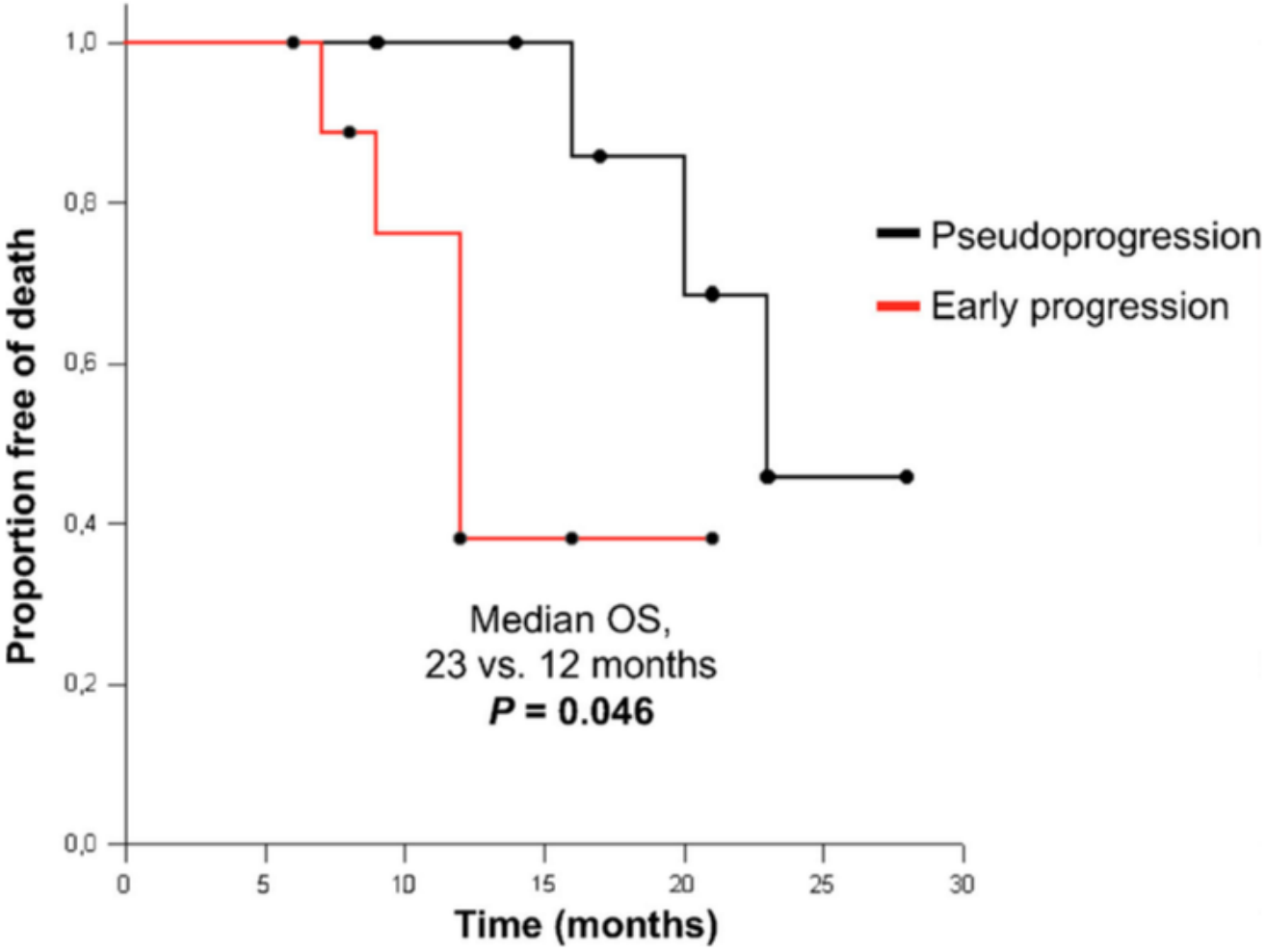
Diagnosis of recurrent glioma vs. necrosis

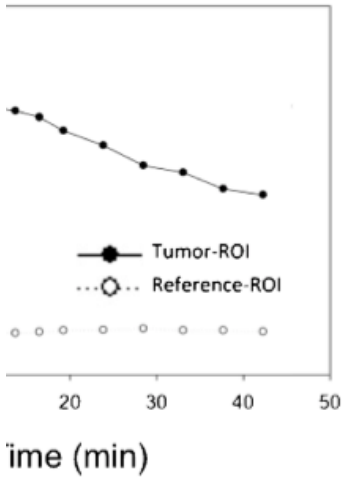


Methionine-PET

Diagnosis of necrosis vs. recurrent glioma







Galldiks N et al. (2015) Diagnosis of pseudoprogression in patients with glioblastoma using O-(2-[18F]fluoroethyl)-L-tyrosine PET. EJNMMI 42:685–695

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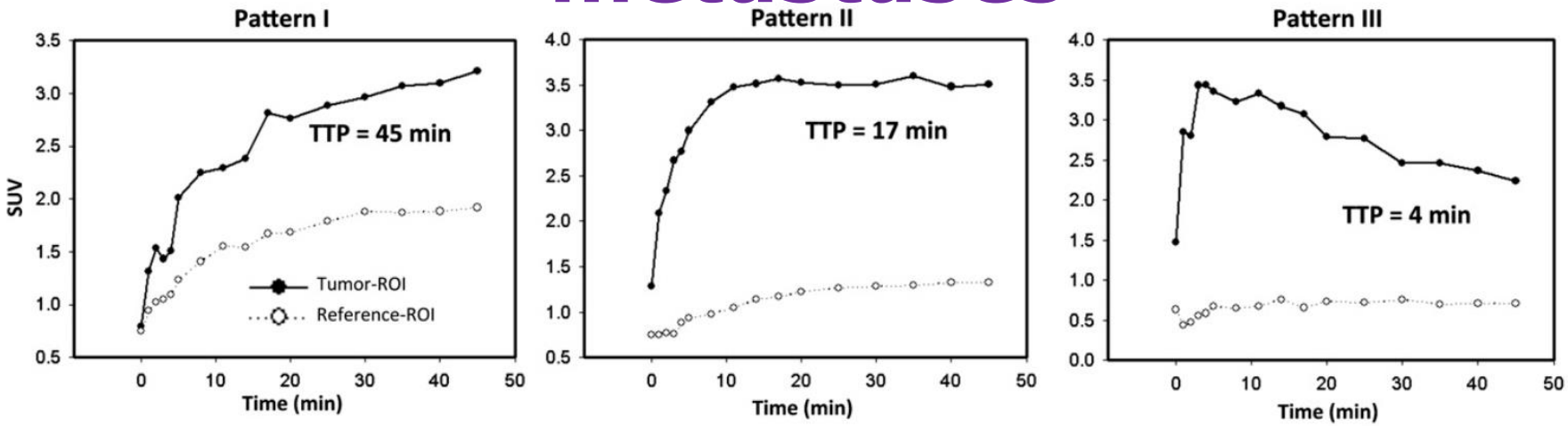
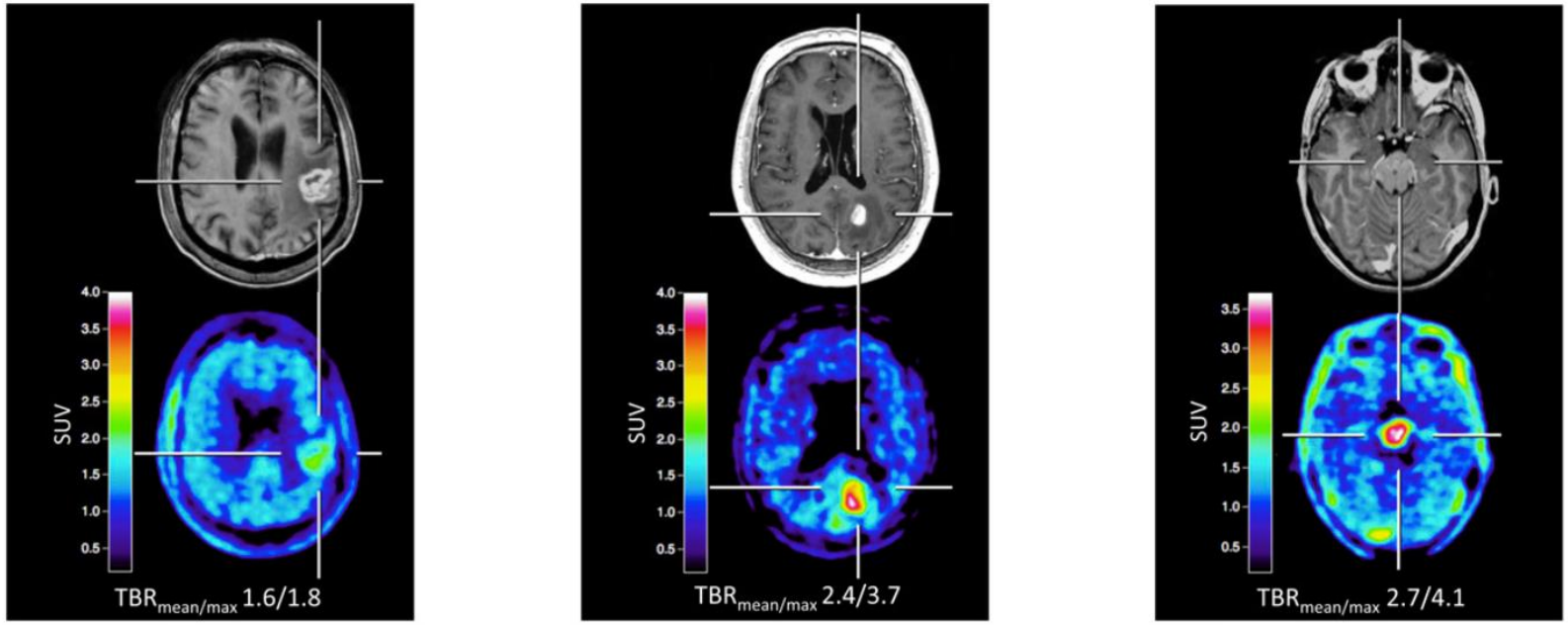
Recurrence vs. necrosis after SRS for brain metastases



TAC of radiation necrosis
Patient 24 (breast cancer)

TAC of recurrent metastasis
Patient 12 (malignant melanoma)

TAC of recurrent metastasis
Patient 9 (Ewing sarcoma)



Galldiks N et al. (2012) Role of O-(2-18F-Fluoroethyl)-L-Tyrosine PET for Differentiation of Local Recurrent Brain Metastasis from Radiation Necrosis. JNM 53;1367-1374.

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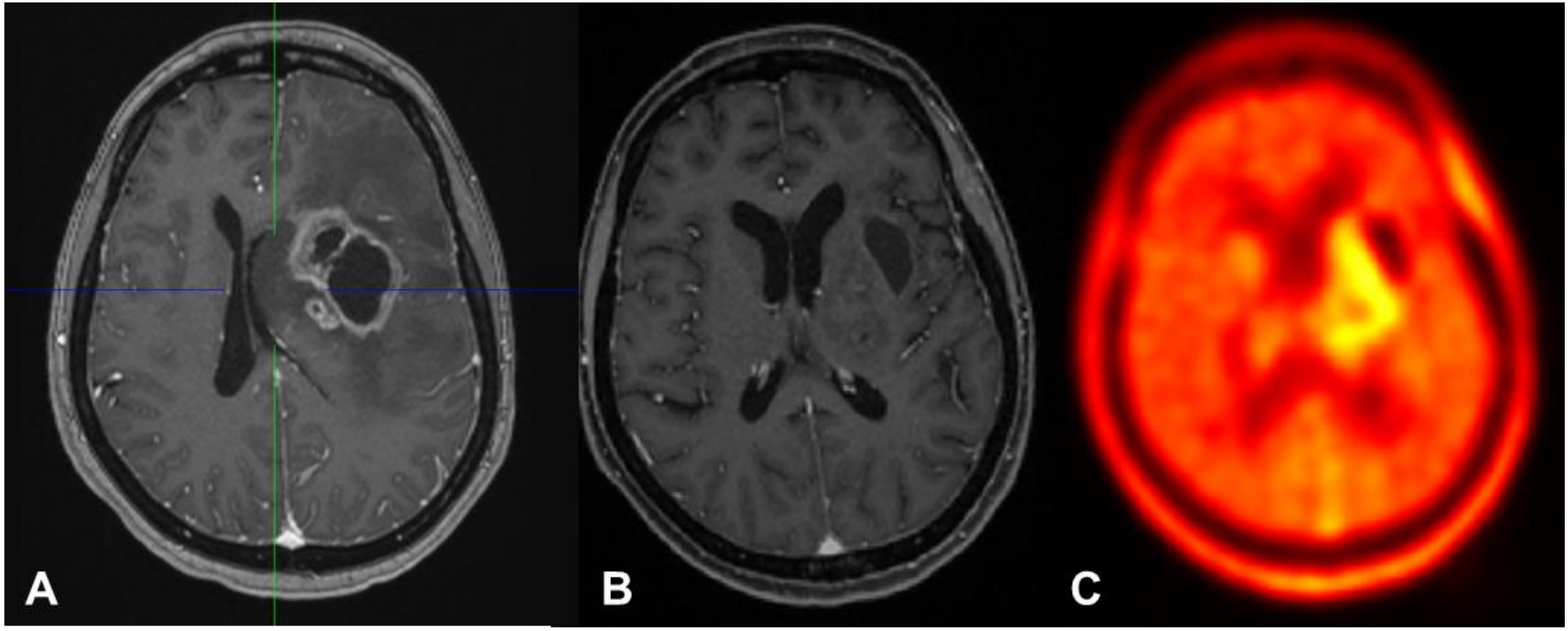
Brain imaging in the era of bevacizumab – Pseudoresponse



Oehlke O and Grosu AL (2016) PET/MRI and Brain Tumors – Focus on Radiation Oncology Treatment Planning. Clin Transl Imaging doi:10.1007/s40336-016-0206-7

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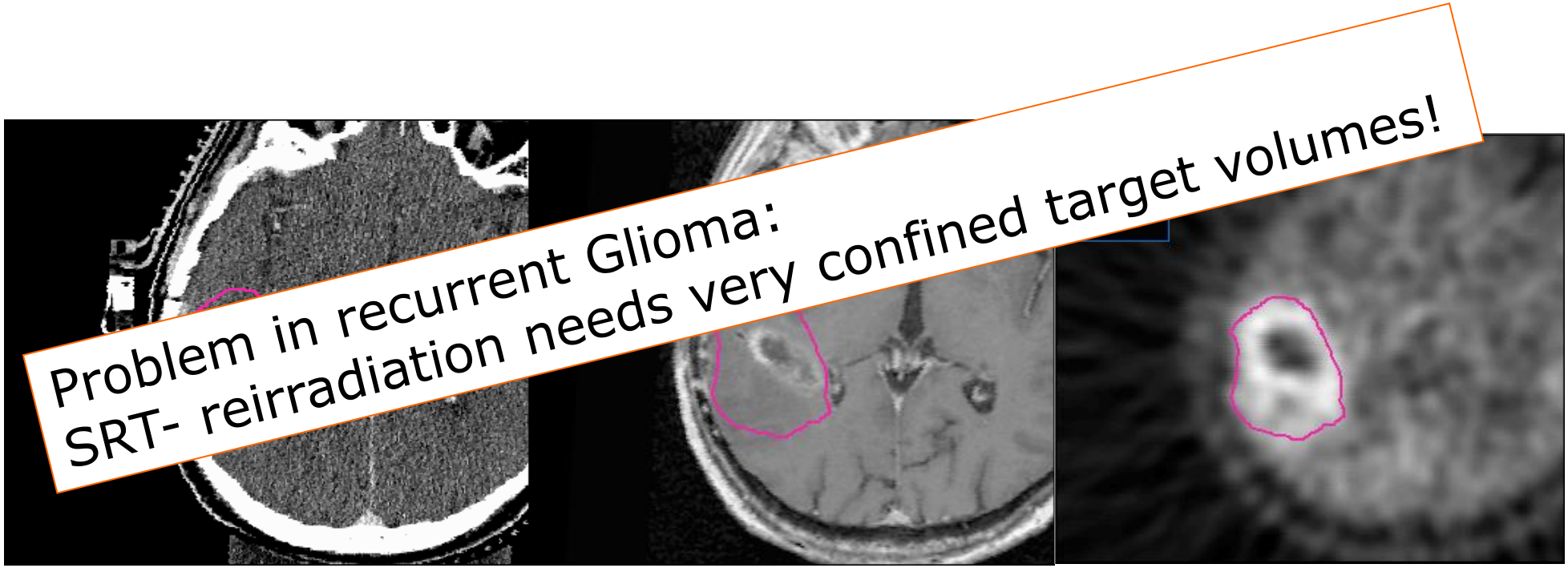

Recurrent-Glioblastoma.
Re-Irradiation, SFR (30 Gy/5Gy + Temodal)
Image Fusion CT/ MRI/ MET-PET

(Grosu et al IJROBP 2003)

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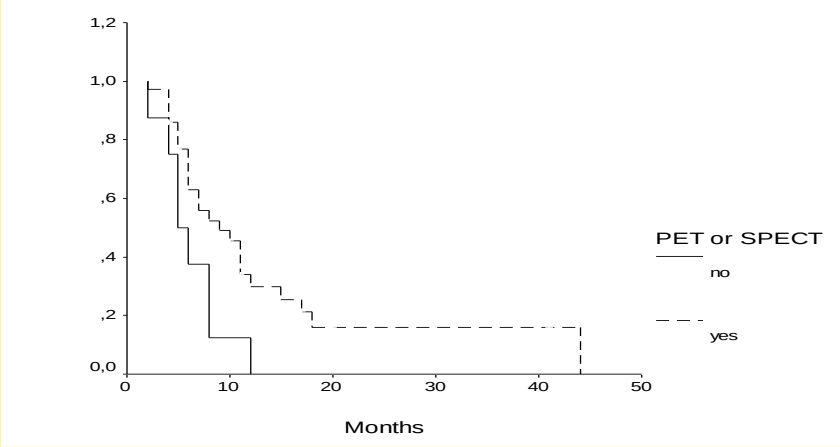
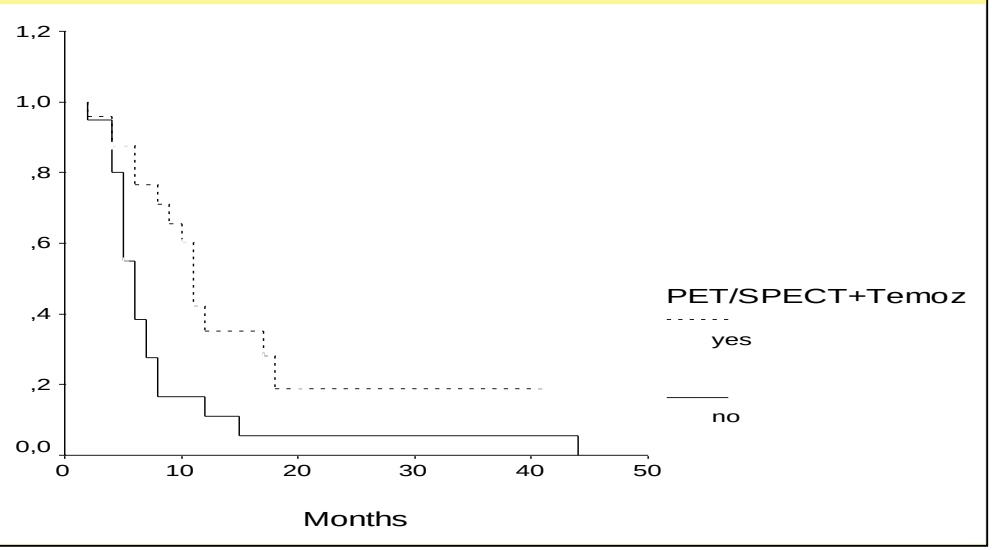
Re-irradiation of recurrent high grade gliomas.
SFR, 30 Gy, 5Gy/f +TMZ : AA-PET/CT/MRI plan vs. CT/MRI plan

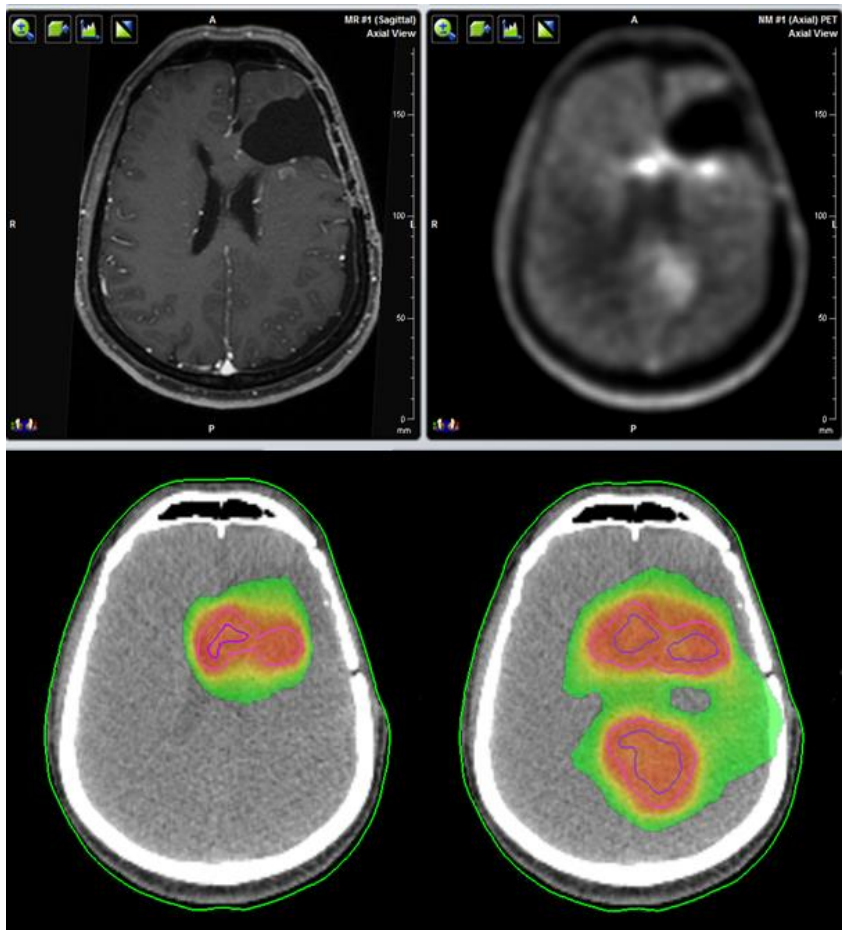
Significant survival advantage for the patients with recurrent gliomas treated with SFR based on AS-PET/SPECT/MRI/CT **(median 9 mo,mean 14 mo)** compared to the patients treated with SFR planned by anatomical imaging (CT/MRI) **(median 5 mo, mean 6 mo), p = 0.031** *(Grosu IJROBP 2005)*



Survival curves for patients with recurrent gliomas treated with SFR based on biological imaging and temozolomide **(median 11 months, mean 16 months)** vs. patients treated with SFR without temozolomide, without biological imaging or without both components **(median 6 months, mean 8 months), p=0.008** ***(Grosu IJROBP 2005)***



GLIAA Study



<u>Arm A (Experimental Intervention)</u>

PTV definition according to FET-PET:

GTV = AA uptake PET

(CTV) = GTV + 3 mm,

(PTV) = CTV + 1-2mm

High precision re-irradiation:

39 Gy; 3 Gy/d 5x/w

<u>Arm B (Control Intervention)</u>

PTV definition according to CET1-MRI:

GTV = CE in T1

(CTV) = GTV + 3 mm,

(PTV) = CTV + 1-2mm

Oehlke O et al. (2016) Amino-acid PET versus MRI guided re-irradiation in patients with recurrent glioblastoma multiforme (GLIAA) - protocol of a randomized phase II trial (NOA 10/ARO 2013-1). BMC Cancer 16:769

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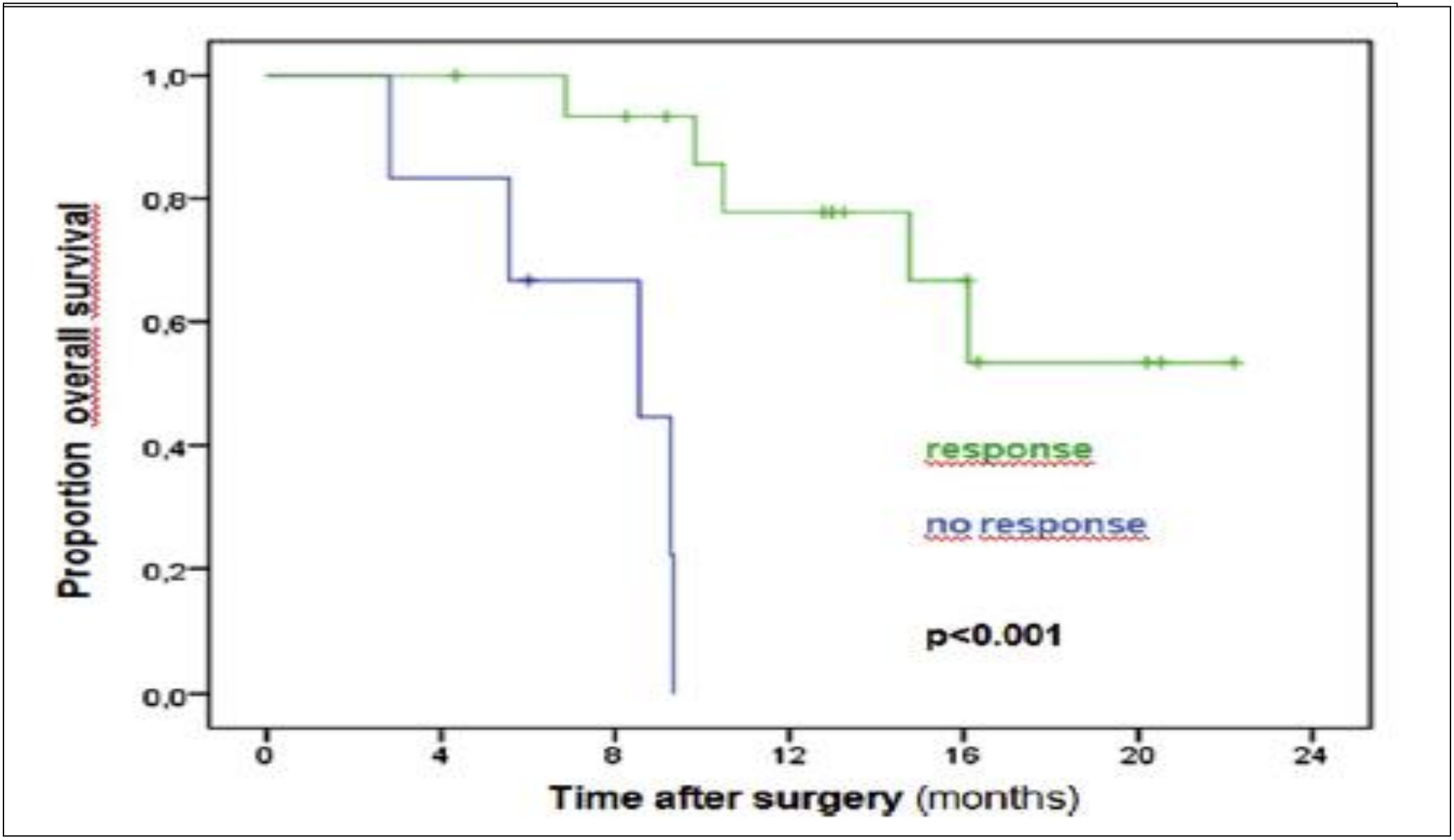
FET-PET Treatment response (Piroth, IJROBP 6-2010



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11C-MET-PET versus 18F-FET-PET

- Despite the considerable number of encouraging results, the application of MET-PET in diagnosis of brain tumors has been mainly limited to a small number of centers. The short physical half-life of carbon-11 (20 min) necessitates an on-site cyclotron for MET-PET examination, making the utilization of this tracer for the PET investigation difficult.

- In contrast to MET the physical half time for 18F of 110 minutes allows performing the FET-PET studies in centers without an on-site cyclotron.

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 4, pp. 1049–1058, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.07.002

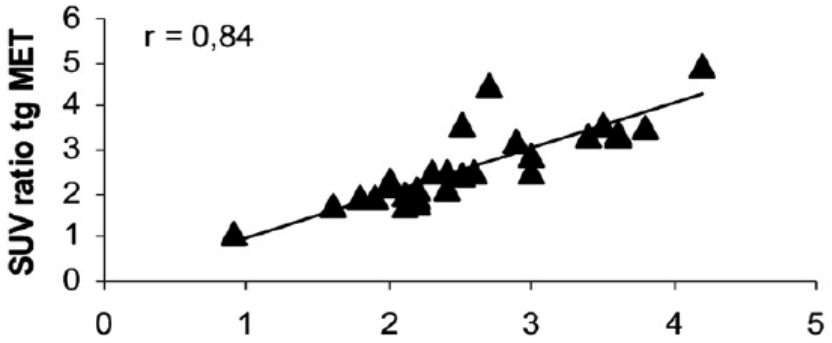
FET vs. MET

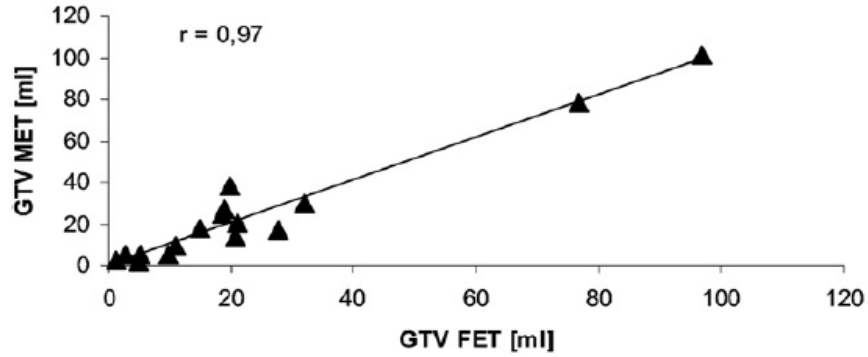
CLINICAL INVESTIGATION **Brain**

AN INTERINDIVIDUAL COMPARISON OF O-(2- [^{18}F]FLUOROETHYL)-L-TYROSINE (FET)– AND L-[METHYL-^{11}C]METHIONINE (MET)–PET IN PATIENTS WITH BRAIN GLIOMAS AND METASTASES

Anca-Ligia Grosu, M.D.,*† Sabrina T. Astner, M.D.,† Eva Riedel, M.D.,‡§ Carsten Nieder, M.D.,†‖ Nicole Wiedenmann, M.D.,*† Felix Heinemann, M.D.,* Markus Schwaiger, M.D.,‡ Michael Molls, M.D.,† Hans-Jürgen Wester, Ph.D.,‡ and Wolfgang A. Weber, M.D.‡¶

Department of *Radiation Oncology and ¶Nuclear Medicine, Albert Ludwigs Universität Freiburg, Freiburg, Germany; Departments of †Radiation Oncology and ‡Nuclear Medicine, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany; §Department of Neurology, Klinikum Grosshadern, Ludwig Maximilians Universität München, Munich, Germany; and ‖Department of Internal Medicine–Oncology, Nordlandssykehuset HF Hospital, Bodø, Norway



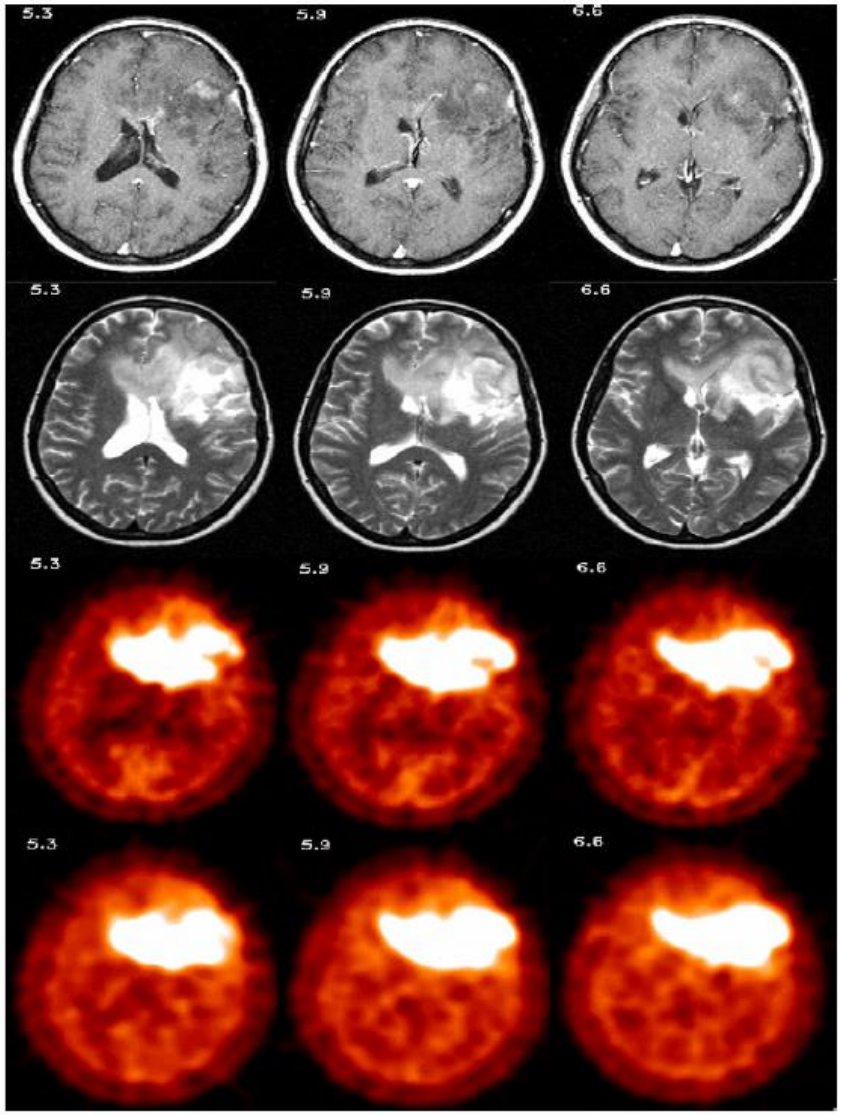


MRI-T1Gd

MRI-T2

MET-PET

FET-PET



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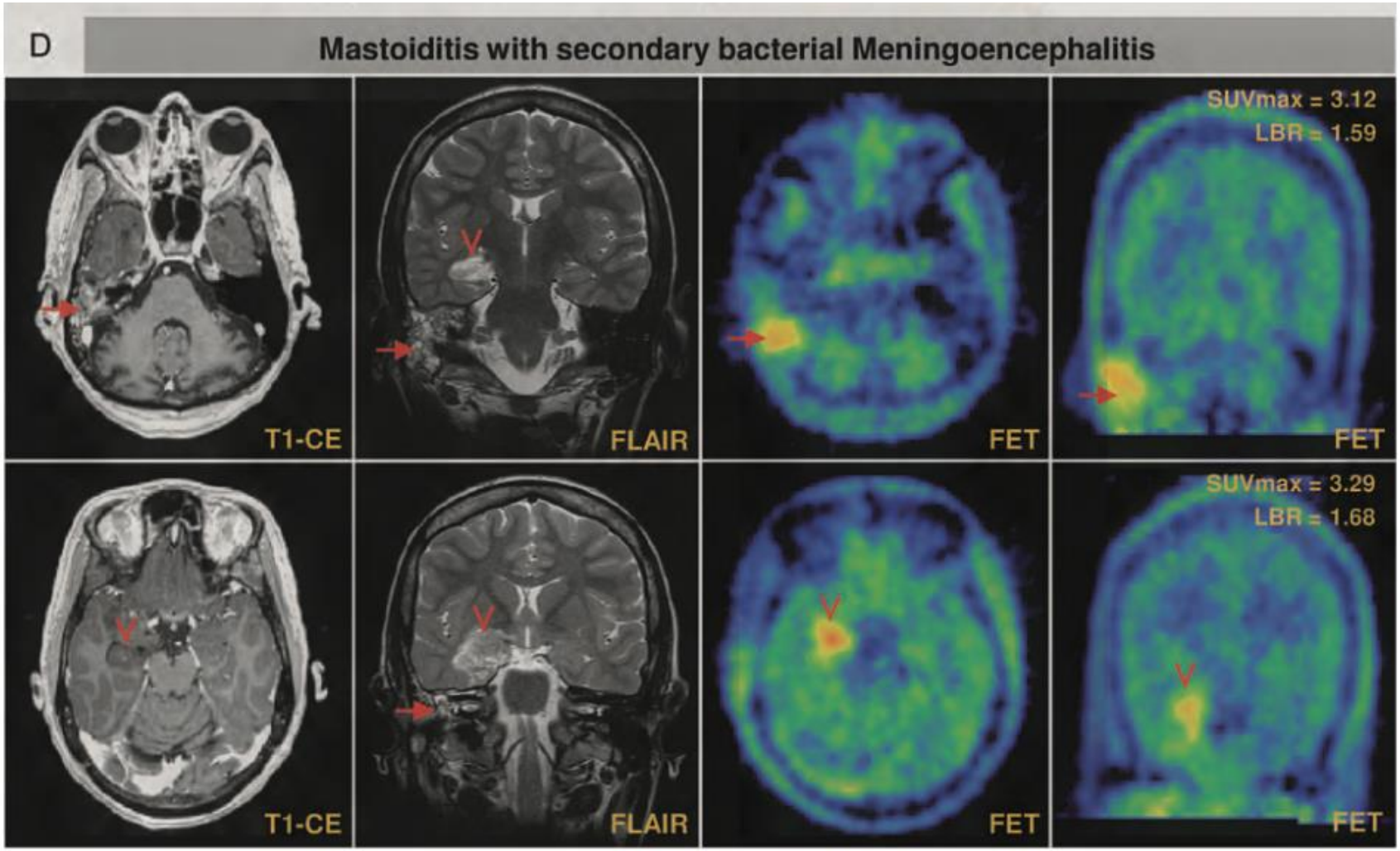
Possible pitfalls – „not all that glitters is glioma“



3) [18F]-
e PET: a
ool in neuro-oncology, but not all that glitters is glioma. Neuro-Oncology 15:341–351

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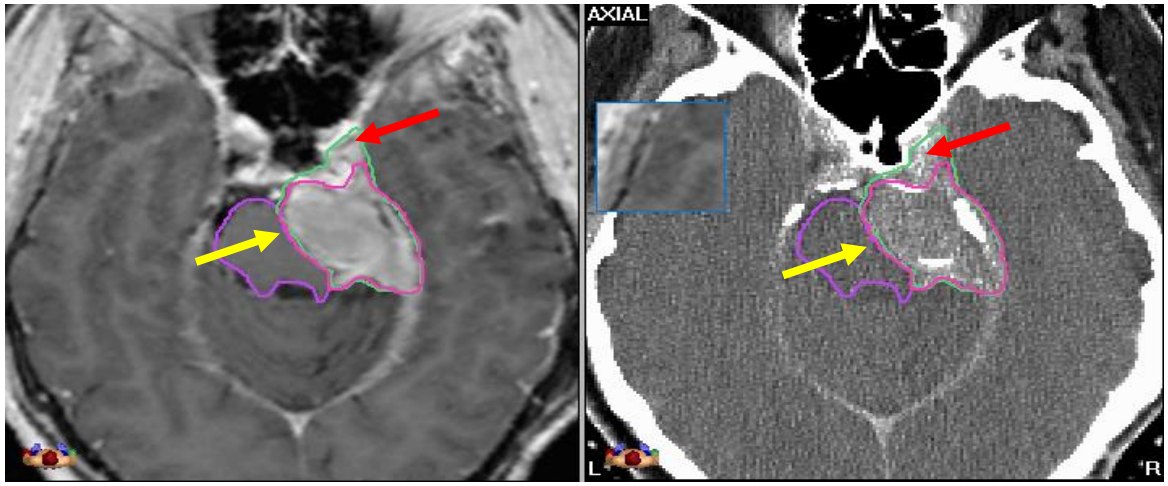
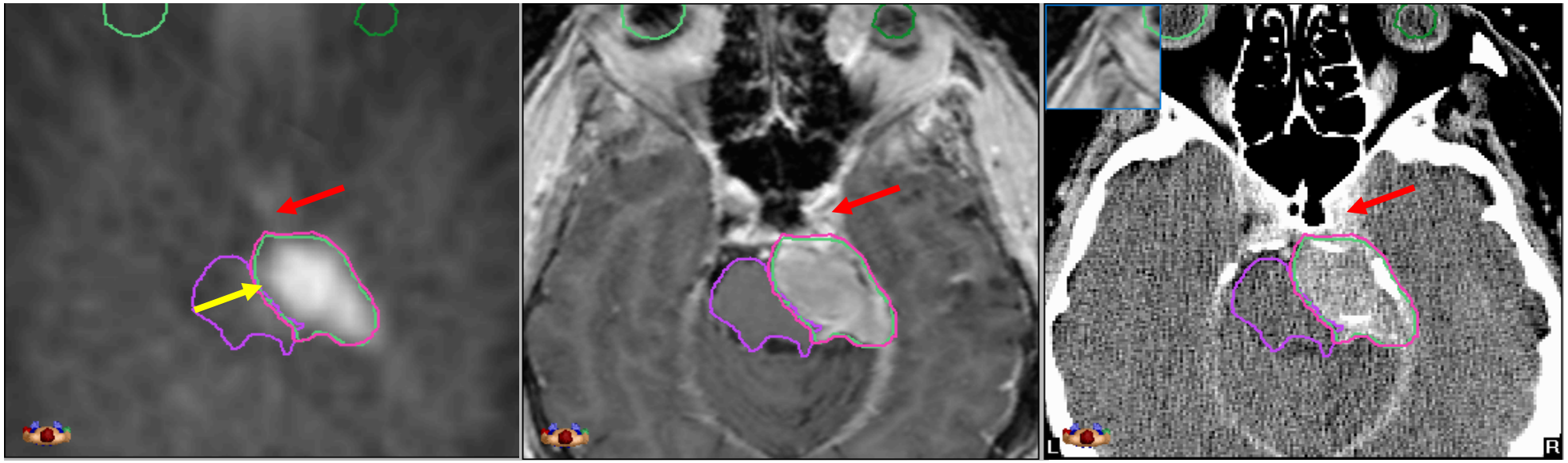
MET-PET for GTV Definition of Meningiomas. Interobserver Variability (CT/MRI/PET Image Fusion)





Grosu et al. IJROBP 2006

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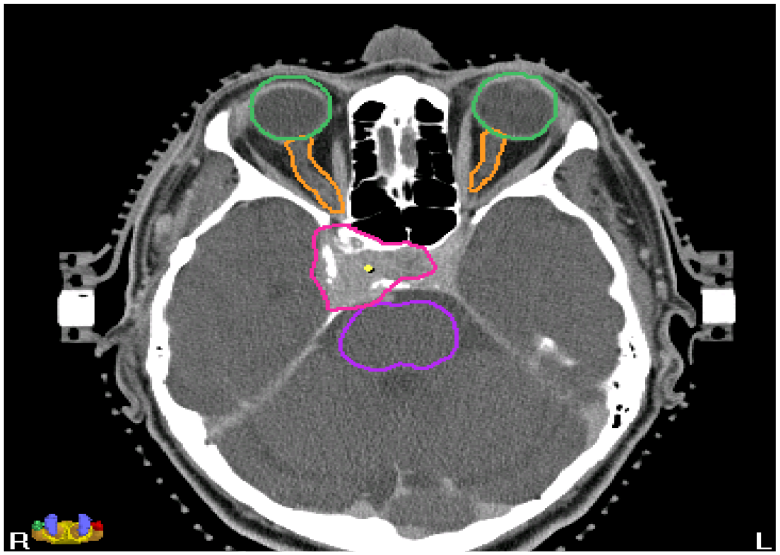
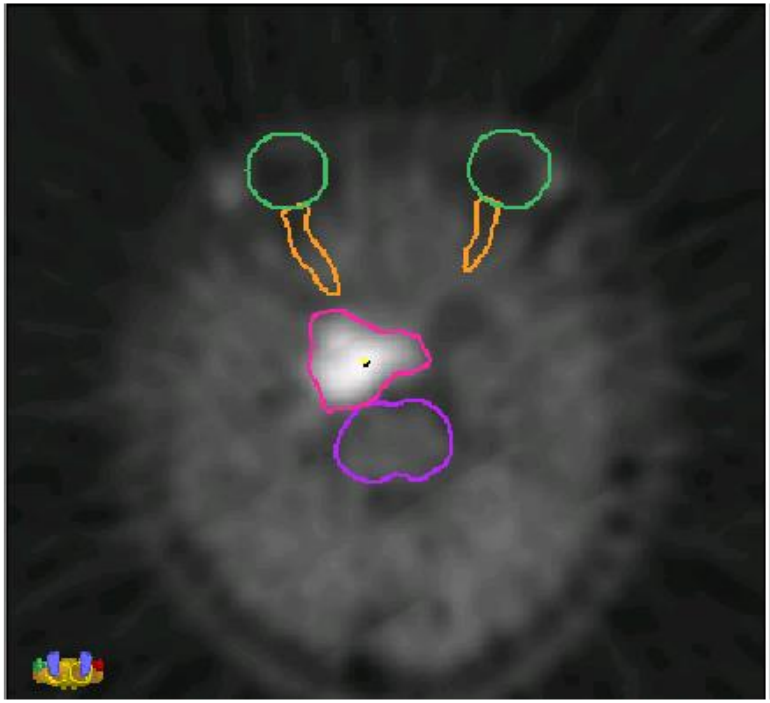
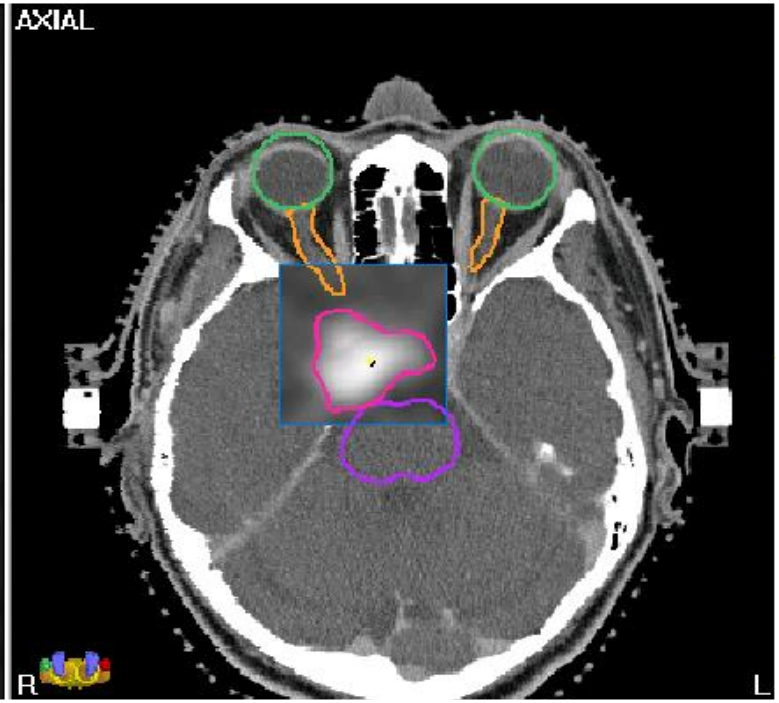


Meningioma

(Grosu IJROBP 2006)
GTV delineated based on
CT/MET-PET/MRI Image Fusion





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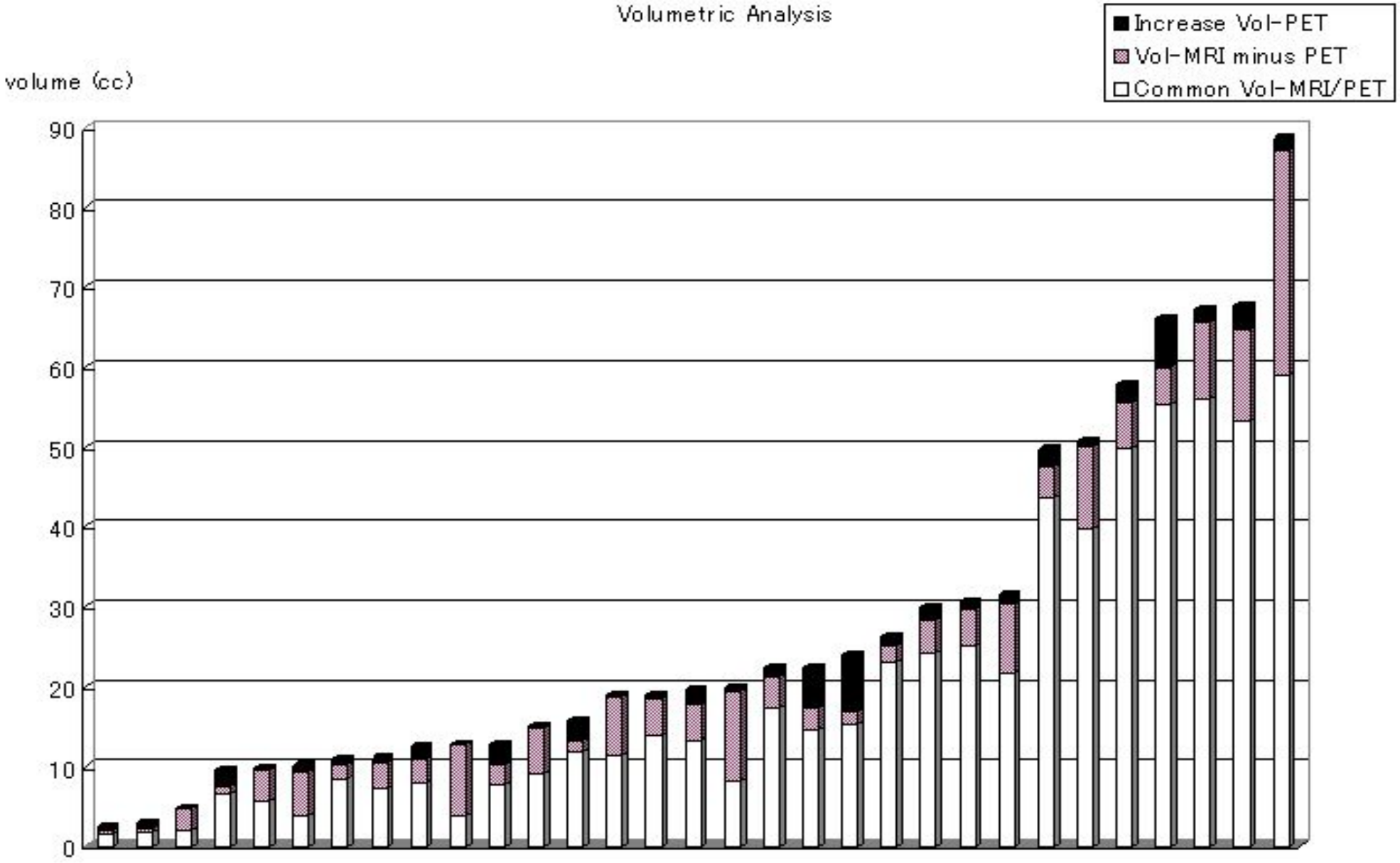
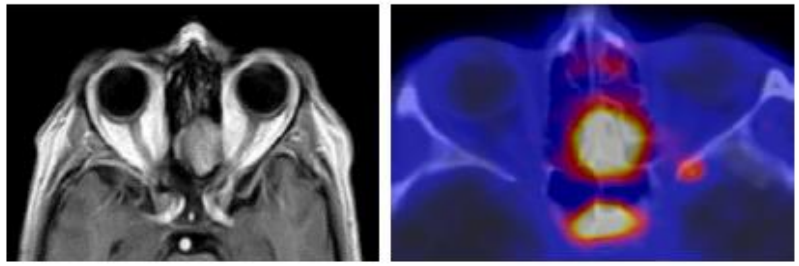
Meningiomas: GTV delineation using MET-PET versus CT/MRI

(Astner IJROBP 2008)



Meningeoma: DOTATOC

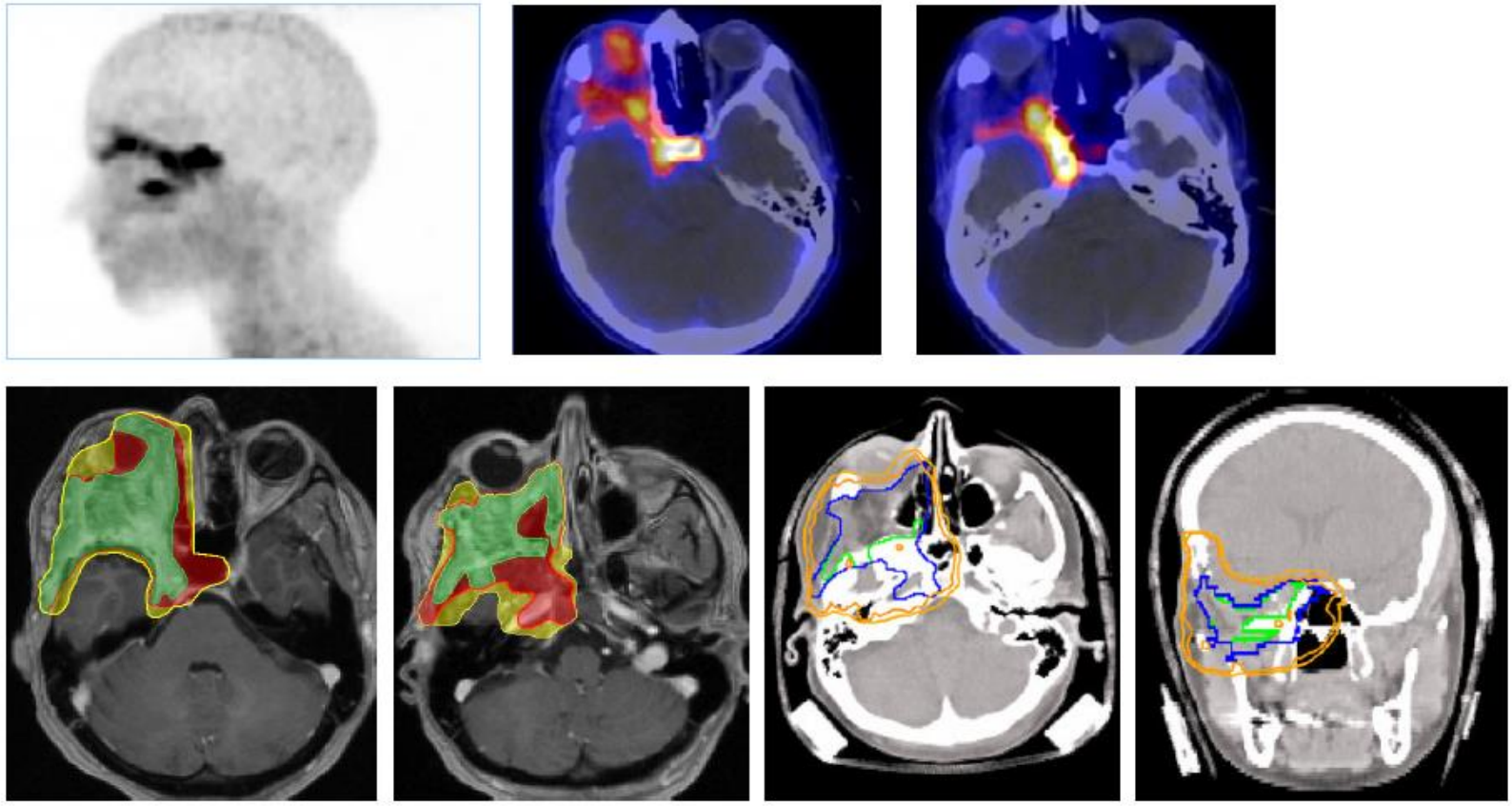
Radiation Oncology *Radiation Oncology* 2009, 4:56



Research **Open Access**

[^{68}Ga]-DOTATOC-PET/CT for meningioma IMRT treatment planning

Barbara Gehler[1], Frank Paulsen[1], Mehmet Ö Öksüz[3,8], Till-Karsten Hauser[4], Susanne M Eschmann[6], Roland Bares[3], Christina Pfannenberg[5], Michael Bamberg[1], Peter Bartenstein[7], Claus Belka[2] and Ute Ganswindt*[2]



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Meningeoma: DOTATOC

Patients and Methods: In 26 consecutive patients with preferentially skull base meningioma, diagnostic magnetic resonance imaging (MRI) and planning-computed tomography (CT) was complemented with data from [^{68}Ga]-DOTA-D Phe^{1}-Tyr^{3}-Octreotide (DOTATOC)-PET/CT.

Results: The integration of the DOTATOC data led to additional information concerning tumor extension in 17 of 26 patients (65%). There were major changes of the clinical target volume (CTV) which modify the PTV in 14 patients, minor changes were realized in 3 patients. Overall the GTV-

Table 2: Treatment characteristics, target volumes

	Median	Maximum	Minimum	SD	Mean
GTV-MRI/CT [cc]	18,1	79,5	1,2	23,5	27,5
GTV-PET [cc]	25,3	106,1	0,6	29,1	33,5
CTV [cc]	37,4	143,2	1,3	34,7	42,2
Intersection-GTV-MRI/CT/PET [cc]	13,4	78,2	0,3	21,5	21,3
Increase-MRI/CT vs Intersection [cc]	5,7	15,5	0,8	4,6	6,2
Increase-PET vs Intersection [cc]	6,1	48,8	0	13,2	12,2
Ratio Increase-MRI/CT to GTV-MRI/CT	0,28	0,75	0,02	0,21	0,33
Ratio Increase-PET to GTV-MRI/CT	0,31	14,36	0,00	2,80	1,03

Radiation Oncology 2009, 4:56

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Conclusion

In brain tumors, amino acids PET improve the detection of tumor tissue and could be used for

- treatment planning
- treatment monitoring
- evaluation of local control after therapy

FDG PET/CT for breast cancer in radiation oncology

Wouter Vogel
NKI-AVL, Amsterdam

May 2016, Lisbon
Course on Molecular Imaging and Radiation Oncology

Imaging overflow

• Mammography 2 directions	(+ spot compression)
• US breast	(+ biopsy)
• US axilla and periclavicular	(+ biopsy)
• (Stereotactic biopsy)	
• MR breasts	(+ new sequences)
• Sentinel node	(+ SPECT/CT)
• X-thorax	(+ CT lungs)
• US liver	(+ biopsy)
• Bone scan	(+ MRI)
• LV ejection fraction	
• DEXA	

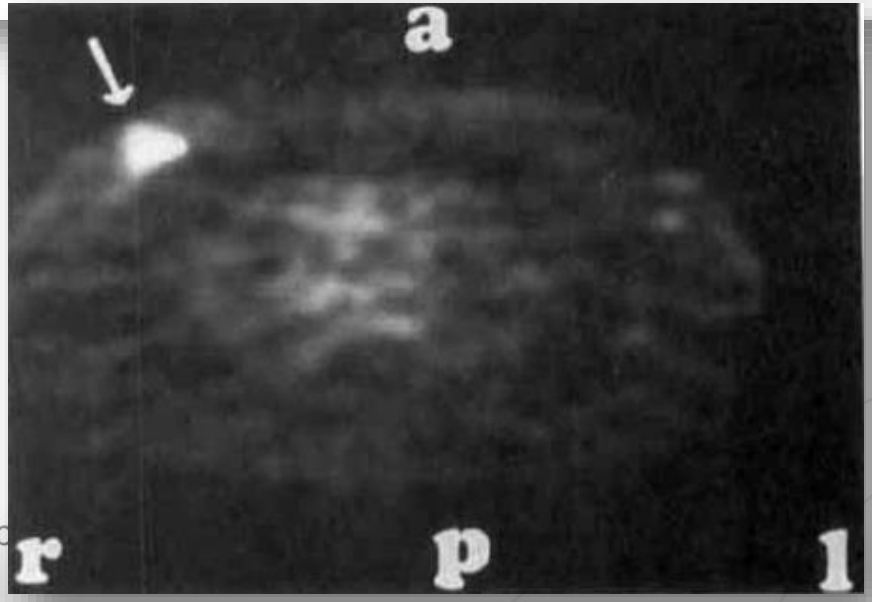
Why add another imaging modality ???

Poor early results - 20 years ago

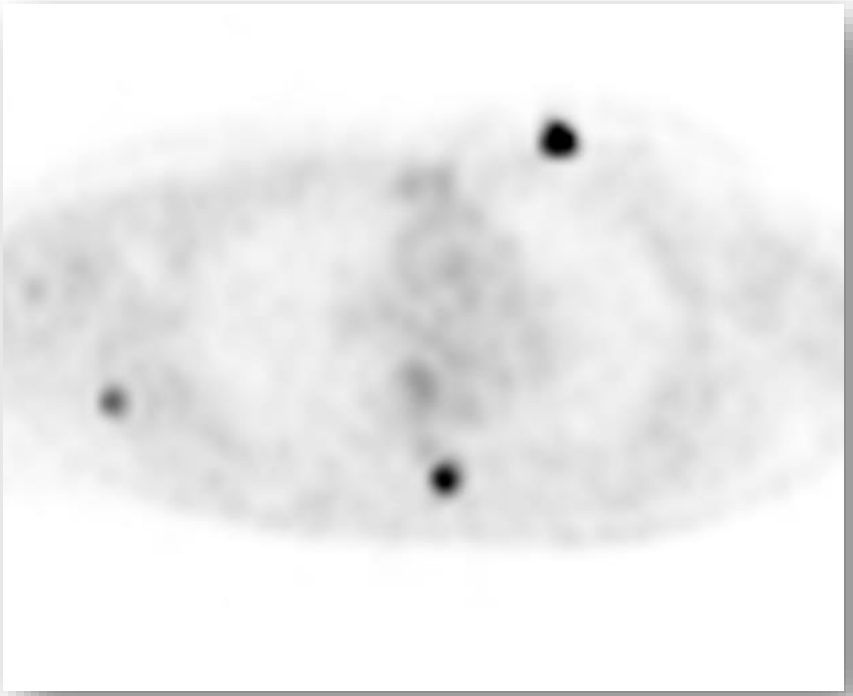
Positron Emission Tomography with Fluorine-18-Deoxyglucose in the Detection and Staging of Breast Cancer

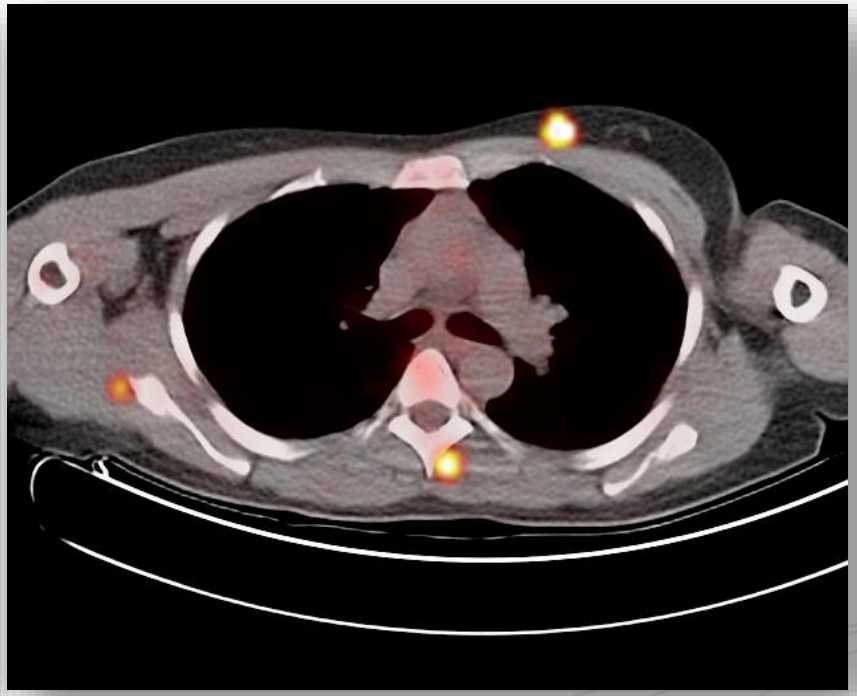
Omgo E. Nieweg, M.D., Ph.D., E. Edmund Kim, M.D., M.S.,† Wai-Hoi Wong, Ph.D.,† William F. Broussard, B.S.,† S. Eva Singletary, M.D.,* Gabriel N. Hortobagyi, M.D.,‡ and Roy S. Tilbury, Ph.D.†*

CANCER *June 15, 1993,* Volume 71, No. 12



Much better today





Current position of FDG PET/CT

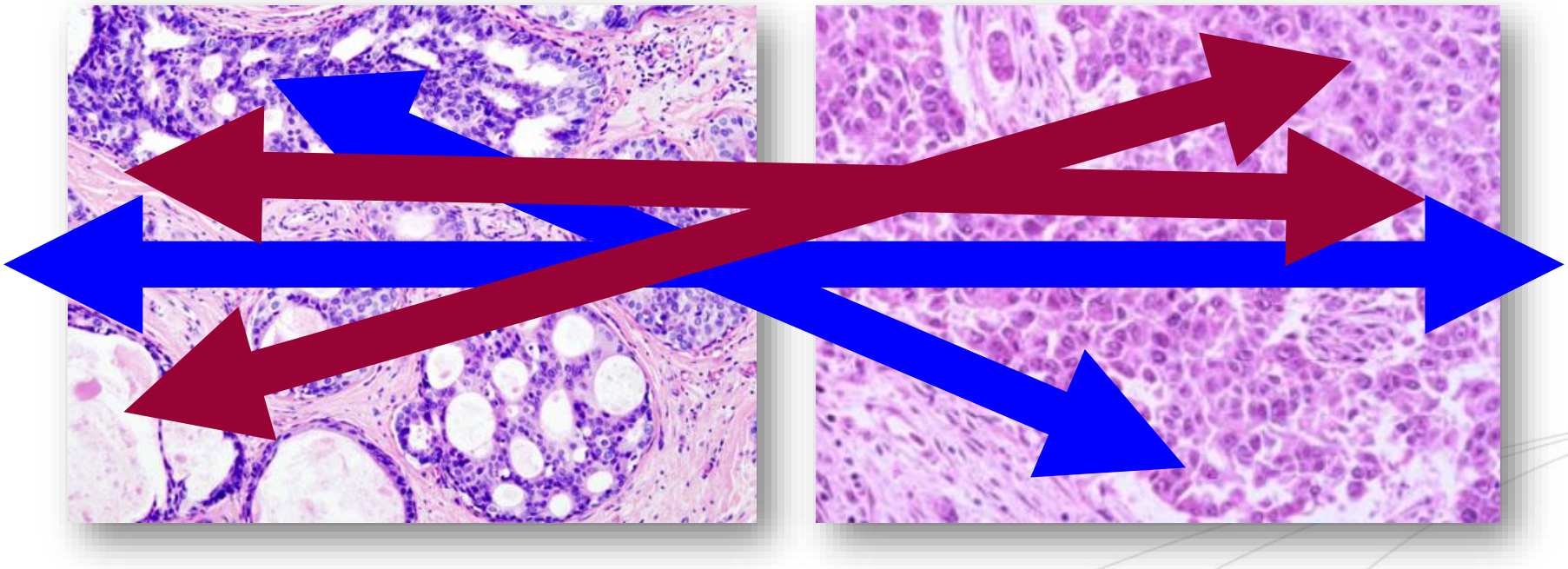
- Biology
- Positioning (prone versus supine)
  - Breast
  - Nodes
  - Body
- Value and indications
  - Primary staging
  - Restaging
  - Response
- PET/MR

Biology

impact on FDG PET/CT

Breast cancer

- A broad spectrum of tumor types
- With highly variable biological behaviour

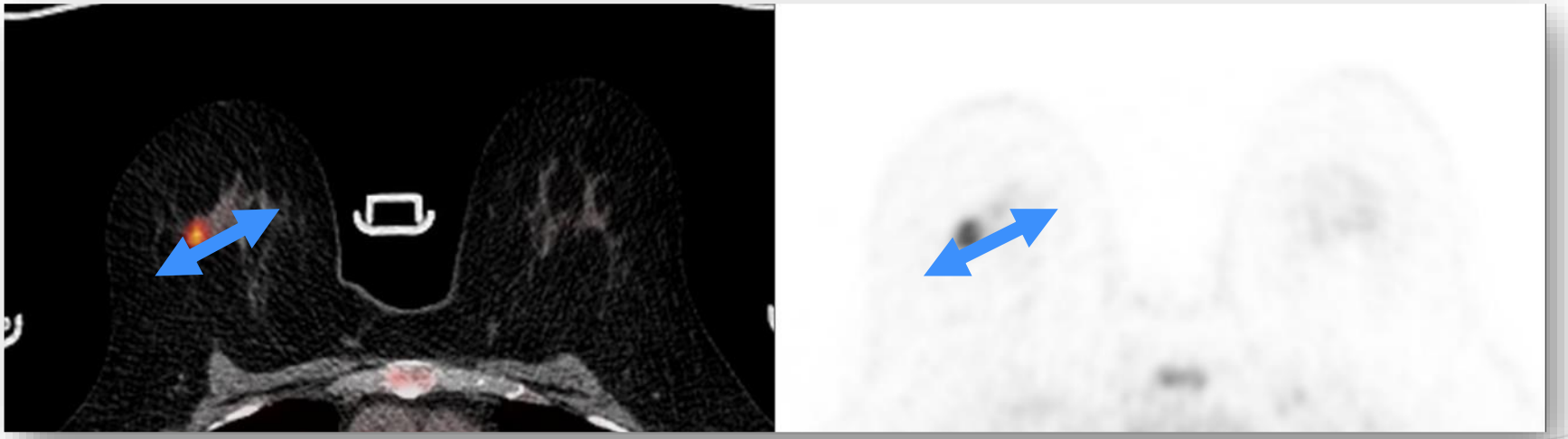


DCIS grade I

IDC grade III

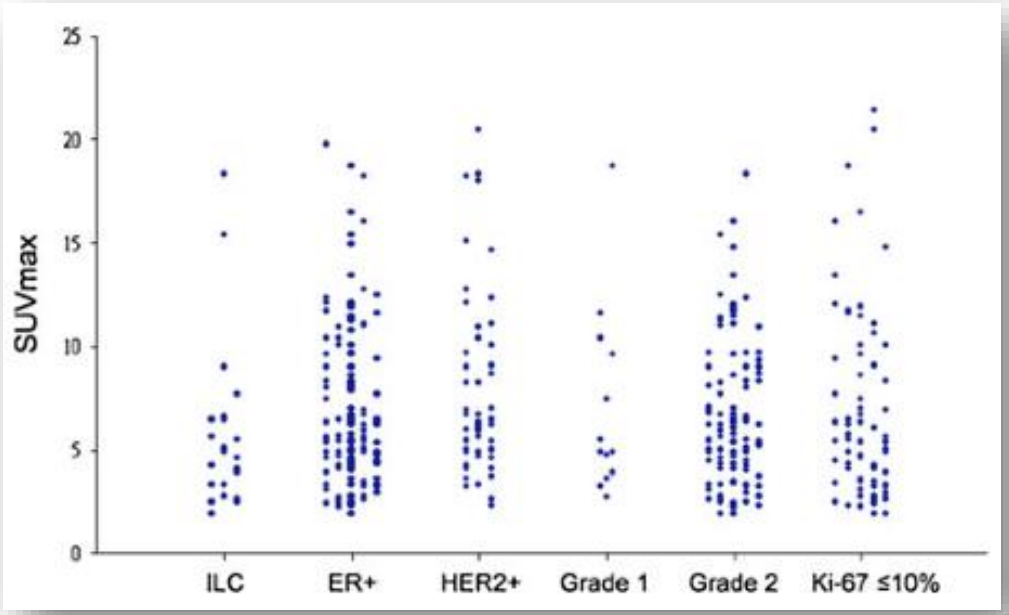
Only invasive carinoma

- IDC grade II, 1.5 cm
- DCIS grade II, about 7 cm



Detection of invasive carcinomas

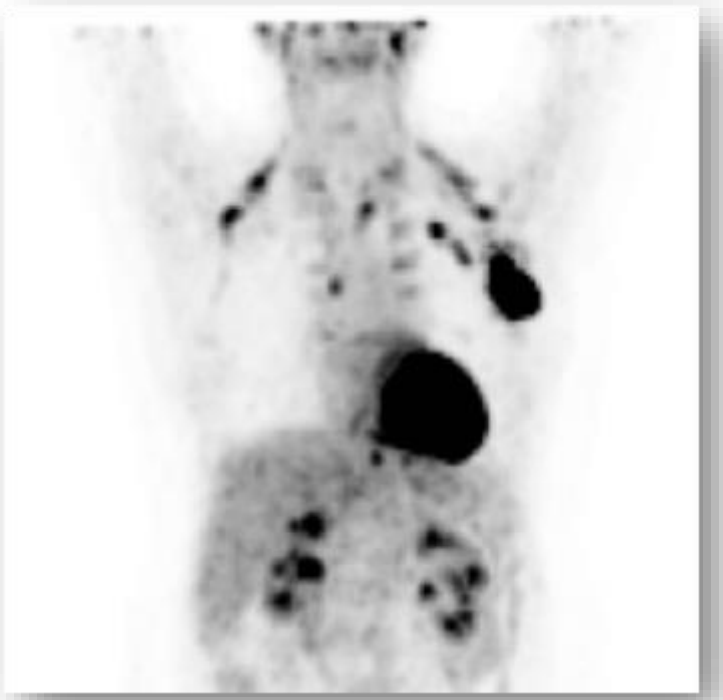
- Highly variable uptake
- No subgroup that will not benefit from FDG-PET



Association of primary tumour FDG uptake with clinical, histopathological and molecular characteristics in breast cancer patients scheduled for neoadjuvant chemotherapy.

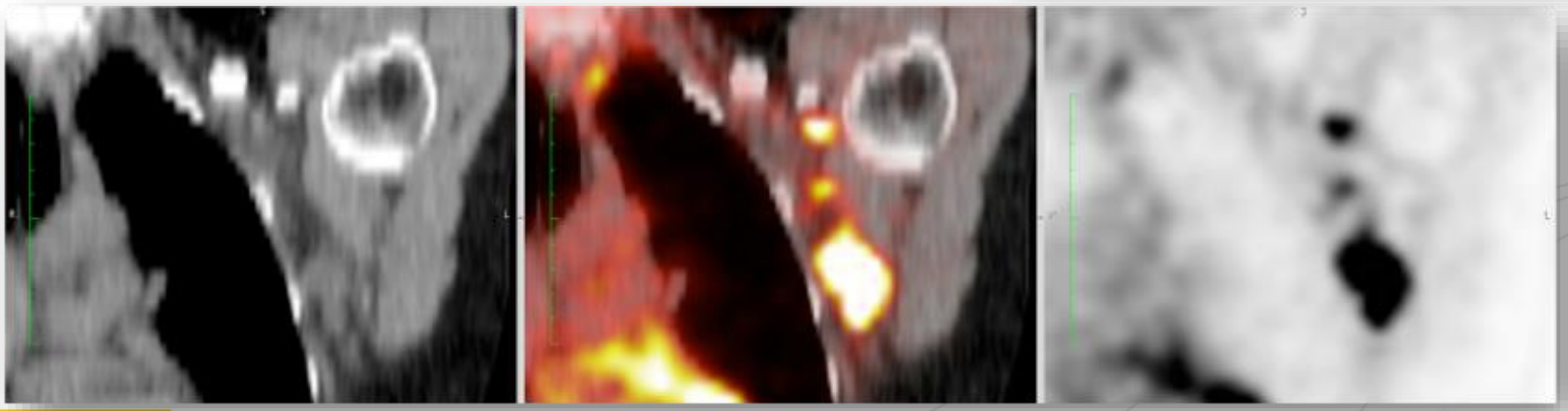
Koolen BB et al. Eur J Nucl Med Mol Imaging. 2012 Dec;39(12):1830-8.

Brown adipose tissue



Our solution

- Arrive 15-30 minutes early
- Diazepam 5-10 mg
- Warm blanket / heating
- Resting
- FDG injection



Patient positioning

Optimal FDG PET/CT
for breast cancer imaging

Imaging strategies

• Compressed	Like mammography
• Prone position – local	“Hanging breast” dedicated PET
• Prone position – regional	“Hanging breast” PET/CT
• Supine position	Standard PET/CT acquisition

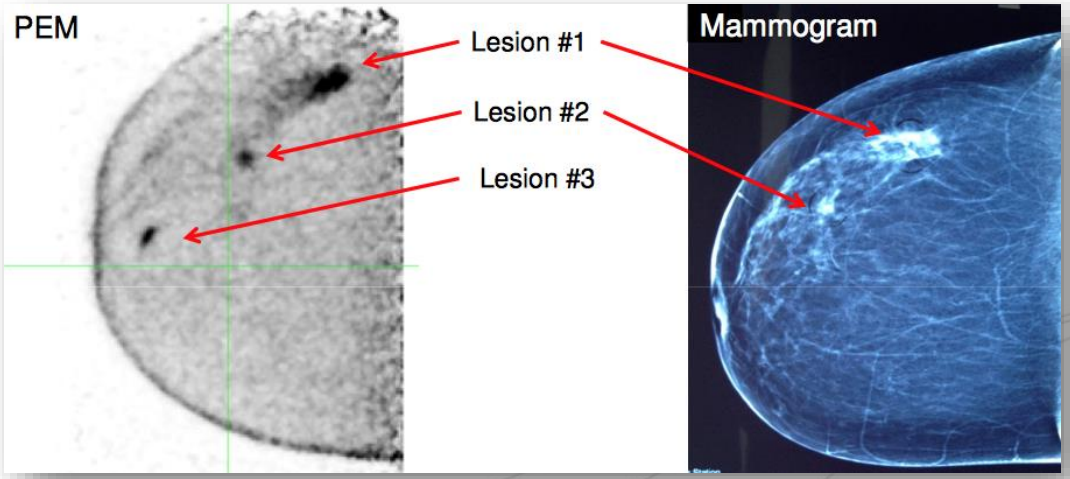
PEM - compressed imaging

Advantages

- High spatial resolution / sensitivity
- “Correlation” with mammography
- Biopsy capable

Disadvantages

- More equipment
- Uncomfortable
- One breast
- Overprojection
- Very small FOV
- No MR match



Naviscan PEM, using 300 – 740 MBq FDG

PEM - clinical results

Prospective evaluation of 178 patients, versus PET/CT

- Better sensitivity 95% v 87%
- More multifocality 57% v 13%
- largest difference in small tumors (<1cm)

Dilemmas

- Clinical impact?
- Indications?

Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):260-75. doi: 10.1007/s00259-013-2553-1. Epub 2013 Oct 2. Breast cancer detection using high-resolution breast PET compared to whole-body PET or PET/CT. Kalinyak JE1, Berg WA, Schilling K, Madsen KS, Narayanan D, Tartar M.

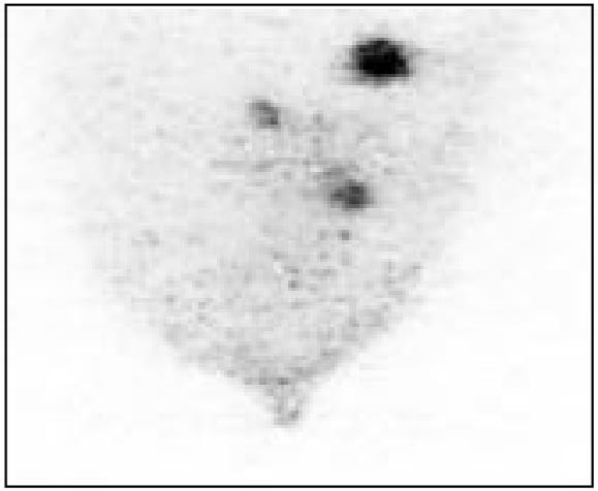
Dedicated breast PET

Advantages

- Good resolution / sensitivity
- No compression
- Reasonable correlation with MR

Disadvantages

- Additional equipment
- No match with mammography
- Small field of view
- One breast



Dedicated PET - clinical results

Prospective eval. 32 stage II-III patients versus PET/CT

- Equal sensitivity 97% v 97%
- Higher spatial resolution 1.5 mm
- Higher SUV values Factor 2-3

Dilemmas

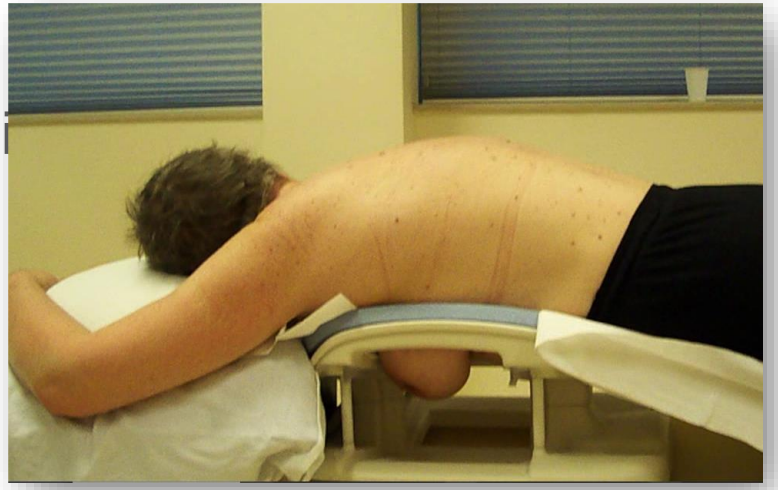
- Clinical impact?
- Indications?

Eur J Nucl Med Mol Imaging. 2014 Feb;41(2):260-75. doi: 10.1007/s00259-013-2553-1. Epub 2013 Oct 2.
Breast cancer detection using high-resolution breast PET compared to whole-body PET or PET/CT.
Kalinyak JE1, Berg WA, Schilling K, Madsen KS, Narayanan D, Tartar M.

Prone position hanging breast on PET/CT

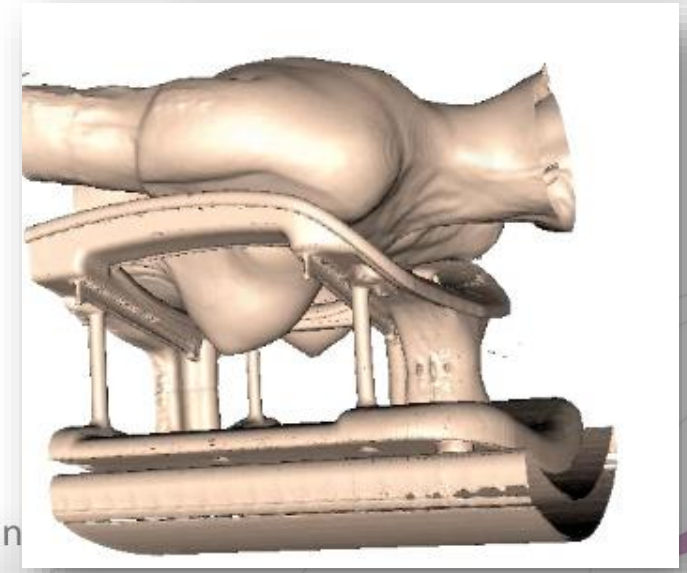
Advantages

- Reasonable resolution / sensi
- No compression
- Good correlation with MR



Disadvantages

- No match with XMG
- Double radiation
- Adaptations needed

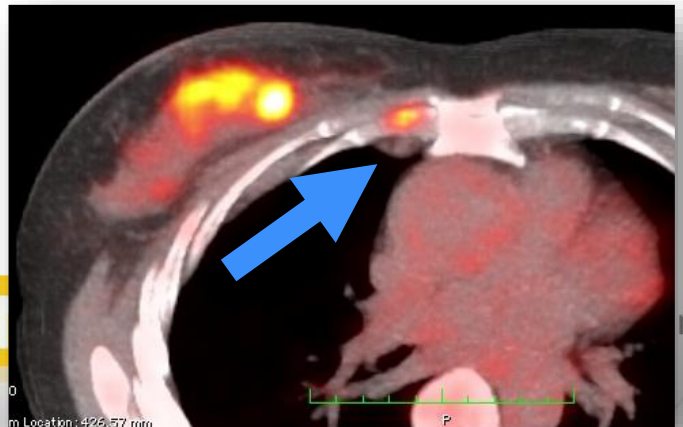


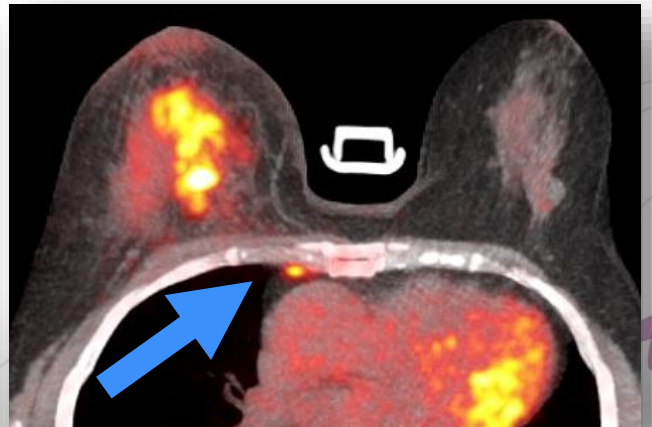
PET/CT supine versus prone

Hanging breast configuration

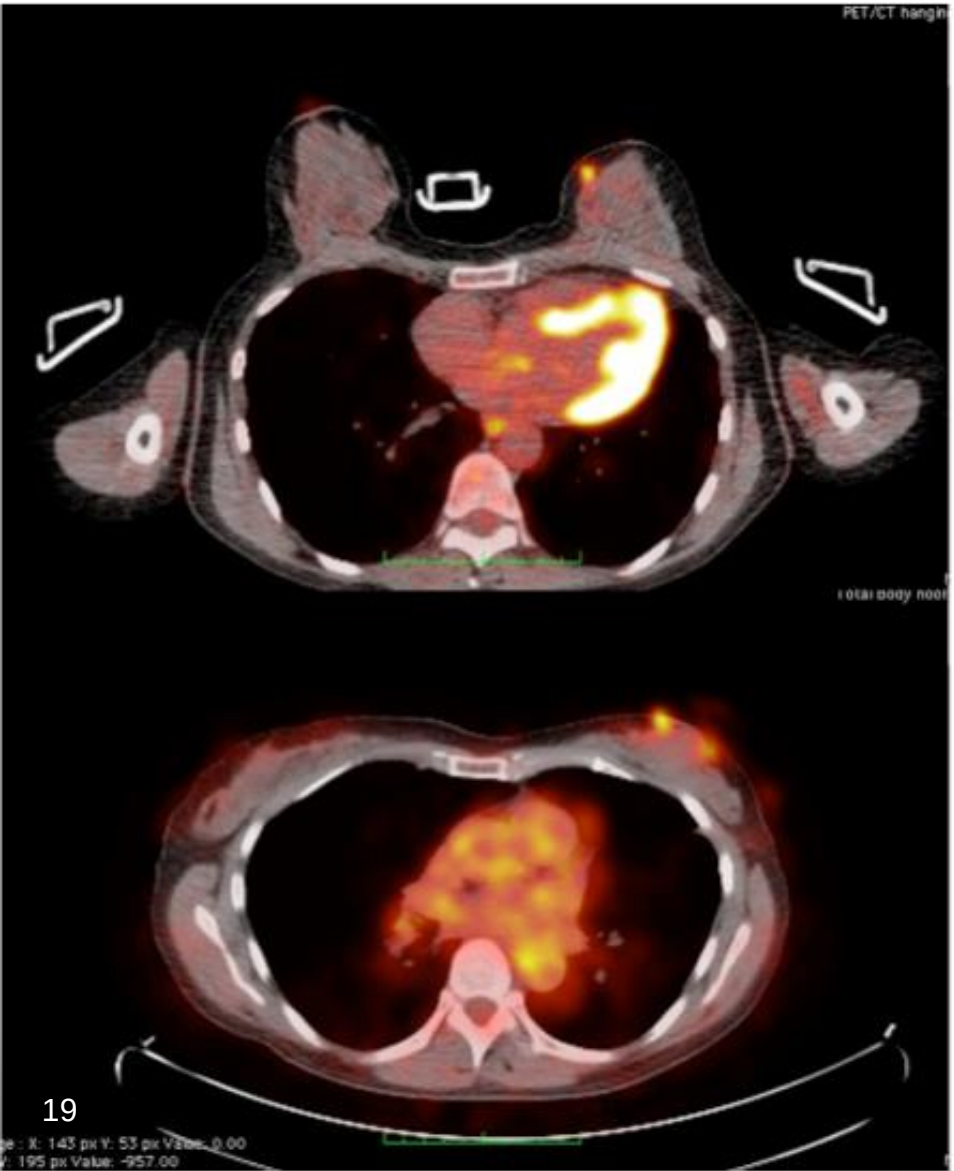
- No breathing artefacts
- Less compression of breast tissue
- Better alignment of PET and CT

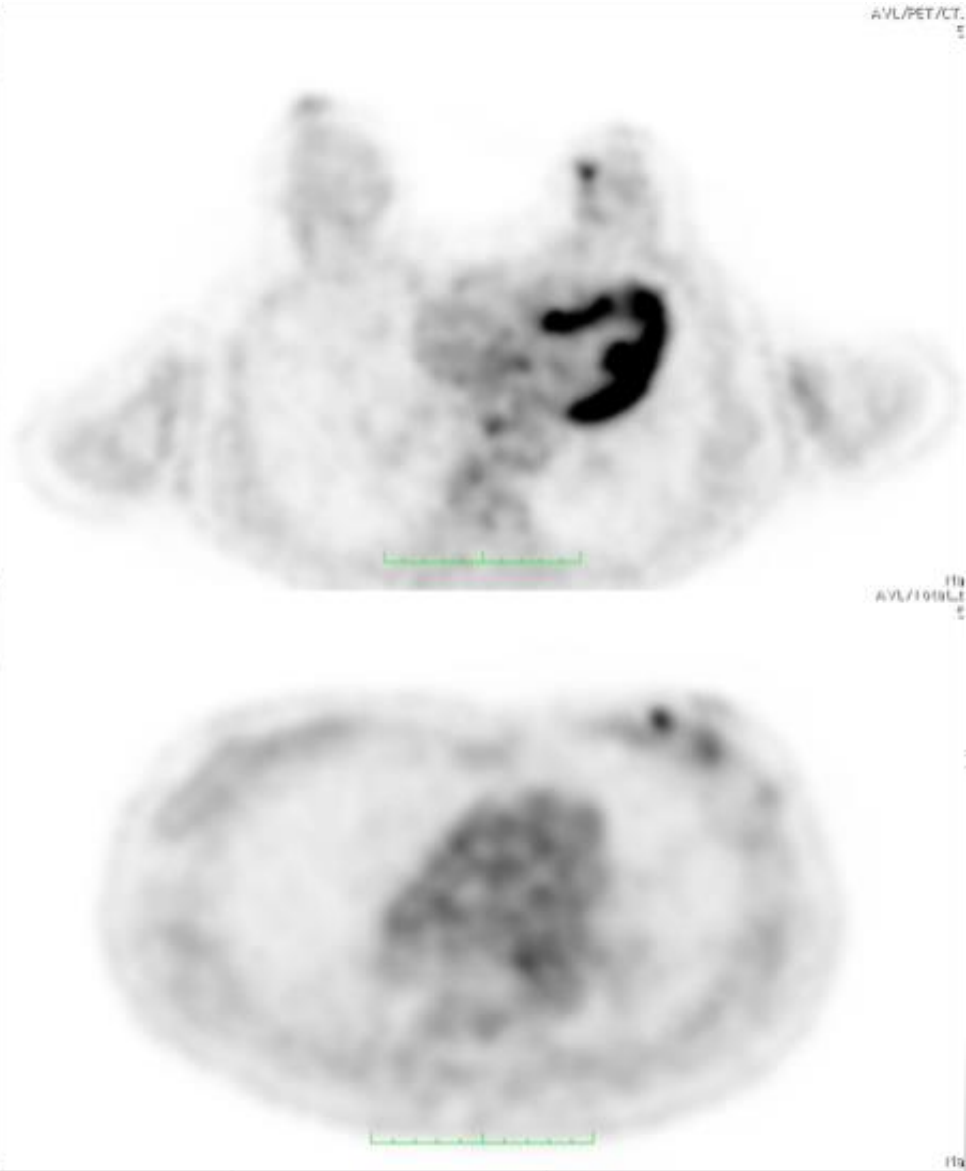
- High resolution reconstruction
- Longer acquisition time (3 min/bp)
- TOF-HR algorithm, voxels 2x2x2 mm



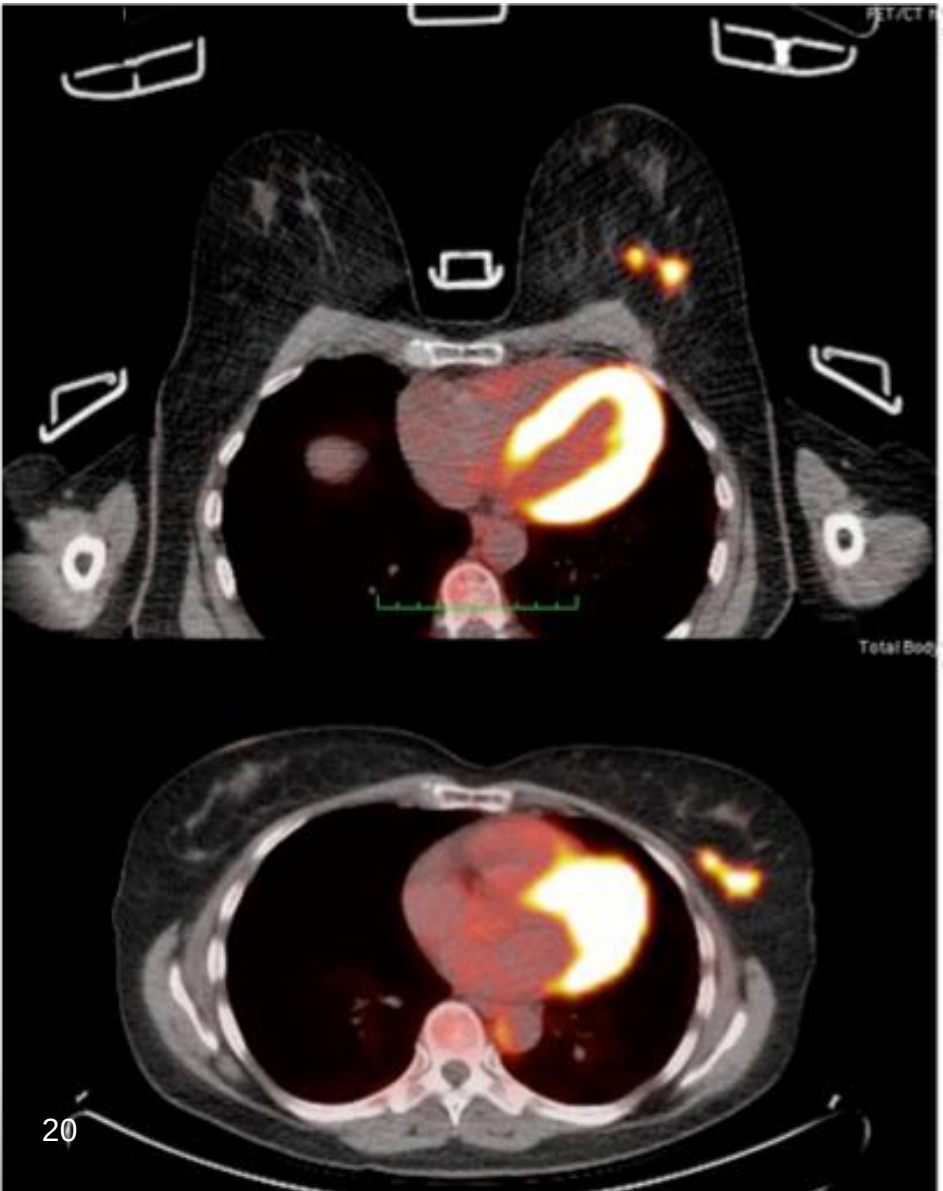


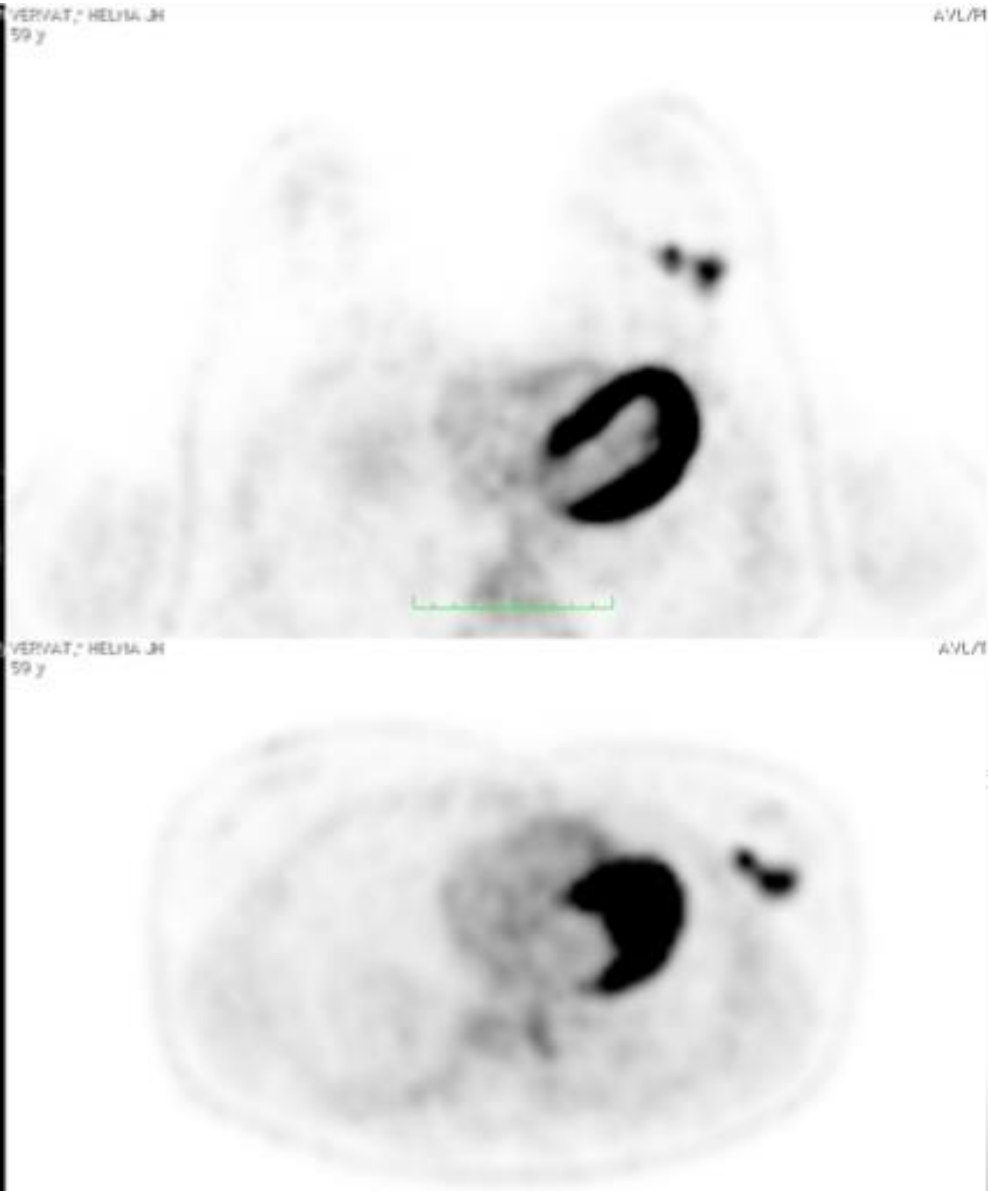
Prone PET/CT – Dense, breath, position



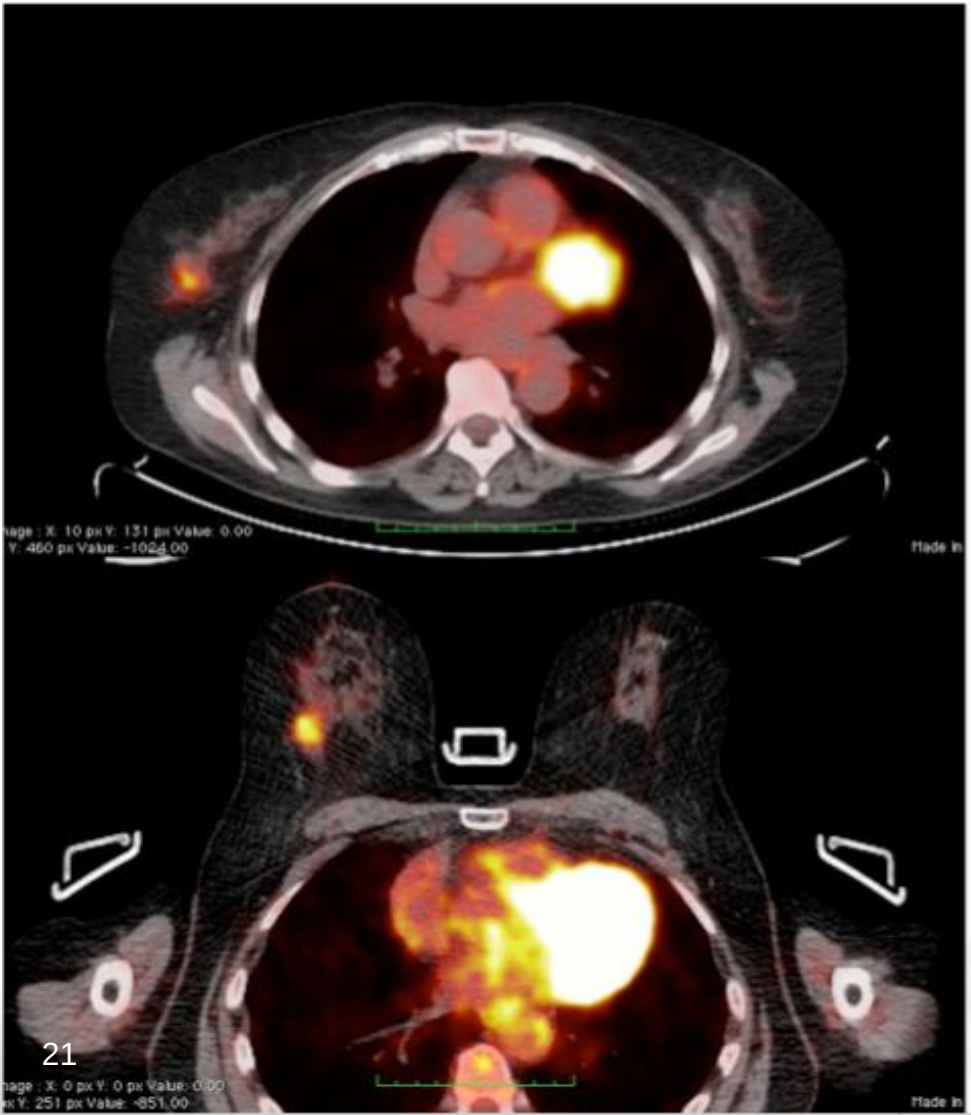


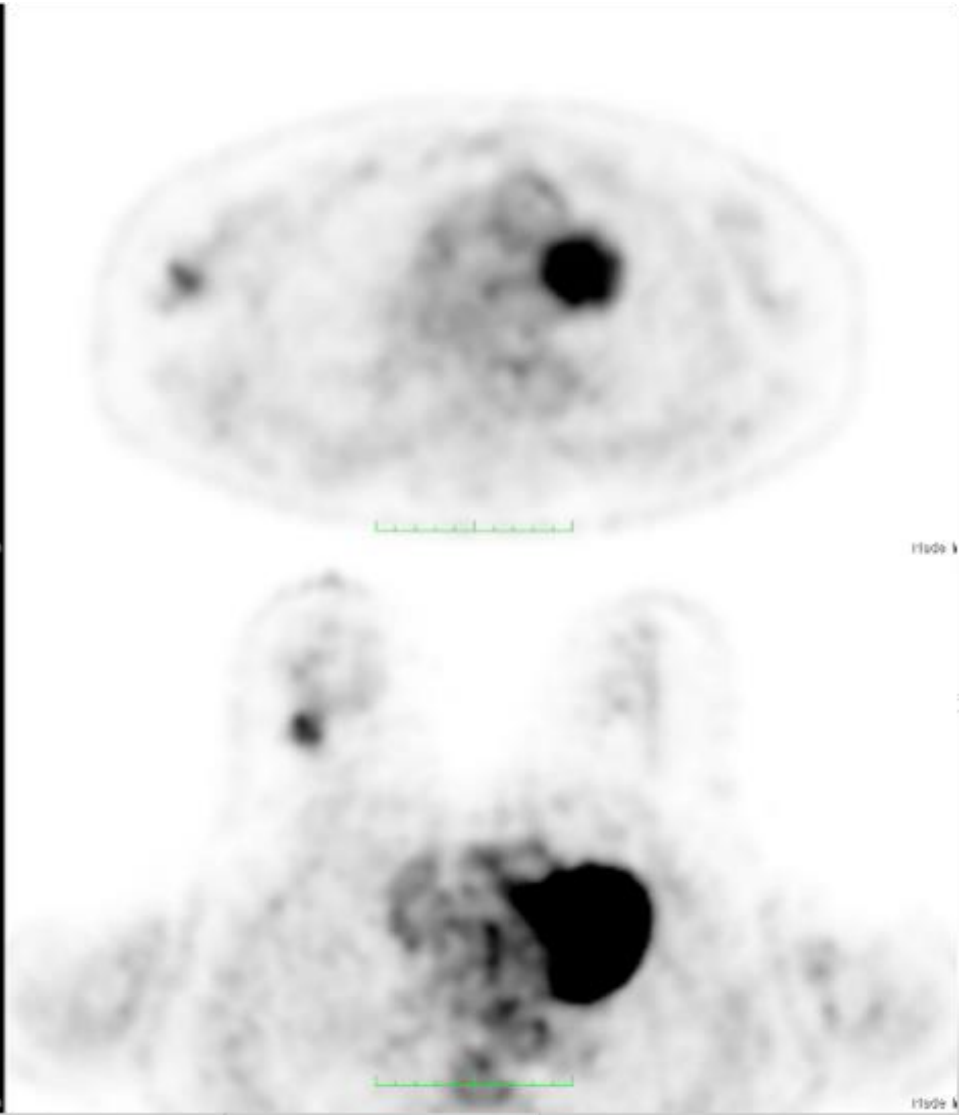
Prone PET/CT – Shape, multifocal





Prone PET/CT – Location, intensity





PET/CT prone – clinical results

Retrospective evaluation of 198 patients

- Visually better image quality
- More primary tumor multifocality
- More positive axillary nodes
- Metabolic tumor volumes smaller
- SUVmax / TBR higher
- Visually less anatomical mismatch of nodes

Unpublished data – manuscript under construction

Value of optimal FDG PET/CT for staging breast cancer

Primary tumor detection

Hanging breast imaging provides good detection of T1 invasive tumors (n=62)

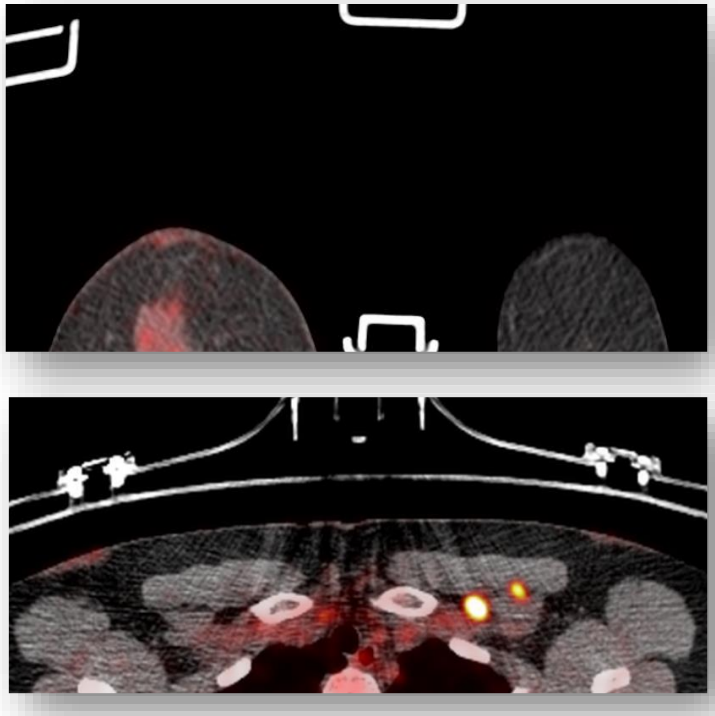
- Tumors <10 mm 59 %
- Tumors 11-20 mm 98 %
- Triple negative tumors 100 %
- HER2+ tumors 100 %
- ER+ HER2- tumors 83 %

Additional supine body imaging has a low yield

- 1 confirmed distant metastasis

Accuracy of 18F-FDG PET/CT for primary tumor visualization and staging in T1 breast cancer. Koolen BB, et al. Acta Oncol. 2014 Jan;53(1):50-7.

Nodal staging (n=311)



Axilla

- Sens 82 % NPV 53 %
- Spec 92 % **PPV 98 %**

58 new node areas in 56 pts

- 32 periclavicular area
- 26 internal mammary chain

Conclusions

- FDG PET/CT cannot replace SLNB when negative
- FDG positive nodes are highly predictive for N+, no SN
- FDG PET/CT frequently upstages to N2 or N3

Pre-chemotherapy 18F-FDG PET/CT upstages nodal stage in stage II-III breast cancer patients treated with neoadjuvant chemotherapy. Koolen BB et al. Breast Cancer Res Treat. 2013 Sep;141(2):249-54.

High impact on RT nodal fields

- Increasing use of neo-adjuvant chemotherapy
- Indication for nodal irradiation based on risk assessment
  - Before NAC and after NAC
- Identify indication for RT as early as possible
- Standard imaging is not adequate
  - SN No number / location of involved nodes
  - US/fna No number / location, not all areas
  - MR No overview of all areas at risk

FDG-PET/CT 18%

- 12% unexpected ≥4 axillary nodes
- 11% unexpected N3

Distant metastasis

Stage II-III, prior to NAC, comparison with standard-of-care (n=154)

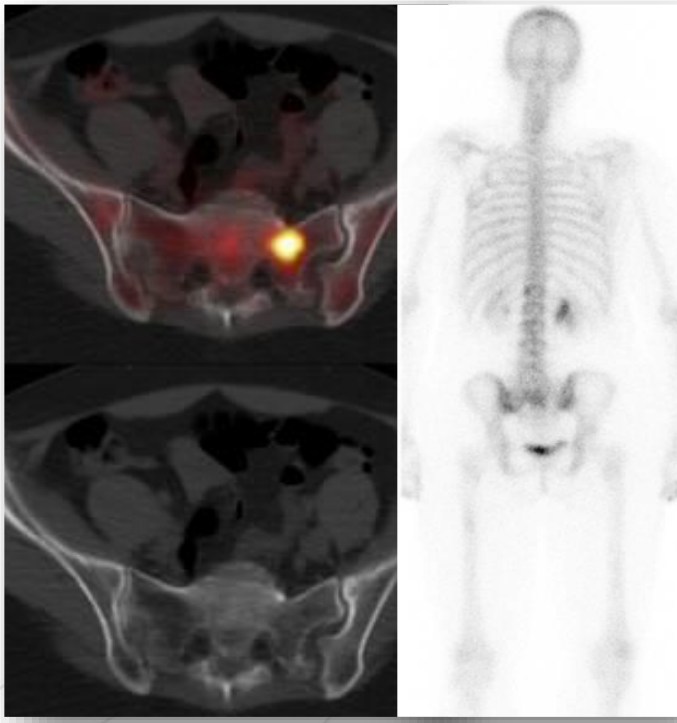
- FDG PET/CT hanging breast + supine body
- X-thorax + US liver + bone scan

Diagnostic value

- Sensitivity 100 %
- Specificity 96 %

Clinical impact of adding FDG PET/CT

- 42 lesions detected in 25 patients
- 13% of patiens change of treatment



18F-FDG PET/CT as a staging procedure in primary stage II and III breast cancer: comparison with conventional imaging techniques. Koolen BB et al. Breast Cancer Res Treat. 2012 Jan;131(1):117-26.

Recurrent disease

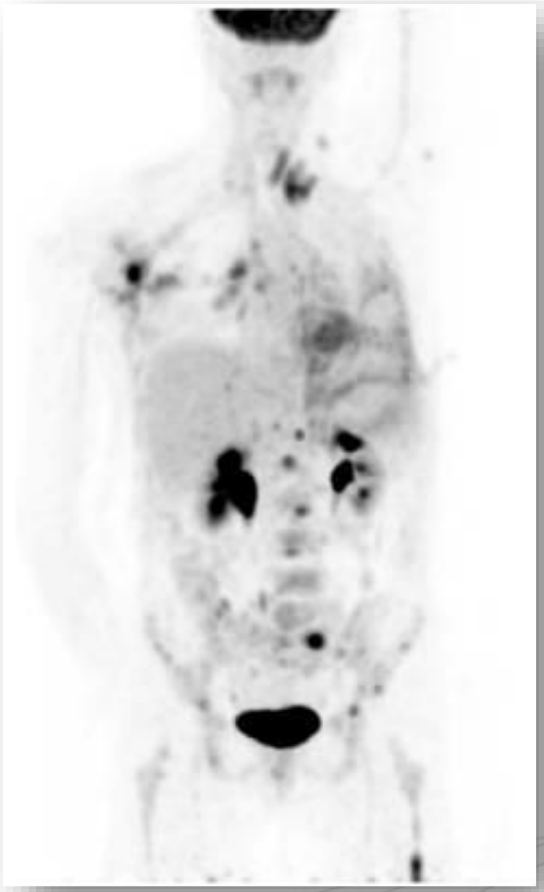
In case of apparently limited disease, aggressive local disease is considered

Diagnostic value

- Sensitivity 97 %
- Specificity 92 %

Clinical impact of FDG PET/CT

~ 50 % of patiens change of treatment



The role of FDG PET/CT in patients with locoregional breast cancer recurrence: a comparison to conventional imaging techniques. Aukema TS et al. Eur J Surg Oncol. 2010 Apr;36(4):387-92.

National guideline NL

FDG PET/CT

- Recommended for stage III
- Can be considered for stage II

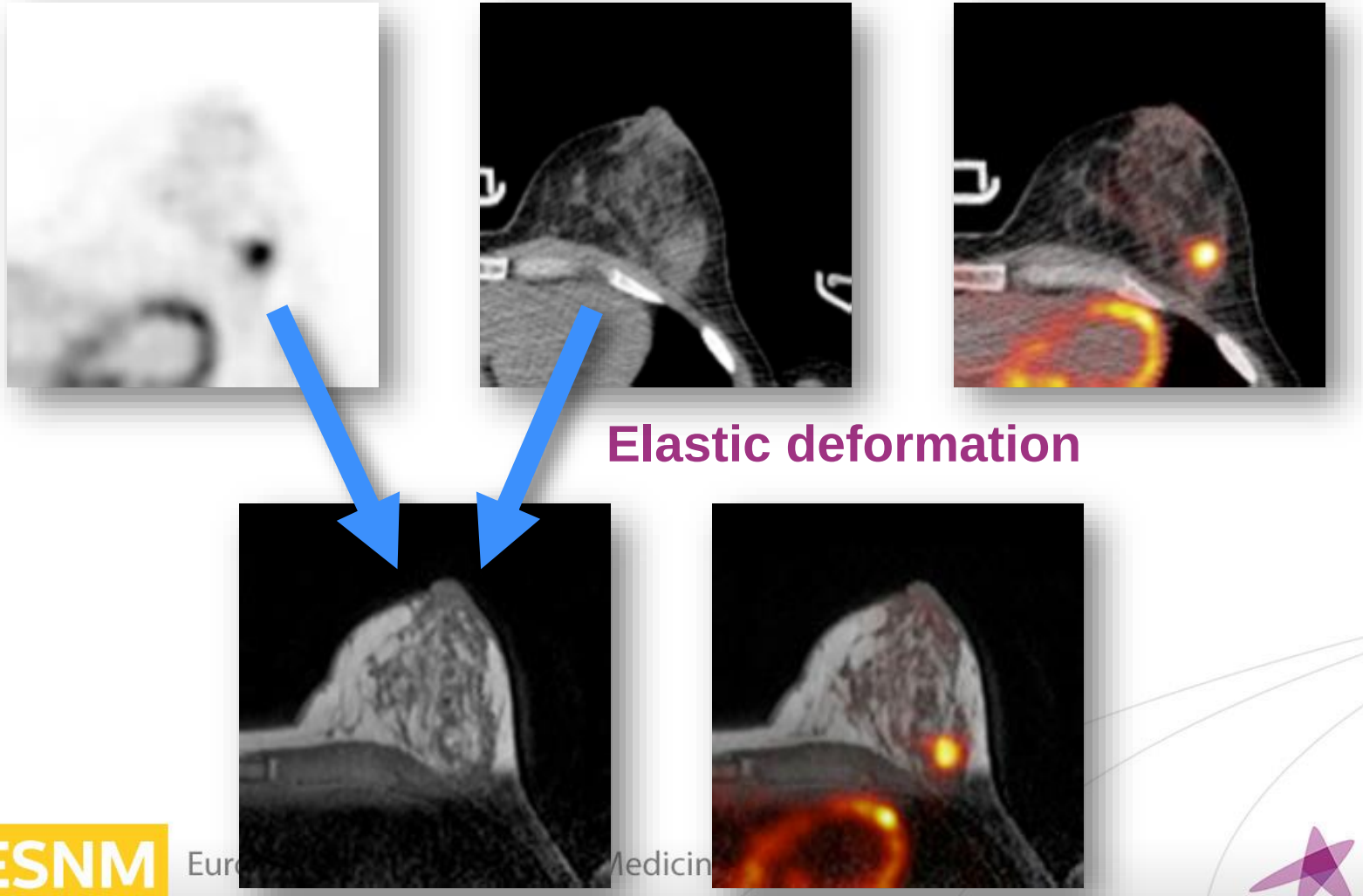
- Essential for recurrent disease

PET/CT is essentially the new standard of care for staging and restaging, and has replaced X-thorax, US liver and bone scan

Combined PET/MR

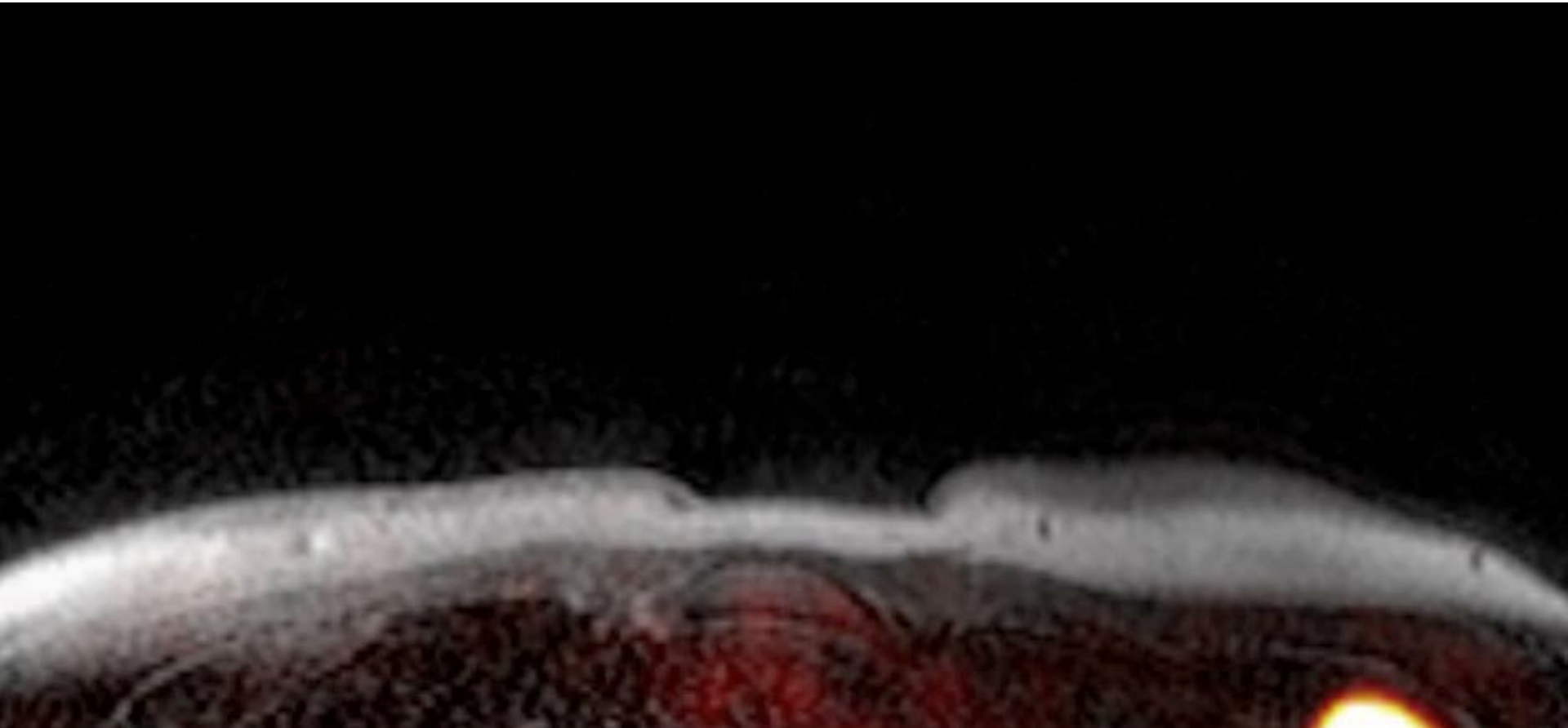
(working towards a perspective)

Software fusion strategy



Example fused PET/MR

- Looks good
- Reliable image correlation



Why combine PET and MR ?

Routine clinical applications

- Detection of small tumors
- Detection of multifocal / multicentric disease
- Lymph node staging
- Distant staging

Research

- Tumor characterization
- Response evaluation

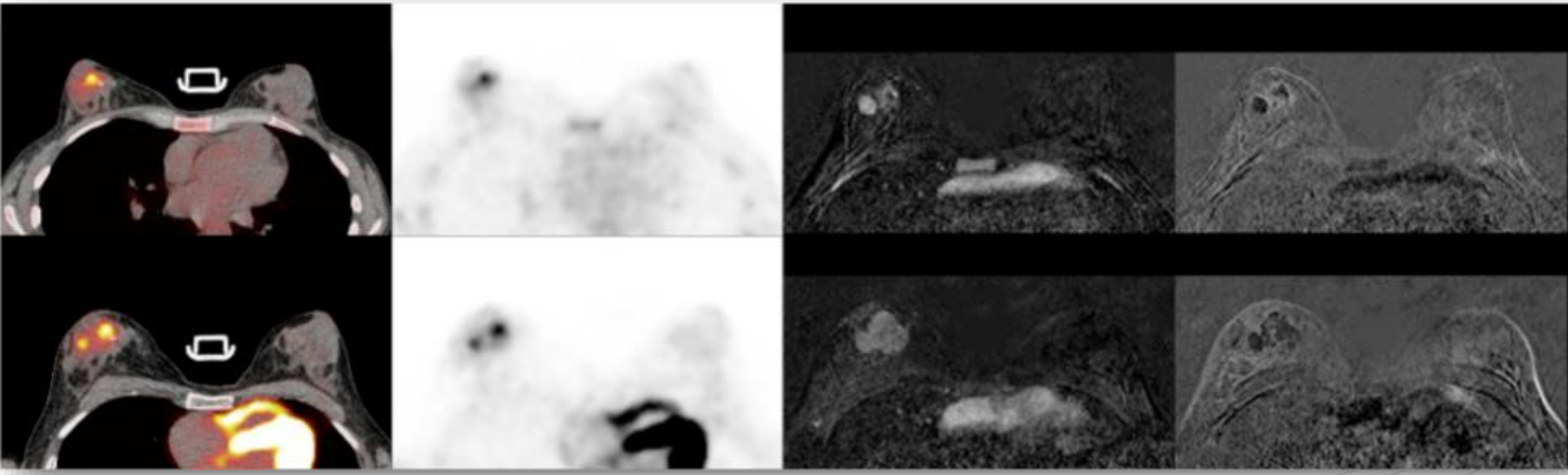
Voxel-based analysis – Example

Potential applications

- Voxel-by-voxel signal correlation
- Guide biopsy

Voxel-based response evaluation

- MRI sometimes fails to predict pCR
- FDG PET sometimes fails to predict pCR

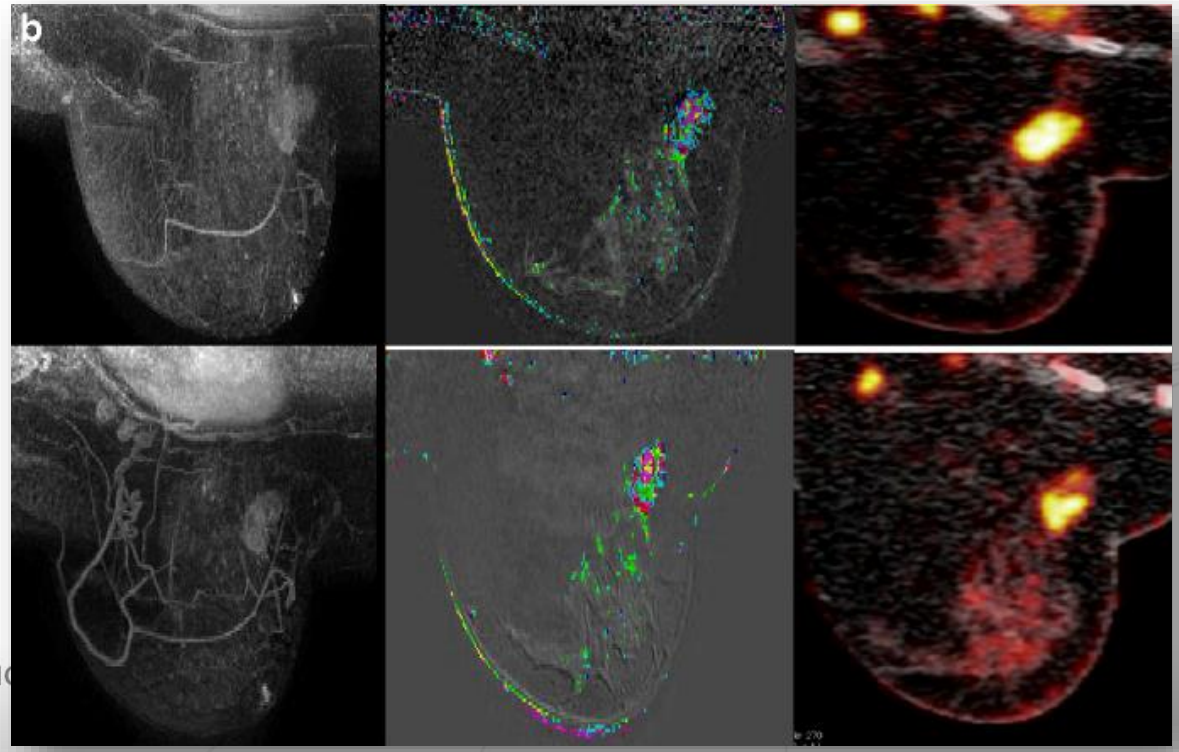


All information needed to fully understand biological response

PET/MR – promising for response

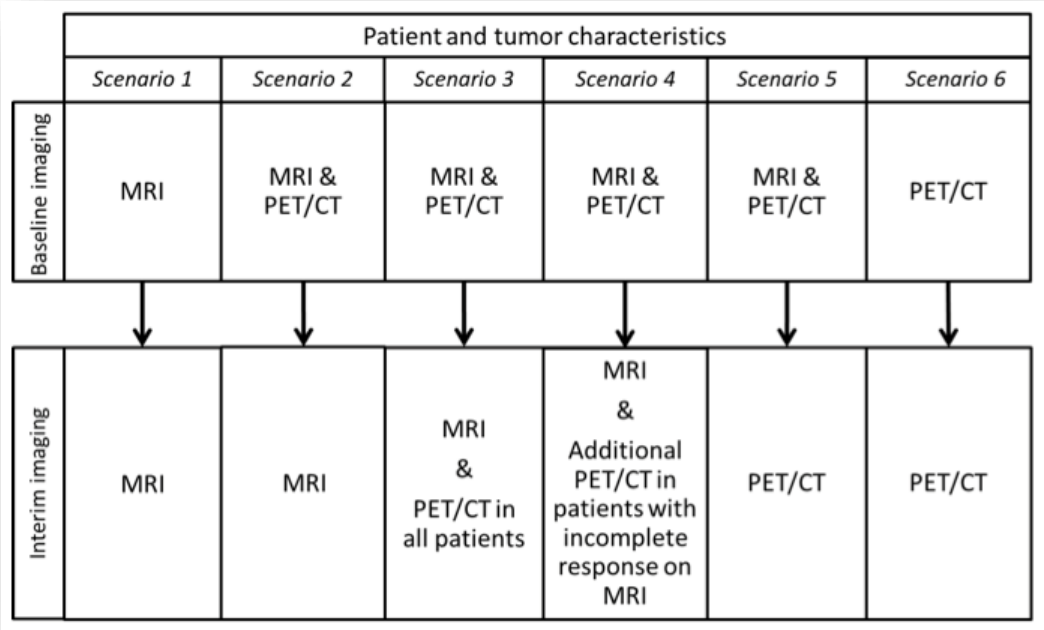
FDG PET and MR have comparable value for response evaluation in predicting pCR halfway NAC

- MR contrast washout diameter AUC 0,79
- FDG PET SUVmax AUC 0,78



Combined use of ^{18}F-FDG PET/CT and MRI for response monitoring of breast cancer during neoadjuvant chemotherapy.
Pengel KE et al. Eur J Nucl Med Mol Imaging. 2014 Aug;41(8):1515-24.

PET/MR – Tumor type dependency



	Patient and tumor characteristics					
	Scenario 1	*Scenario 2*	*Scenario 3*	*Scenario 4*	*Scenario 5*	*Scenario 6*
Baseline imaging	MRI	MRI & PET/CT	MRI & PET/CT	MRI & PET/CT	MRI & PET/CT	PET/CT
Interim imaging	MRI	MRI	MRI & PET/CT in all patients	MRI & Additional PET/CT in patients with incomplete response on MRI	PET/CT	PET/CT

Tentative conclusion

- Triple - MR preferred, FDG PET good alternative
- HER2+ MR preferred
- ER+HER2- Combined MR and PET highest accuracy

Manuscript in development. Schmitz A et al.

Thank you for your attention

Questions ?

PET/CT
Gynaecological and Gastrointestinal Malignancies

Maria Picchio, Milan, Italy

Ursula Nestle, Freiburg, Germany

ESNM European School of Nuclear Medicine

ESTRO School

PET/CT and Gynaecological Malignancies

PET/CT and Gynaecological Malignancies

Uterus:

- **Cervical**
- **Endometrial**

Ovarian

PET/CT and Gynaecological Malignancies

Uterus:

- **Cervical**
- **Endometrial**

Ovarian

Which is the role of PET/CT for radiotherapy treatment in Gynaecological Malignancies?

PET/CT and Cervical cancer

Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and Cervical cancer

Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and Cervical cancer

Different treatment according to tumor stage and nodal status

- Early-stage: surgery alone

- Locally advanced / node-positive disease: external beam radiotherapy (EBRT) + concomitant Cisplatin chemotherapy (followed by intrauterine brachytherapy)

Barwick et al. Curr Oncol Rep, 2013

PET/CT and Cervical cancer

Nodal status significantly influence disease outcome (Overall Survival)

- 90% in pts with small tumors and negative lymph nodes

- less than 50% in pts with positive pelvic lymph nodes

- <20–30% at 5years for pts with positive para-aortic lymph nodes

Herrera and Prior. Frontiers in Oncology, 2013

PET/CT and Cervical cancer

Table I. *Diagnostic accuracy of ^{18}F-fluoro-D-glucose - positron-emission tomography (FDG-PET)/computerized tomography (CT) for cervical cancer lymph node metastases.*

Reference	Number of patients	Lymph node	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
Yildrim *et al.* (25)	16	PAN	50%	83.3%	75%	50%	83.3%
Loft *et al.* (24)	120	PLN	75%	96%	NA	75%	96%
		PAN	100%	99%	NA	94%	96%
Sironi *et al.* (10)	47	PAN	72%	99.7%	99.6%	81%	99.5%
Choi *et al.* (9)	22	PLN	57.6%	92.6%	85.1%	NA	NA
Havrilesky *et al.* (23)	200	PLN	79%	99%	NA	NA	74%
		PAN	84%	95%	NA	NA	74%

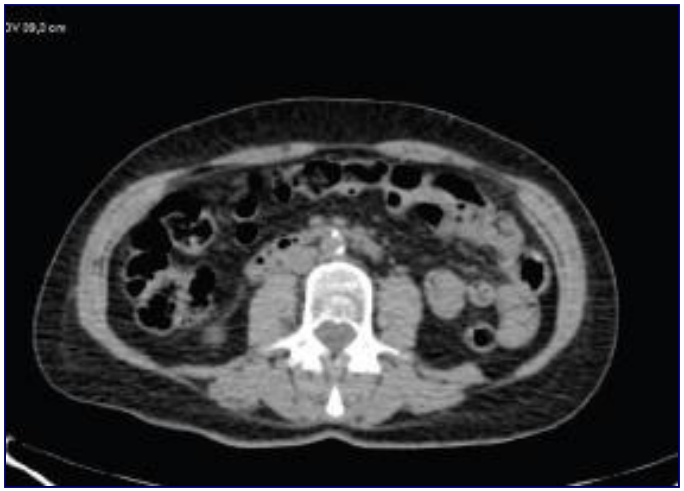
PLN: Pelvic lymph node. PAN: para-aortic lymph node. NA: not available.

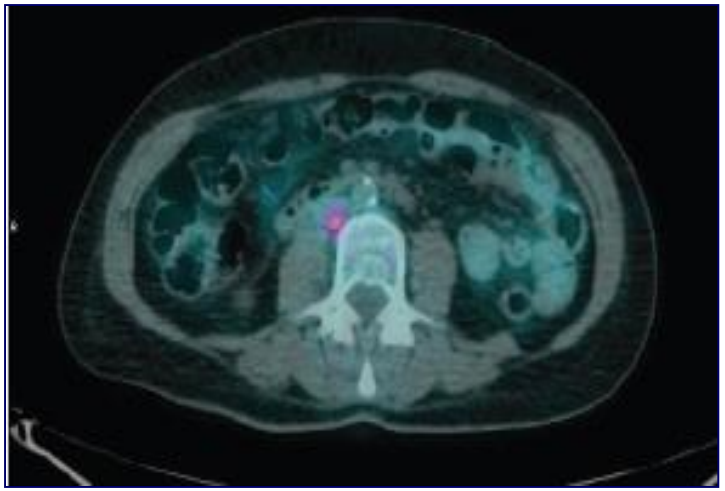
Nogami et al. Anticancer Res, 2014

PET/CT and Cervical cancer

66 patients

CT, MRI and FDG PET/CT to exclude distant metastasis



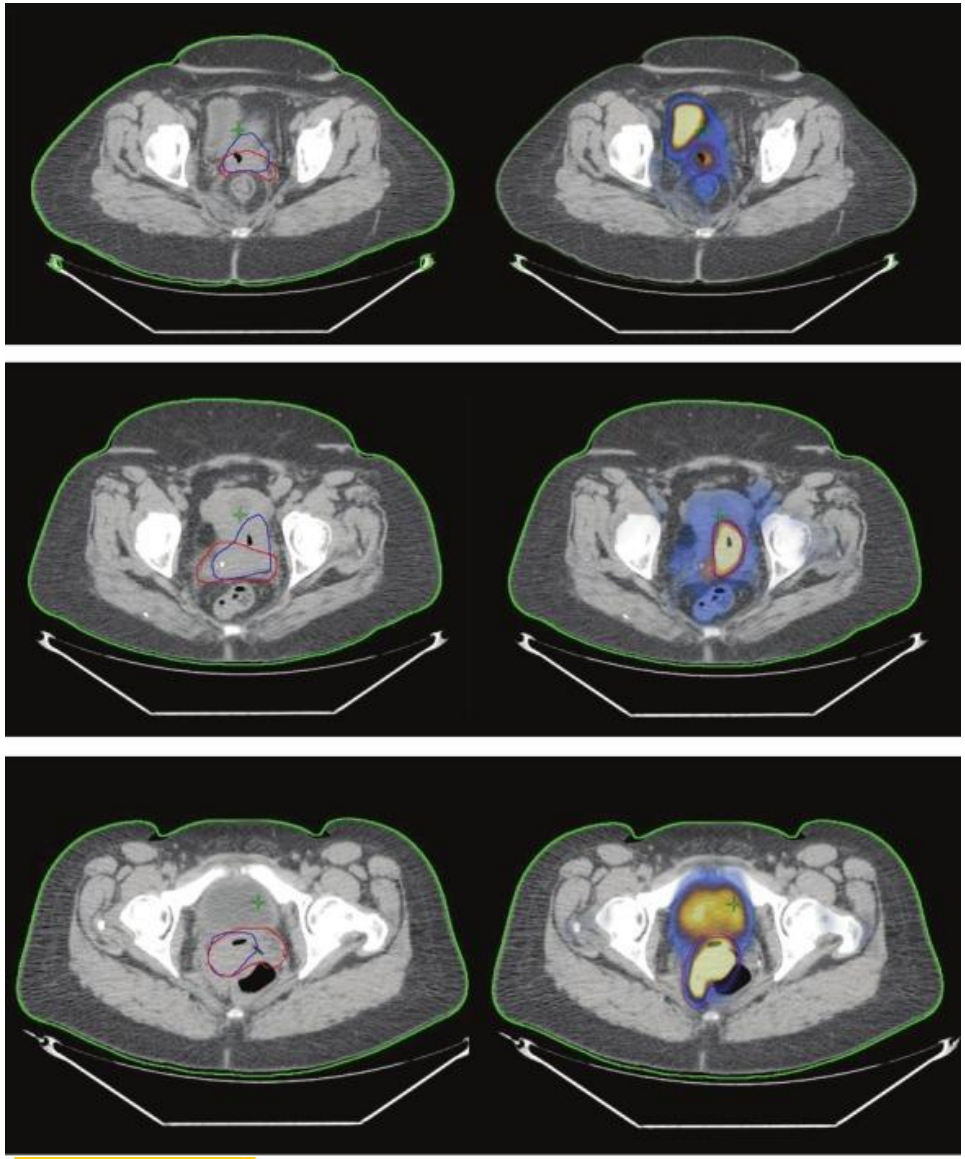


FDG PET/CT changed the stage showing metabolically active tumor in lymph nodes area.

Radiotherapy treatment planning was modified in 25% and 8% of patients that received definitive and adjuvant radiotherapy, respectively.

Lazzari et al. Ecancer, 2014

PET/CT and RT in Cervical cancer



42 patients with stages II-IIIB

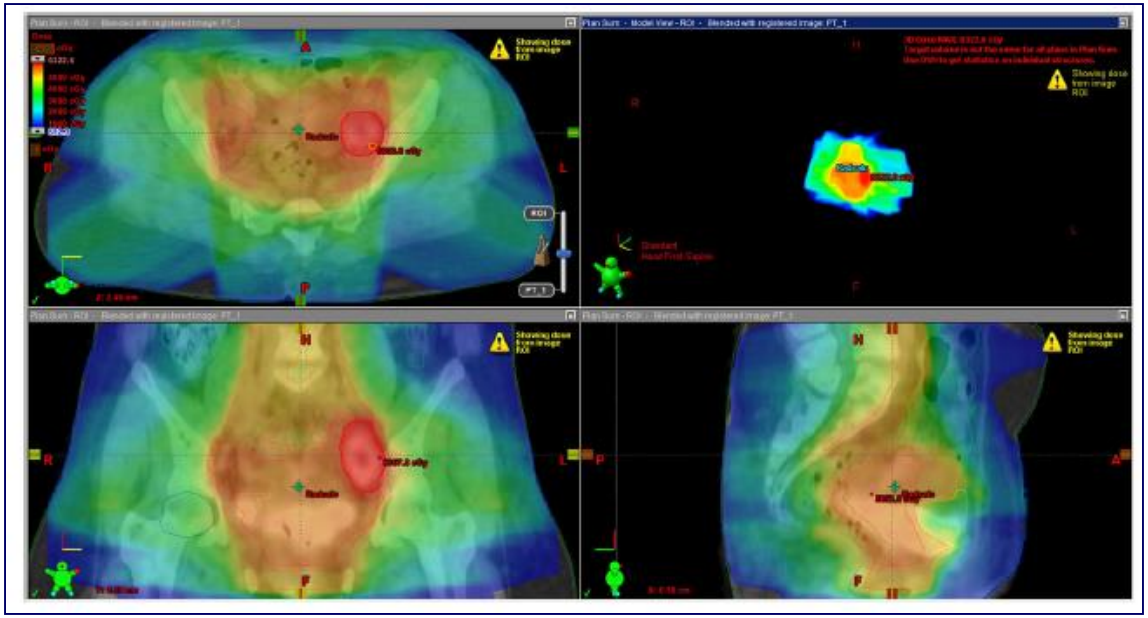
FDG PET/CT for planning RT

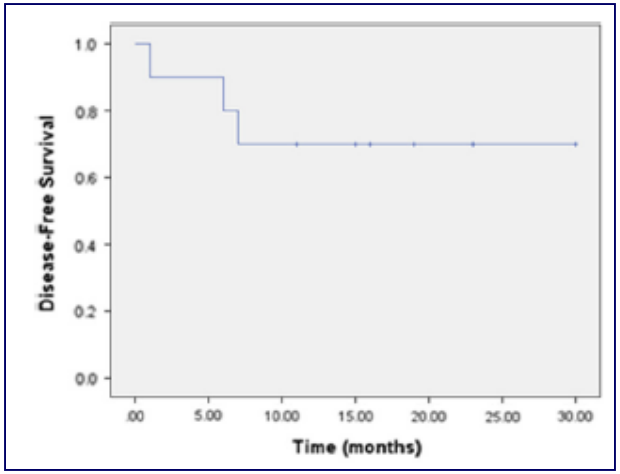
- PET/CT simulation for tumor delineation of disease progression
- FDG-PET is a crucial component in delineating clinically relevant and reproducible tumor volumes given the difficulty of tumor volume visualization on CT alone

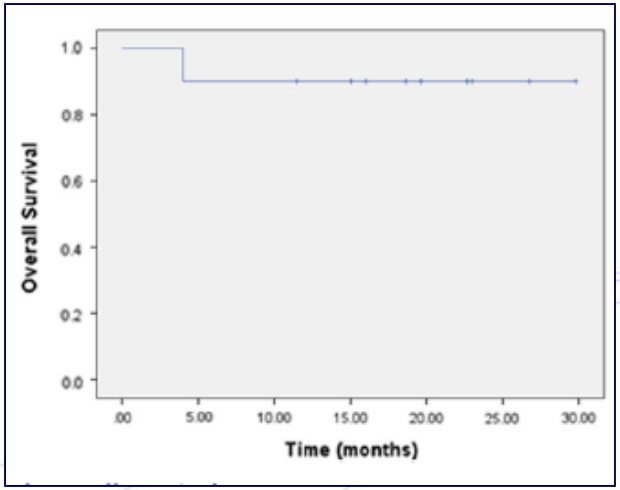
Teiwani et al. Am J Nucl Med Mol Imaging, 2012

PET/CT and RT in Cervical cancer

10 pts with 18F-FDG positive nodes treated with chemoradation with IMRT and SIB







IMRT with SIB on 18FDG-PET positive LN is an effective therapy with acceptable toxicity.

Cihoric et al. Rad Onc, 2014

PET/CT and Cervical cancer

Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and Cervical cancer

One third of patients with locally advanced cervical cancer will have disease recurrence, usually within 2 years of completing treatment.

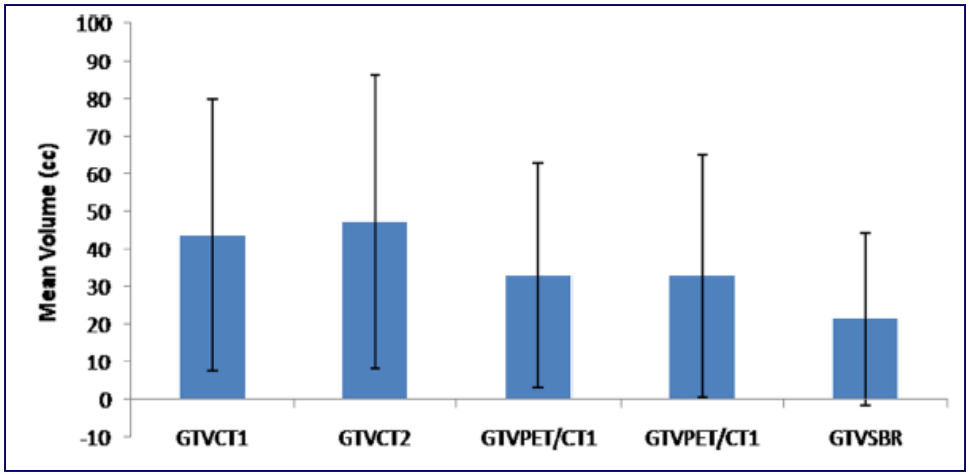
Predictors of disease recurrence include clinical stage, lymph node status at diagnosis and tumor response after treatment.

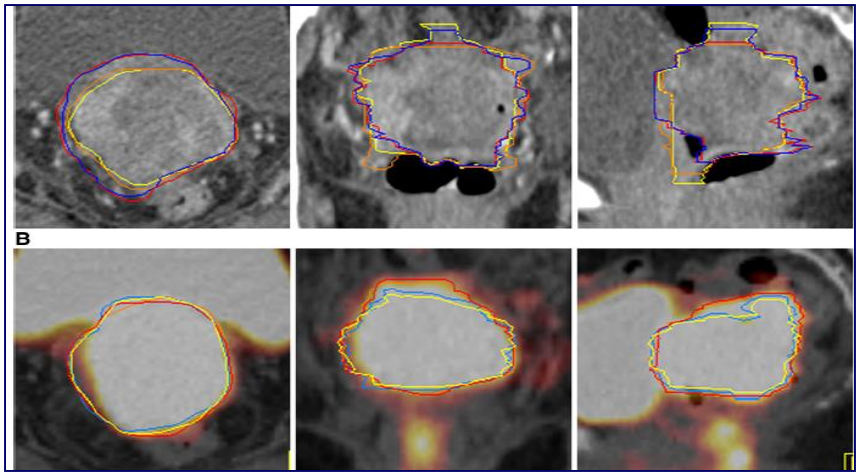
Herrera and Prior. Front in Onc, 2013

PET/CT and RT in Gynaecologic cancer

Impact of ^{18}F-FDG PET/CT on target volume delineation in recurrent or residual gynaecologic carcinoma

10 pts: 5 locally recurrent and 5 post-surgical residual cancer





18F-FDG PET/CT alters the GTV compared to standard CT-definition.

SBR-based auto-delineation showed significantly smaller GTVs.

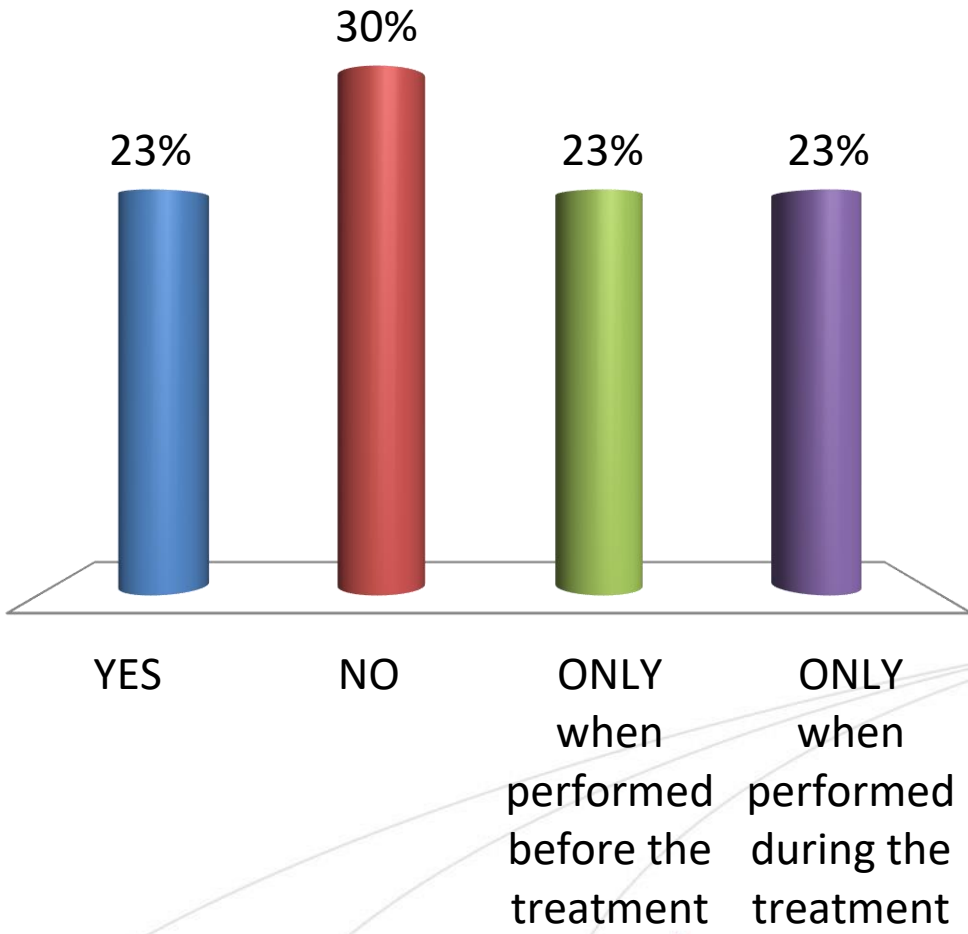
PET/CT based target volume delineation may improve the accuracy of RT treatment planning.

Vees et al. Rad Onc, 2014

QUESTION 1.

Is PET/CT able to predict RT response in Cervical cancer?

A. YES
B. NO
C. ONLY when performed before the treatment
D. ONLY when performed during the treatment



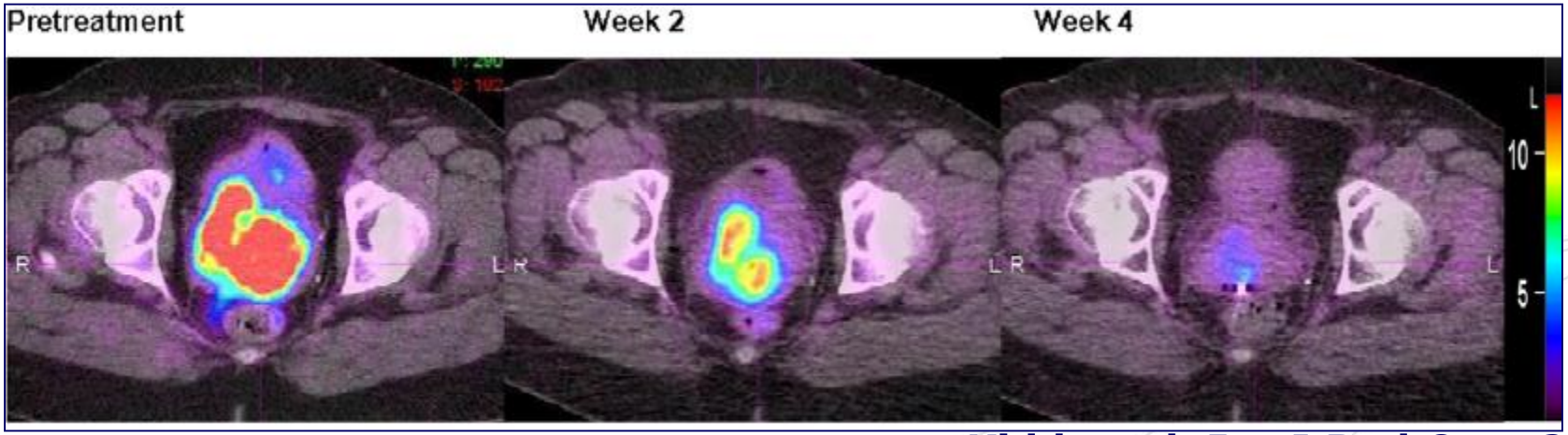
PET/CT and RT in Cervical cancer

Changes in Cervical Cancer FDG Uptake During Chemoradiation and Association With Response

25 pts, FDG PET/CT pre-treatment, week 2 and 4, 3-mo after therapy

Poor response on the 3-month post-treatment PET was associated with week 4 SUVmax and with pre-treatment MTV.

Pre-treatment and week 4 of treatment represent the best time points for prediction of response

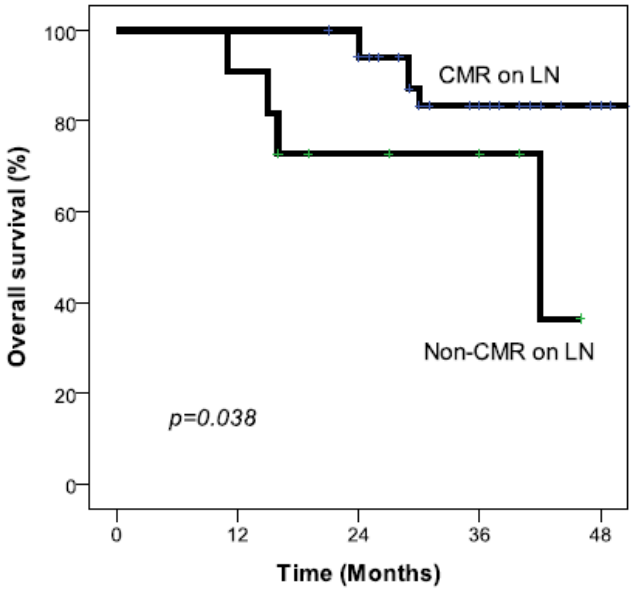


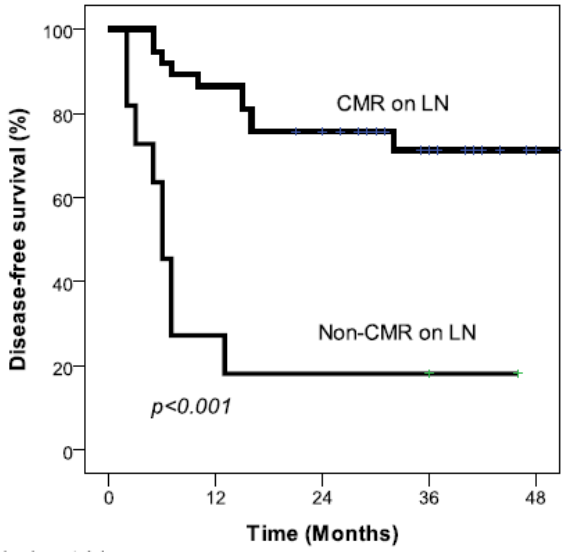
Kidd et al. Int J Rad Onc, 2013

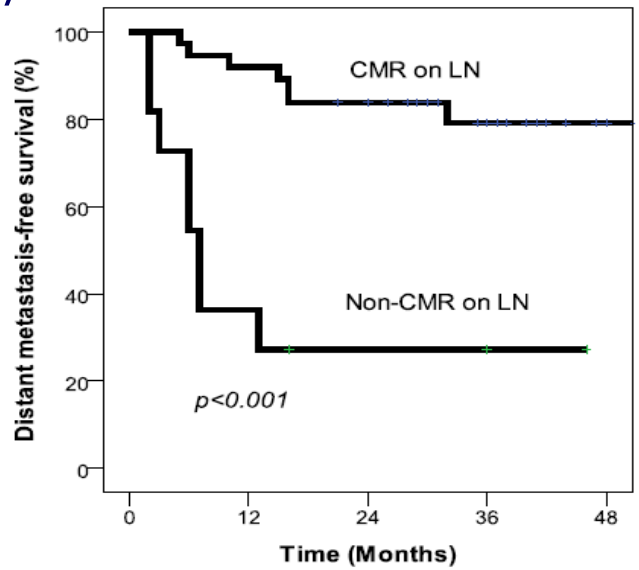
PET/CT and RT in Cervical cancer

48 pts with CC and positive pelvic LNs

Pre and immediately after post treatment PET/CT







PET/CT immediately after RT can be a useful tool for the evaluation of interim response of LNs, identifying a subset of pts with higher risk of recurrence and poor survival in pts with initial positive LNs.

Soon et al. Int J Rad Onc, 2012

PET/CT and RT in Cervical cancer

CLINICAL OUTCOMES OF DEFINITIVE INTENSITY-MODULATED RADIATION THERAPY WITH FLUORODEOXYGLUCOSE–POSITRON EMISSION TOMOGRAPHY SIMULATION IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER

Prospective study, 452 pts
- 135 IMRT
- 317 non-IMRT

For all patients, post-therapy FDG-PET response correlated with overall recurrence risk ($p<0.0001$) and cause-specific survival ($p<0.0001$)

Cervical cancer patients treated with FDG-PET/CT-guided IMRT have improved survival and less treatment-related toxicity compared with patients treated with non-IMRT radiotherapy.

Kidd et al. Int J Rad Onc, 2010

PET/CT and RT in Cervical cancer

38 patients, FDG PET/CT pre and post chemo-radiotherapy

RESEARCH **Radiation Oncology, 2016** Open Access

[^{18}F]FDG-PET/CT metabolic parameters as useful prognostic factors in cervical cancer patients treated with chemo-radiotherapy

Fernanda G. Herrera[1], Thomas Breuneval[1], John O. Prior[2], Jean Bourhis[1] and Mahmut Ozsahin[1*]

Table 3 Cox multivariate analysis in 38 patients with cervical cancer treated with chemo-radiotherapy

Variable	OS		DFS		LRC	
	RR	*p*	RR	*p*	RR	*p*
Three-month post-treatment partial metabolic response by [^{18}F]FDG-PET/CT	1:1.5	0.08	1:7.7	<0.0001*	1:22.6	0.0003*
Pre-treatment TGV (cutoff >562 cm^3)	1:2	0.03*	1:2.75	0.05*	1:3.3	0.07

OS Overall survival, *DFS* Disease-free survival, *LRC* Loco-regional control, *RR* Relative risk, *[^{18}F]FDG-PET* ^{18}F-labeled fluorodeoxyglucose positron emission tomography, *CT* Computed tomography, *TGV* Total glycolytic activity within the tumor volume
*p-value statistically significant

Pre- and post-treatment PET parameters provide important prognostic information - predictive of disease outcome

PET/CT and RT in Cervical cancer

Time point	FDG-PET/CT
Baseline	Baseline tumor SUV_{max} predicts local tumor response to therapy and survival [20–23]. Baseline MTV predicts PFS and OS [24, 25]. Lymph node status on PET is more predictive of outcome than FIGO stage [27, 28••, 29, 30]
Early during CRT	A CMR on PET as early as 4 weeks during therapy carries a good prognosis. The PPV of a PMR at this stage is less reliable [43, 44•, 45]
3 months after completion of CRT	Visual response criteria (CMR, PMR, PD) is highly predictive of PFS at 3 months post CRT [34, 35]. Metabolic response 3 months after completion of CRT predicts the pattern of treatment failure [36•]

Adapted from Barwick et al. Curr Oncol Rep, 2013

PET/CT and Gynaecological Malignancies

Uterus:

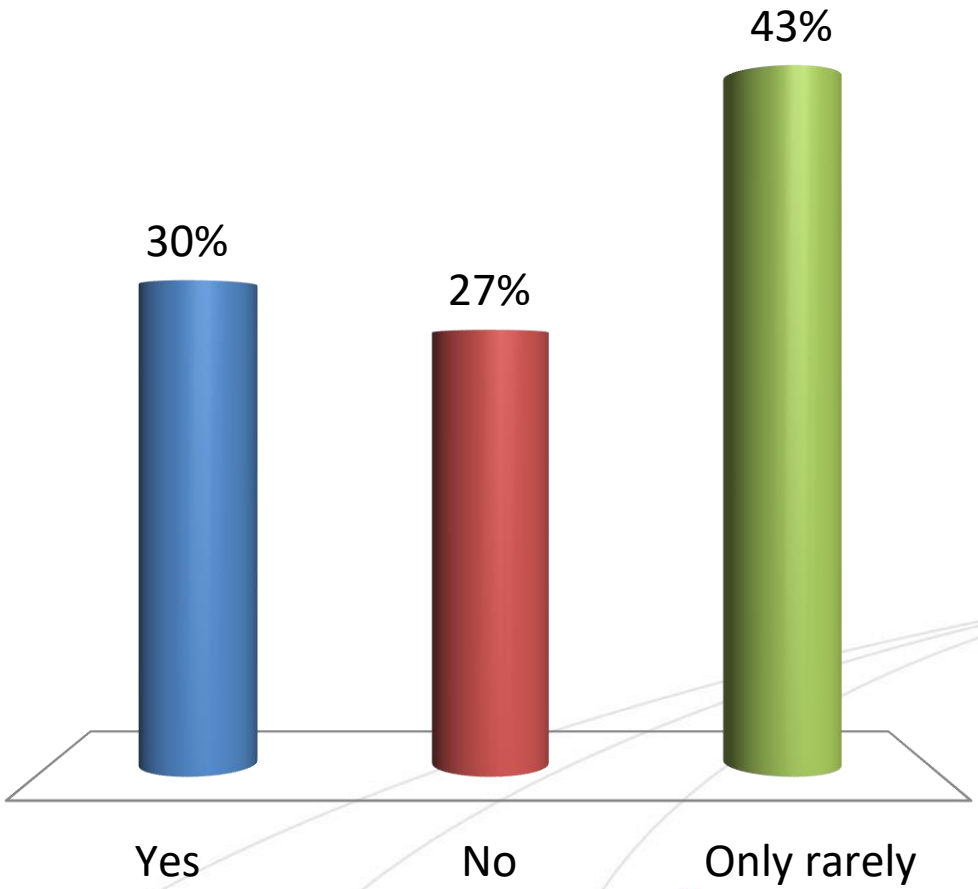
- Cervical
- **Endometrial**

Ovarian

QUESTION 2.

Are you routinely using PET/CT in clinical practice in endometrial cancer patients?

A. Yes
B. No
C. Only rarely



PET/CT and Endometrial cancer

- Generally good prognosis

- Advanced stage and relapse: poor outcome

- Less than 20% of pts have positive lymph nodes at initial diagnosis→ imaging for pts selection (sparing lymphadenecomy)

-Mainly surgical treatment

<u>Role of PET/CT</u>:
- to detect positive nodes avoiding unneccessary LDN
- Detecion of recurrent disease

Limited role of Radiotherapy in endometrial cancer

PET/CT and Endometrial cancer

Table II. *Diagnostic accuracy of 18F-fluoro-D-glucose - positron-emission tomography (FDG-PET)/ computerized tomography (CT) for endometrial cancer lymph node metastases.*

Reference	Number of patients	Lymph node	Sensitivity	Specificity	Accuracy	Positive predictive value	Negative predictive value
Kitajima *et al.* (11)	40	PAN+PLN	53%	99.6%	97.8%	NA	NA
Park *et al.* (12)	53	PLN	83%	91%	NA	36%	99%
		PAN	57%	88%	NA	57%	88%

PLN: Pelvic lymph node, PAN: para-aortic lymph node, NA: not available.

Nogami et al. Anticancer Res, 2014

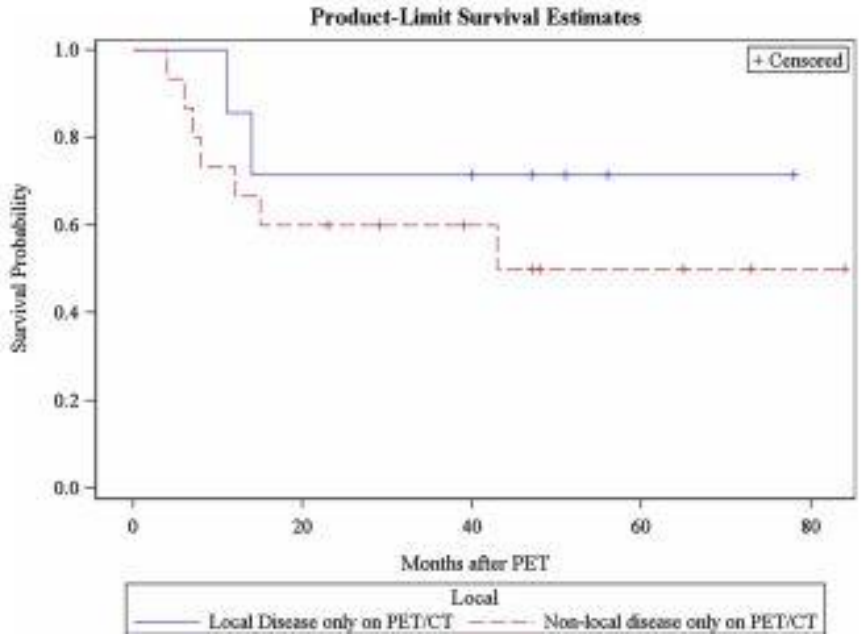
PET/CT and Endometrial cancer

48 patients PET/CT post-operative before adjuvant treatment

25 patients PET/CT before radiotherapy for recurrent disease

TABLE 4. Accuracy of PET/CT in detection of disease and method of confirmation (all cases)

Accuracy	n Stage	% Stage	n Restage	% Restage
True positive	16	33	21	84
True negative	23	48	1	4
False negative	6	13	1	4
False positive	1	2	0	
Equivocal	2	4	2	8
Method of confirmation				
Clinical follow-up	30	62	13	52
Imaging	11	23	3	12
Pathology	7	15	7	28
Equivocal	0	0	2	8



PET/CT seems to offer useful additional information both post-operatively and in the setting of recurrent disease. The 2- and 5-year survival was 75%.

Simcock et al. International Journal of Gynecological Cancer, 2015

PET/CT and Gynaecological Malignancies

Uterus:

- Cervical
- Endometrial

Ovarian

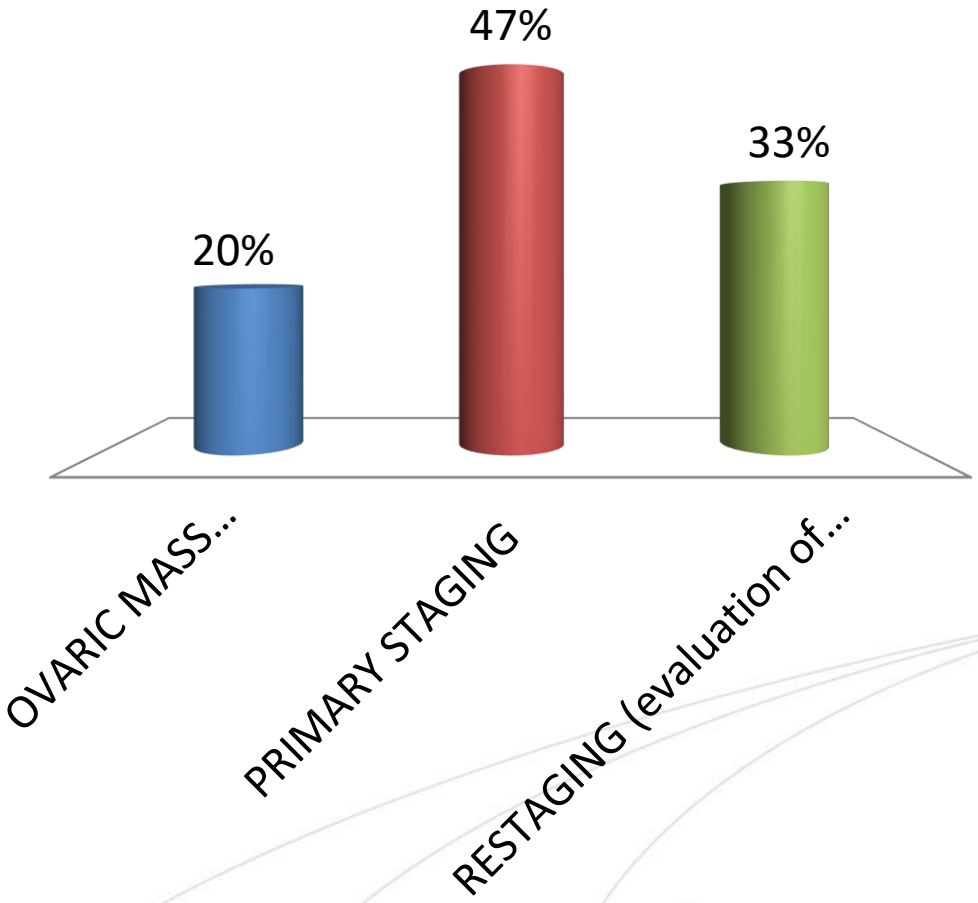
QUESTION 3.

Which is the main clinical indication to perform PET/CT in ovarian cancer patients in your department?

A. **OVARIC MASS CHARACTERISATION**

B. **PRIMARY STAGING**

C. **RESTAGING (evaluation of recurrent disease)**



PET/CT and Ovarian cancer

The value of PET/CT imaging is currently limited to the evaluation of recurrent disease when other conventional diagnostic modalities are negative or equivocal.

Amit et al. Curr Opin Obstet Gynecol 2013

PET/CT and Ovarian cancer

Detection of recurrent disease

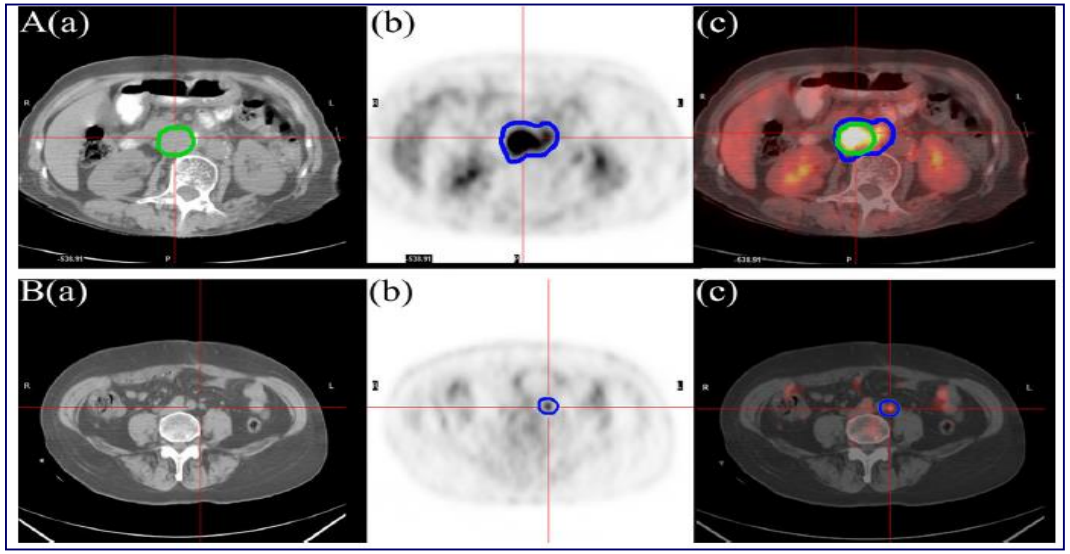
-multidrug resistance after cycles of chemo

- some recurrent tumors are unresectable (intestinal invasion/poor physical status) → RT as an alternative adjunctive therapy although severe acute and chronic toxicities of total abdominal irradiation (TAR) constraint its application

Few sistematic studies on the role of PET/CT in RT for ovarian cancer

PET/CT and RT in Ovarian cancer

58 pts with recurrent ovarian cancer → 28 PET/CT-IMRT
→ 30 CT-IMRT



Changes in GTV (PETvsCT) delineation in 10 pts (35.7%) **inclusion of metastatic LN and distant mts**.

Tumor response: 64.3% vs. 46.7%

3-year overall survival: 34.1% vs. 13.2

PET/CT guided IMRT in recurrent ovarian cancer patients improve the delineation of GTV and reduce the likelihood of geographic misses and therefore improve the clinical outcome.

Gynaecological Malignancies

Conclusions

- **Staging:** detection on lymphnode and distant metastases
- **Treatment planning:** detection and inclusion in TV of gross-para-aortic and pelvic lymphnodes → functional data can modify treatment delivery (IMRT, brachitherapy)
- **Treatment response:** Prognostic significance (interim PET/CT may predict the final outcome)

PET/CT and Gastrointestinal Malignancies

PET/CT and Gastrointestinal Malignancies

Esophageal

Colorectal

PET/CT and Gastrointestinal Malignancies

Esophageal

Colorectal

PET/CT and Esophageal cancer

Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and Esophageal cancer

Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and Esophageal cancer

Surgical resection is the most important part of a potentially curative treatment.

5-year survival rates after esophagectomy rarely exceed 40%

Combined chemoradiotherapy (CRT) is increasingly applied, either as definitive therapy or in the neoadjuvant setting prior to a curatively intended surgical resection.

Blom et al. EJNMMI, 2013

PET/CT and RT in Esophageal cancer

Table 1
Overview eligible original studies concerning the use of PET/CT for the detection of esophageal cancer.

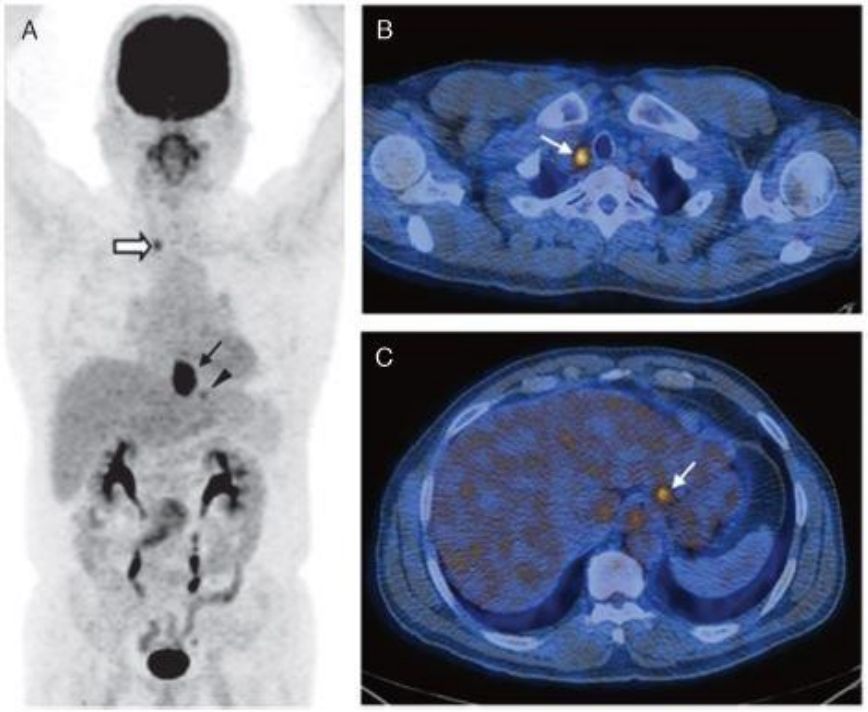
Author	N	Primary tumour		Lymph node metastases						Remarks
		Detection rate on CT (%)	Detection rate on PET (%)	Sensitivity of PET for LN (%)	Specificity of PET for LN (%)	Sensitivity of CT for LN (%)	Specificity of CT for LN (%)	Sensitivity of PET/CT for LN (%)	Specificity of PET/CT for LN (%)	
Pfau et al. [28]	44	80	92	–	–	–	–	–	–	4 of 5 undetected were T1–T2
Rankin et al. [29]	19	95	100	–	–	–	–	–	–	
Salahudeen et al. [30]	25	–	100	–	–	–	–	–	–	
Wren et al. [43]	21	–	–	71	86	57	71	–	–	
Kato et al. [17]	149		80	32	99	23	97	–	–	Most undetected were T1
Kato et al. [16]	32	–	78	78	93	61	71	–	–	The not visible tumours were T1
Flamen et al. [10]	39		95	33	89	0	100	–	–	All false negative on PET were T1
Himeno et al. [13]	22	–	68	42	100	38	96	–	–	All undetected tumours were T1
Block et al. [3]	58	–	94	52	79	29	79	–	–	2 undetected lesions were T1a
Kato et al. [15]	167	–	74	33	99	27	98	–	–	Most undetected were T1–2
Kim et al. [18]	52	98	94	52	94	42	97	–	–	False negative on PET was T1 tumour
Meltzer et al. [23]	47	97	87	35–41	90	63–87	14–43	–	–	
Yoon et al. [44]	79	82	92	30	90	11	95	–	–	All undetected tumours were T1
Kole et al. [19]	26	81	96	92	88	38	100	–	–	
Sihvo et al. [33]	55	69	82	35	100	42	82	50	100	Of the false negative 7 T1 tumours and 3 T2 tumours
Yuan et al. [46]	45	–	–	82	87	–	–	94	92	
Schreurs et al. [32]	85	–	–	–	–	–	–	87	87	

Muijs et al. Rad Onc, 2010

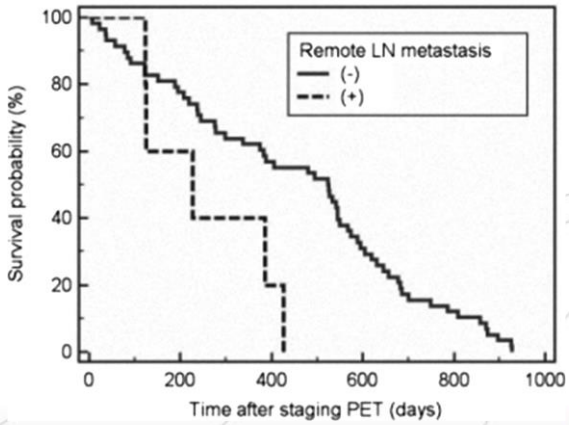
PET/CT and RT in Esophageal cancer

Patterns of Nodal Metastases on ^{18}F-FDG PET/CT in Patients With Esophageal Squamous Cell Carcinoma are Useful to Guide Treatment Planning of Radiotherapy

Chia-Ju Liu, MD, Jason Chia-Hsien Cheng, MD, PhD,†‡§ Jang-Ming Lee, MD, PhD,‡‖ Mei-Fang Cheng, MD,*‡§ Kai-Yuan Tzen, MD,*§ and Ruoh-Fang Yen, MD, PhD*‡§*



- 75 patients who underwent 18F-FDG PET/CT for staging
- Remote nodal metastasis was associated with higher SUV of the primary tumor (P = 0.02) and worse survival (P = 0.03).



ESNM European School of Nuclear Medicine

Clinical Nuclear Medicine, 2015

ESTRO School

PET/CT and RT in Esophageal cancer

Accurate delineation and irradiation of the GTV is a prerequisite for a successful treatment of esophageal cancer with radiotherapy.

Adequate tumour delineation is often hampered by the poor discriminative value of CT and the inability to relate ultrasound information to CT images.

Addition of PET/CT information may improve the accuracy in the delineation process, especially for IMRT.

Muijs et al. Rad Onc, 2010

PET/CT and RT in Esophageal cancer

Table 3
Changes in target volume by addition of PET(/CT) in tumour delineation process.

Authors	TV changes					TV of interest	PET interpretation	Contour method	Fusion/ integrated PET/ CT
	Overall	Increase		Decrease					
	Proportion	Proportion	Size	Proportion	Size				
Vrieze et al. [40]	20 (6/30)	10 (3/30)	Not defined	10 (3/30)	Not defined	CTV	Not described	I	Fusion
Gondi et al. [11]	94 (15/16)	31 (5/16)	Not defined	62.5 (10/ 16)	>5%	GTV	SBR (liver activity)/ visual	II	Integrated
Hong et al. [14]	84 (21/25)	–	Δ sup/inf extent > 1 cm	–	Δ sup/inf extent > 1 cm	GTV	Visual/⩾mean liver activity + 2SD	II	Integrated
Moureau-Zabotto et al. [25]	56 (19/34)	21 (7/34)	20% ± 8.7	35 (12/34)	21.3% ± 4.7	GTV	Visual	I	Fusion
	53 (18/34)	21 (7/34)	22% ± 11	33 (11/34)	9.8% ± 7.4	PTV2			
Leong et al. [21]	>69 (11/ 16)	–	Not defined	–	Not defined	GTV	SBR (liver activity)/ visual	II	Integrated
Muijs et al. [26]	76 (16/21)	24 (5/21)	>3 mm	52 (11/21)	>3 mm	GTV	SBR (liver activity)/ visual	II	Integrated

Muijs et al. Rad Onc, 2010

PET/CT and Esophageal cancer

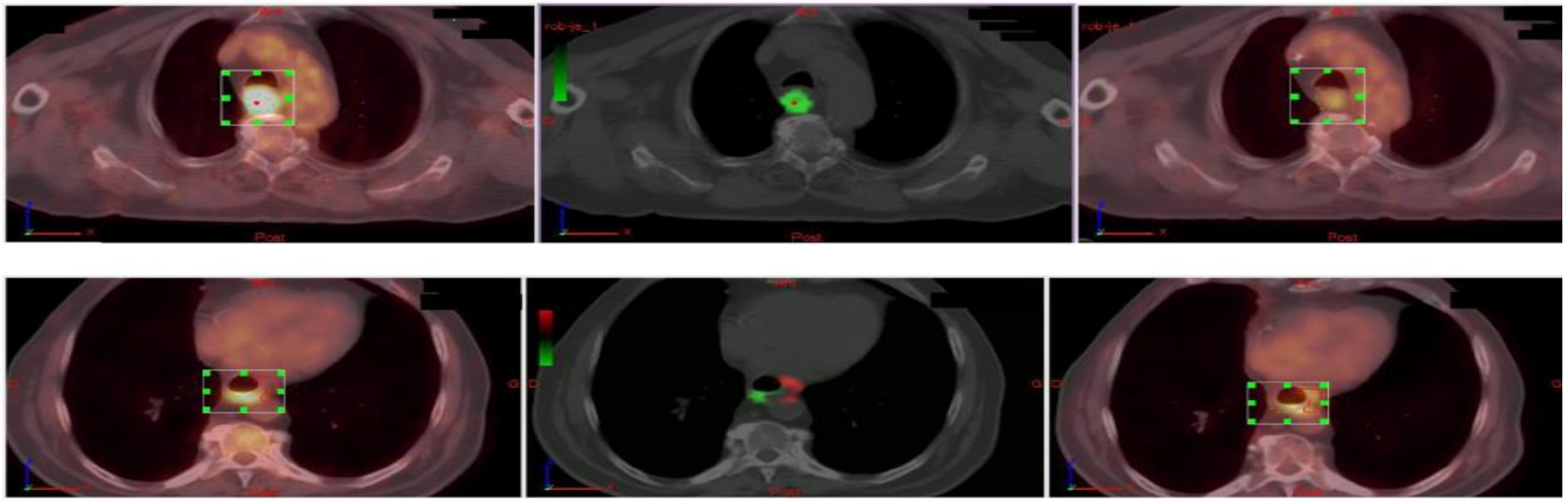
Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and RT in Esophageal cancer

57 pts with esophageal cancer underwent FDG-PET/CT before CRT (PET1) and at 21 ± 3 days after the beginning of CRT (PET2)



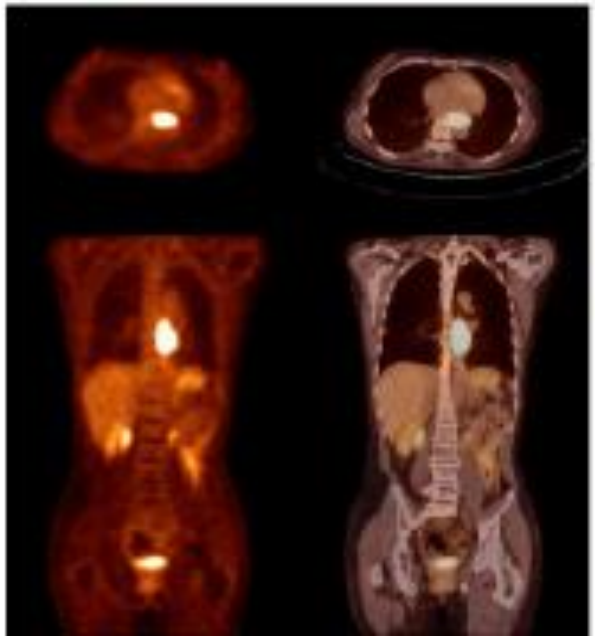
Monitoring of heterogeneous tumour response patterns on serial FDG-PET/CT images acquired during radiotherapy.

Early metabolic changes (i.e. variations in FDG uptake) provided additional prognostic information in multivariate analyses

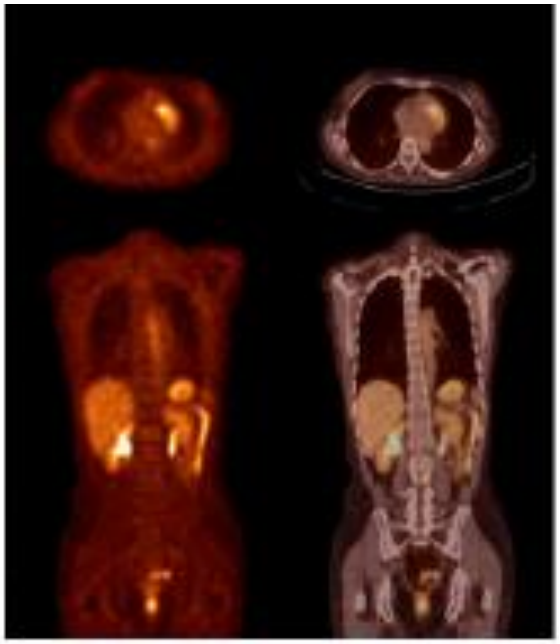
Vera et al. EJNMMI Research, 2014

PET/CT and RT in Esophageal cancer

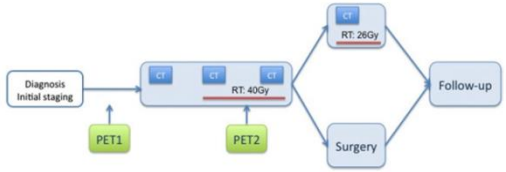
Evaluation of early response to concomitant chemoradiotherapy by interim ^{18}F-FDG PET/CT imaging in patients with locally advanced oesophageal carcinomas



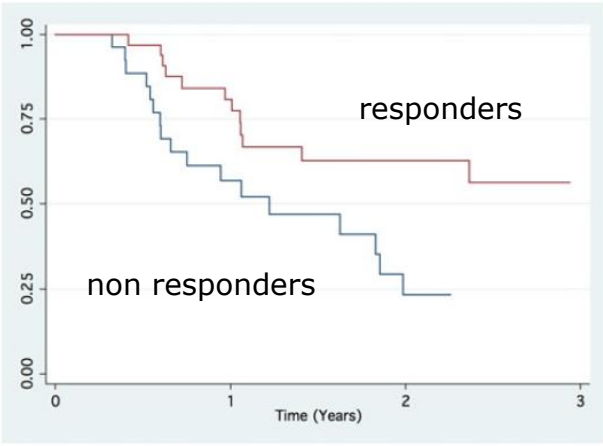
Pre-treatment



Post-treatment



survival probability



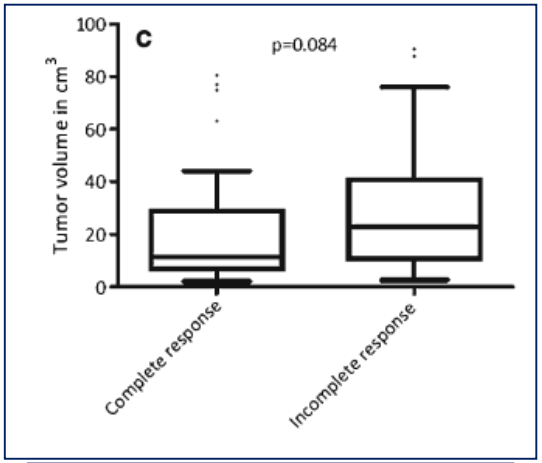
Interim 18F-FDG PET/CT during chemoradiation of locally advanced oesophageal cancer could play an important role in early assessing tumour response with great prognostic value, helping in identifying good responders pts to ChemoRT.

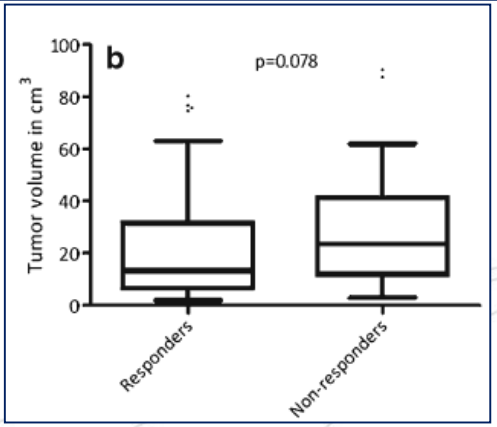
Cuenca et al. EJNMMI, 2013

PET/CT and RT in Esophageal cancer

PET/CT-based metabolic tumour volume for response prediction of neoadjuvant chemoradiotherapy in oesophageal carcinoma

Conclusion This study demonstrated a trend towards a correlation between response to chemoradiotherapy in oesophageal cancer patients and smaller MTVs as determined on diagnostic PET/CT prior to neoadjuvant chemoradiotherapy. However, tumour volumes overlapped between groups, indicating the need for multifactorial parameters as predictors. In addition, a complete local tumour response may be accompanied by residual disease in the regional lymph nodes.





Blom et al. EJNMMI, 2013

PET/CT and RT in Esophageal cancer
Conclusions

- **Staging and Treatment planning:**

- detection of lymph node and distant metastases
- changes in Target Volume contoured with consequent changes in treatment planning

- **Treatment response:** Prognostic significance (interim PET/CT may predict final outcome)

PET/CT and Gastrointestinal Malignancies

Esophageal

Colorectal

PET/CT and RT in Colorectal cancer

Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and Colorectal cancer

Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and RT in Colorectal cancer

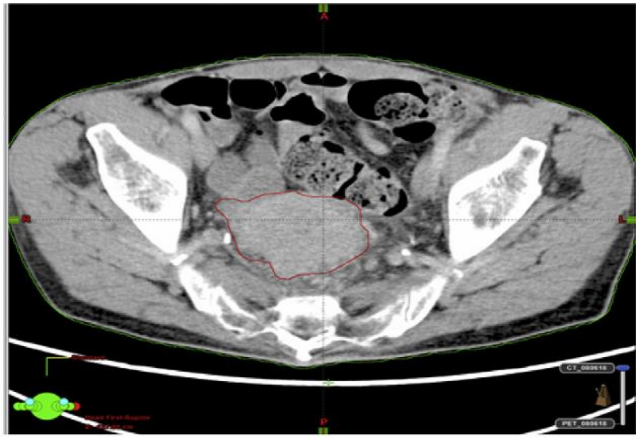
Accurate delineation of target volumes is essential for optimal radiation treatment for locally advanced rectal cancer (LARC).

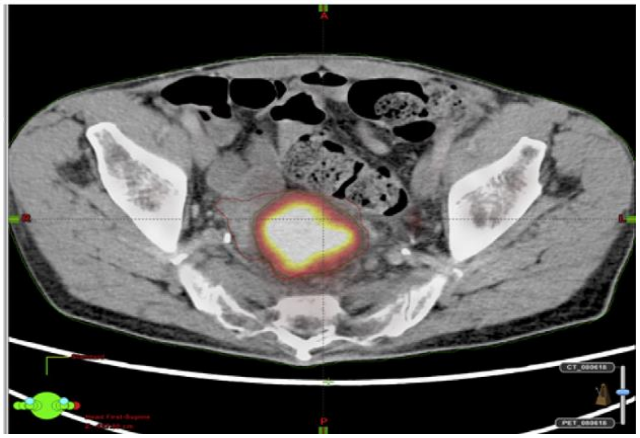
The main goal is a high dose of radiation to the tumor, maintaining an acceptable dose to adjacent tissues.

Positive impact of PET/CT on tumor delineation for radiation planning.

PET/CT and RT in Colorectal cancer

DELINEATION OF GROSS TUMOR VOLUME (GTV) FOR RADIATION TREATMENT PLANNING OF LOCALLY ADVANCED RECTAL CANCER USING INFORMATION FROM MRI OR FDG-PET/CT: A PROSPECTIVE STUDY





68 pts with locally advanced rectal cancer (LARC)

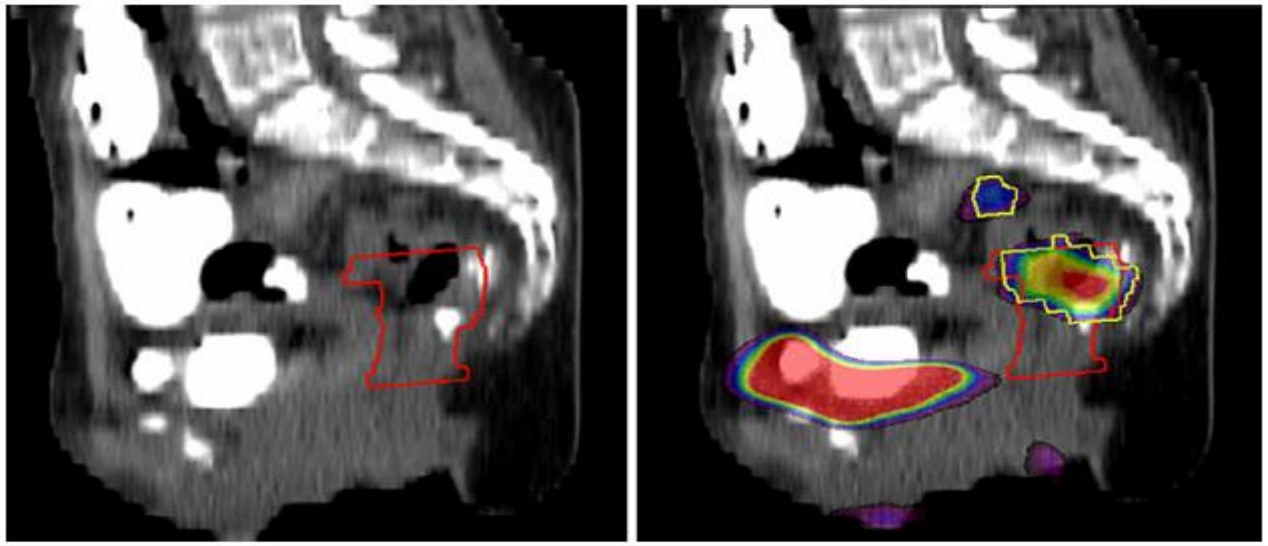
The median volume of GTV-MRI was larger than that of GTV-PET.

New lesions were seen in **15%** of the patients for whom **PET/CT** was used.

Braendengen et al. Int J Rad Onc Biol Phys, 2011

PET/CT and RT in Colorectal cancer

25 pts rectal cancer



CT (red) shows a more caudal extension of GTV and PET shows uptake in a presacral lymph node <1.5 cm in size

PET/CT for preoperative radiotherapy of rectal cancer lead to a change in staging and target volume delineation.

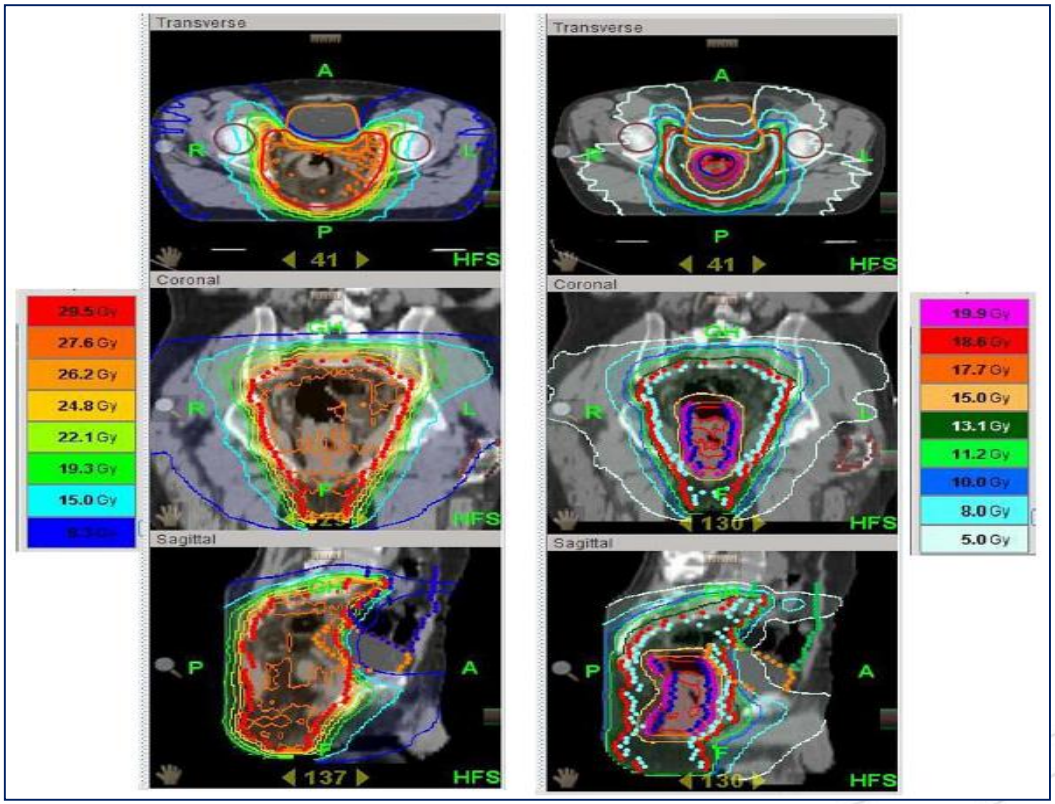
Stage variation was observed in 12% of cases and a change of treatment intent in 4%.

The GTV and CTV changed significantly, with a mean increase in size of 25% and 4%, respectively.

Bassi et al. Int J Rad Onc Biol Phys, 2008

PET/CT and RT in Colorectal cancer

Feasibility of an Adaptive Strategy in Preoperative Radiochemotherapy for Rectal Cancer With Image-Guided Tomotherapy: Boosting the Dose to the Shrinking Tumor



Passoni et al. Int J Rad Onc Byol Phys, 2013

PET/CT and RT in Colorectal cancer

Staging

Treatment planning (target definition)

Treatment response / recurrent disease

PET/CT and RT in Colorectal cancer

Voxel-based dual-time ^{18}F-FDG parametric imaging for rectal cancer: differentiation of residual tumor from postchemoradiotherapy changes

41 patients diagnosed with LARC and candidates for neoadjuvant RCT

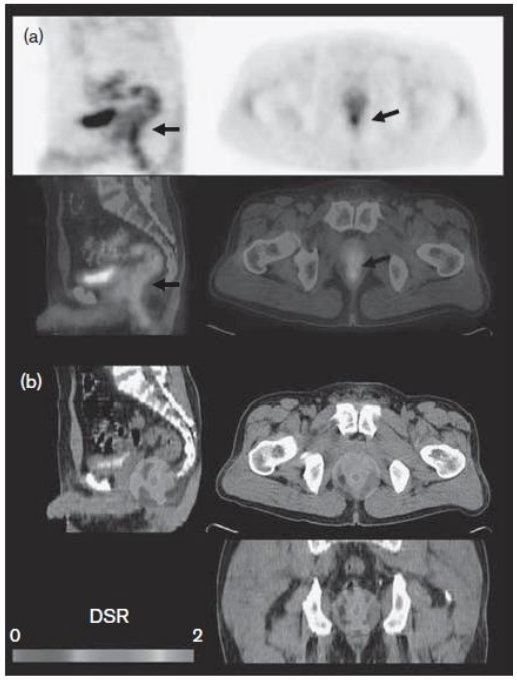


Table 2 Comparison between PET/CT after neoadjuvant treatment and histopathological results

PET/CT scan result	Histopathology result		Total
	Positive (nonresponders: TRG III, IV and V)	Negative (responders: TRG I and II)	
Positive	24	1	25 (60.97 %)
Negative	3	13	16 (39.03 %)
Total	27 (65.85 %)	14 (34.15 %)	41 (100 %)

PET/CT is a reliable technique for assessing response to neoadjuvant RCT in LARC, with a view to considering more conservative surgical treatment.

Choi et al. Nuc Med Comm, 2013

PET/CT and RT in Colorectal cancer
Conclusions

- **Staging and Treatment planning:**
- detection of hepatic and extrahepatic metastases
- positive impact on tumor delineation for radiation planning

- **Treatment response:**
- Assessing early response and in monitoring for relapse after treatment
- prediction response during preoperative CRT

PET/CT in Gastrointestinal Malignancies

Digestive and Liver Disease 47 (2015) 443–454

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Review Article

Role of fluorine 18 fluorodeoxyglucose positron emission tomography/computed tomography in gastrointestinal cancers

Mathieu Gauthé[a,b,*], Marion Richard-Molard[c], Wulfran Cacheux[d], Pierre Michel[e,f], Jean-Louis Jouve[g], Emmanuel Mitry[h,i], Jean-Louis Alberini[a,i], Astrid Lièvre[h,i], on behalf of the Fédération Francophone de Cancérologie Digestive (FFCD)

Table 3
Recommendations for the use fluorodeoxyglucose positron emission tomography/computed tomography in gastrointestinal malignancies.

Cancer	Diagnosis	Initial workup	Assessment of therapeutic efficacy	Radiotherapy treatment planning	Recurrence workup
Esophageal and EGJ cancers	No	Yes (if no evidence of metastatic disease)	Emerging evidence	Yes	No
Gastric cancer	No	No (may be considered if curative surgery is planned)	No	No	No
Pancreatic cancer	No	No (may be considered if curative surgery is planned)	No	–	No
HCC	No	No	No	–	May be considered in case of rising AFP
Cholangiocarcinoma and gallbladder	No	Emerging evidence		–	No
Colorectal cancer	No (colonoscopy is recommended in case of incidental focal colonic uptake)	No (should be considered before resection of metastatic disease)	No	–	No (may be considered in case of rising CEA and ambiguous or negative CT)
Anal canal cancer	No	Yes	Emerging evidence	Emerging evidence	No (may be considered if salvage surgery is planned)
GIST	No	No (may be considered if early response to therapy is of importance in preoperative setting)	No (except if CT is ambiguous)	–	No

EGJ, esophagogastric junction; HCC, hepatocellular carcinoma; GIST, gastrointestinal stromal tumor; CT, computed tomography scan; AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen.

Gauthè et al. 2015

ESNM/ESTRO COURSE
MOLECULAR IMAGING & RADIATION ONCOLOGY
10-13 APRIL BORDEAUX

Magnetic Resonance Imaging: Prostate Cancer

Professor Vicky Goh
Division of Imaging Sciences & Biomedical Engineering, Kings College London
Department of Radiology, Guy's & St Thomas' NHS Trust
London, UK

Email: vicky.goh@kcl.ac.uk

KING'S College LONDON

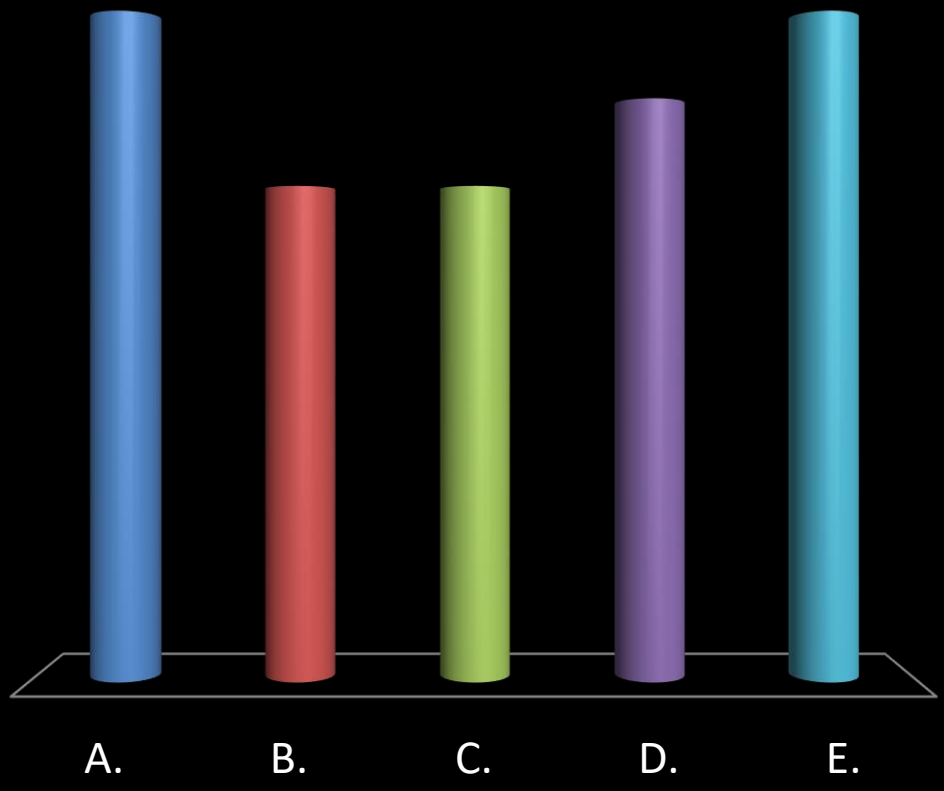
KING'S HEALTH PARTNERS

Learning Objectives

- To understand how MRI is performed and analysed for assessing prostate cancer:
  - Detection
  - Staging
- To appreciate the limitations & challenges of MRI

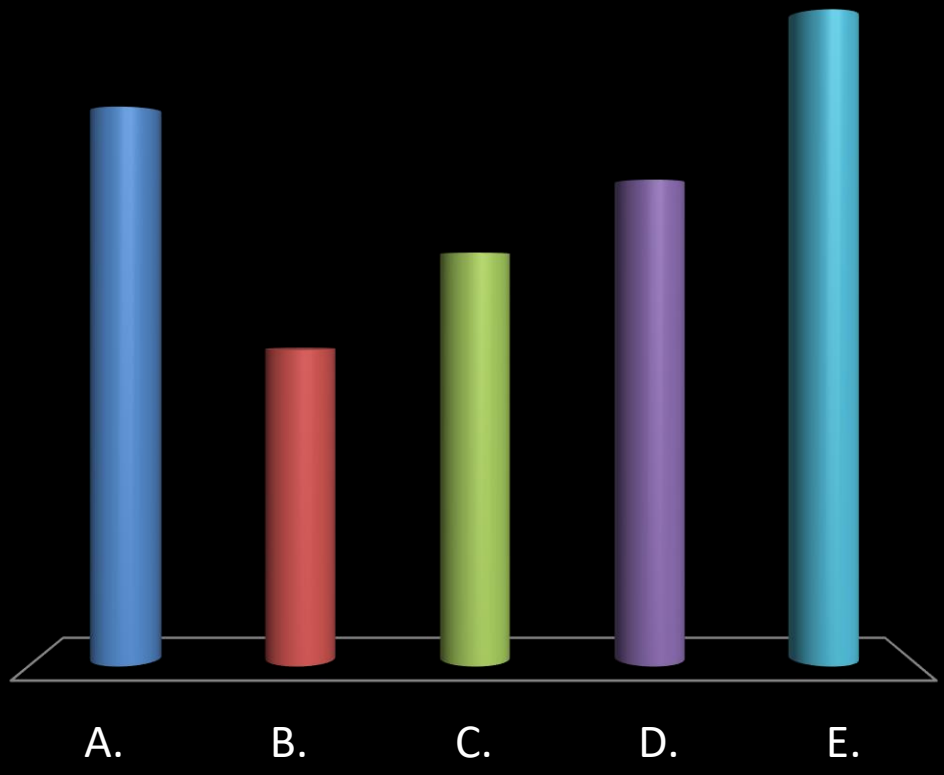
Test: Where are we?

A. Lisbon
B. Bordeaux
C. Barcelona
D. London
E. Paris



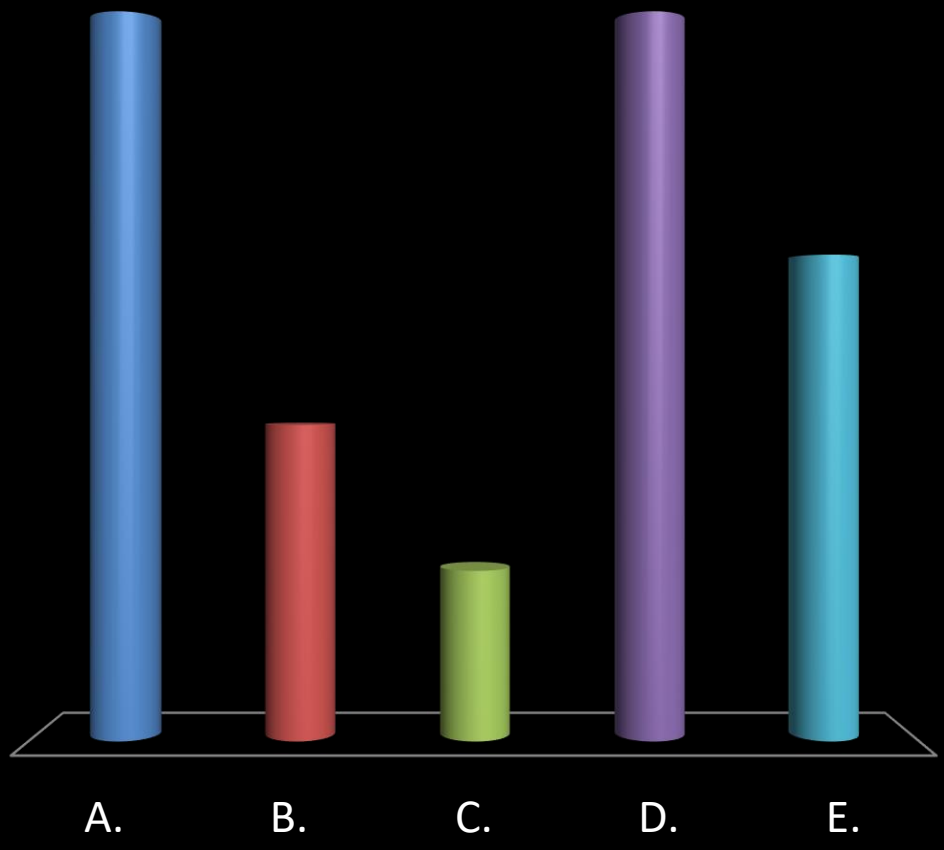
With respect to prostate cancer, which of the following is correct?

A. Its is a multifocal disease with multiple dominant lesions
B. All cancer foci are visible on MRI
C. A high risk cancer is a cT2c cancer, PSA >20ng/dl, Gleason 7+
D. A stage T3a cancer is invading the seminal vesicle
E. A PIRADS score of 4 & above is highly suspicious of cancer

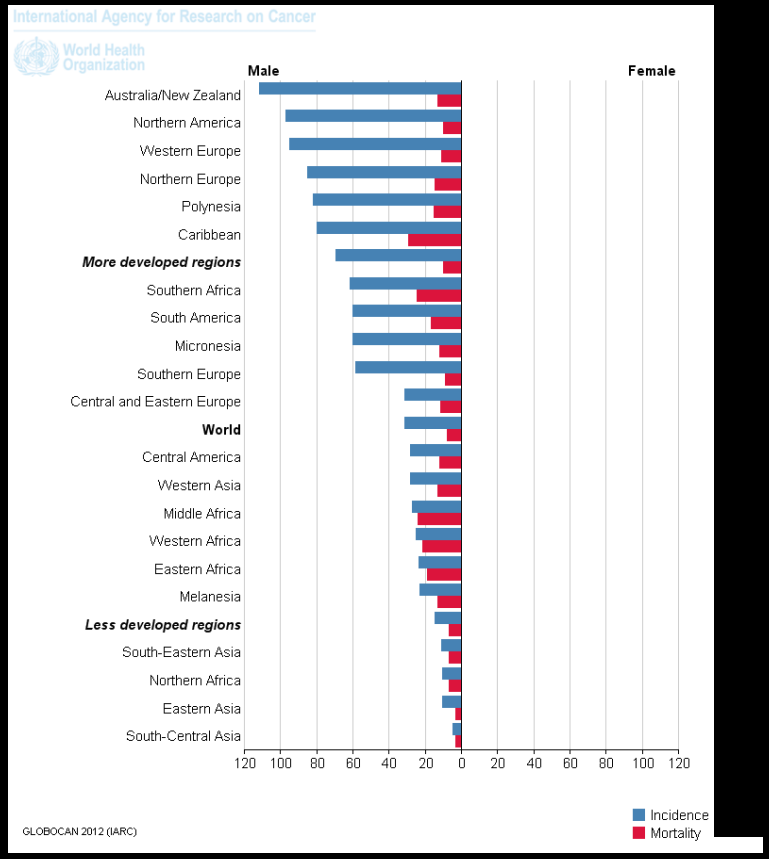


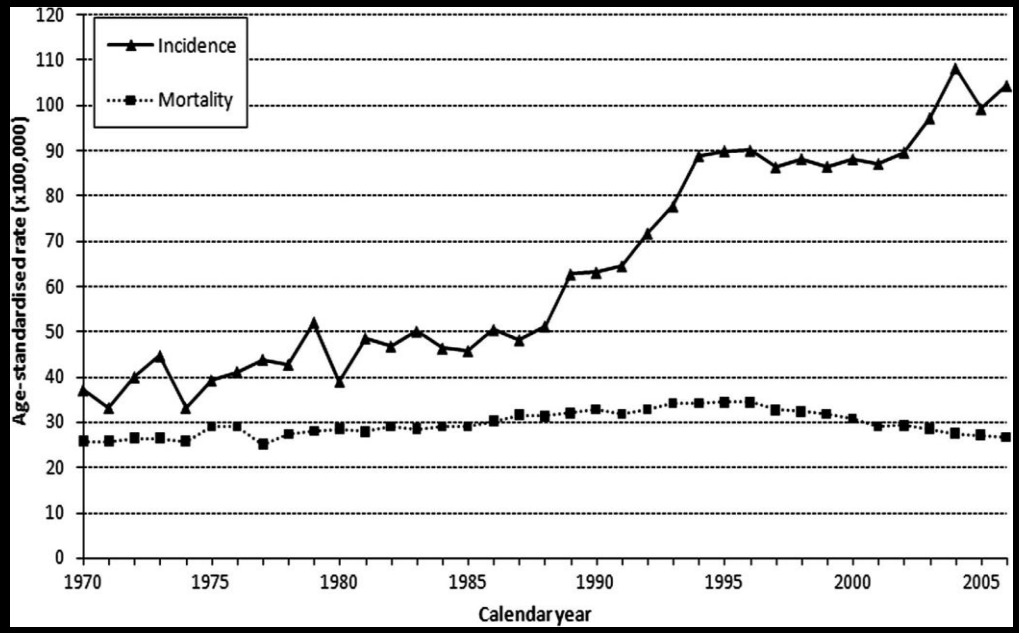
With respect to prostate imaging, which of the following is correct?

A. Ultrasound is the initial modality of choice to diagnose prostate cancer
B. MRI should be performed at 3T
C. Multiparametric MRI (T2-, diffusion & multiphasic contrast enhanced) should be used to diagnose prostate cancer
D. Multiparametric MRI (T2-, diffusion, multiphasic contrast enhanced & spectroscopy) should be used to diagnose prostate cancer
E. Multiparametric MRI is essential for staging



Incidence of Prostate Cancer





The Netherlands
Cremers RG et al. Eur J Cancer 2010; 46(11): 2077-87

Source: Globocan 2012

Increasing incidence in Western & Northern Europe

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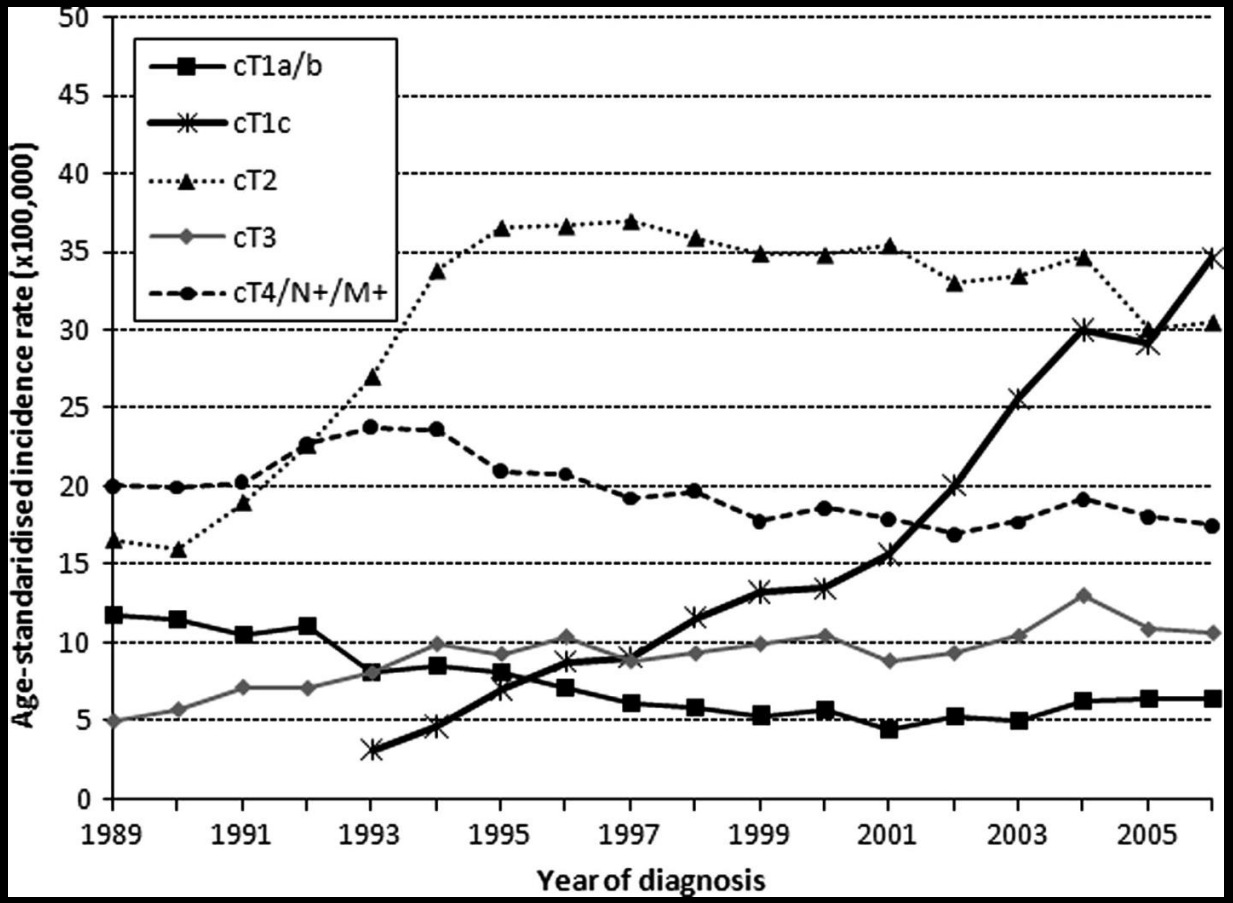
Stage at Initial Diagnosis

The Netherlands



- Downward stage migration
- Increase in cT1c disease
- Introduction of PSA testing

Cremers RG et al. Eur J Cancer 2010; 46(11): 2077-87

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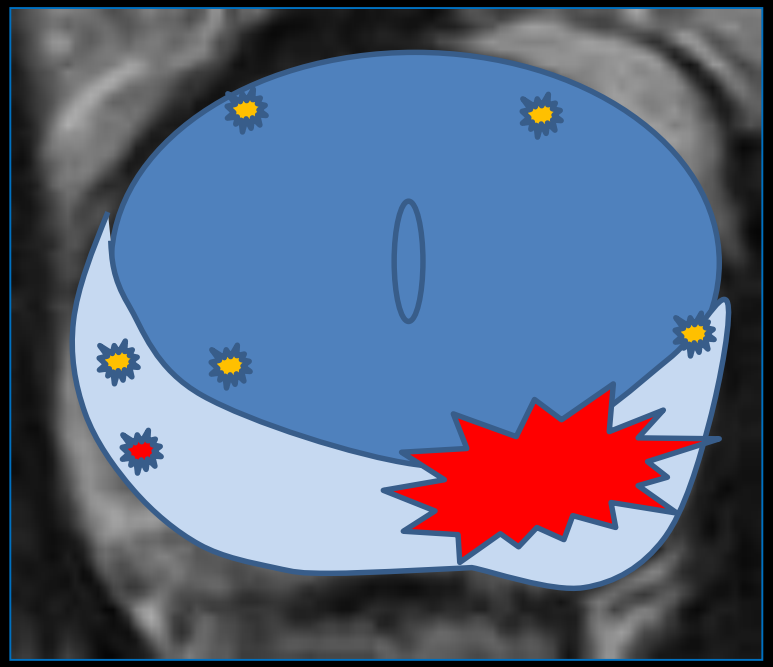
Prostate Cancer: A Multifocal Disease

- 85% of cancers are multifocal
- Index lesion: 90% of total tumor volume
- Other lesions: small (80% <0.5ml; average 0.3ml), similar to cancers found in asymptomatic men



Management of Prostate Cancer

Localised Disease:

Low risk

cStage	T1-2a
& PSA ng/mL	<10
& Gleason	≤6

- Active surveillance
- Offer radical treatment if progression

Intermediate risk

cStage	T2b-c
or PSA ng/mL	10-20
or Gleason	7

- Radical prostatectomy
- Radical radiotherapy
- Active surveillance if patient does not wish to proceed to radical treatment immediately

High risk

cStage	≥T3a
or PSA ng/mL	>20
or Gleason	8-10

- Radical prostatectomy
- Radical radiotherapy ± androgen deprivation therapy ± brachytherapy

Source: NICE UK
Updated Jan 2014

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Challenges for Diagnosis & Characterisation

Serum PSA:

- 15-30% men with prostate cancer have normal PSA
- Abnormal PSA ≠ cancer: 7 of 10 no cancer present

Systematic biopsies:

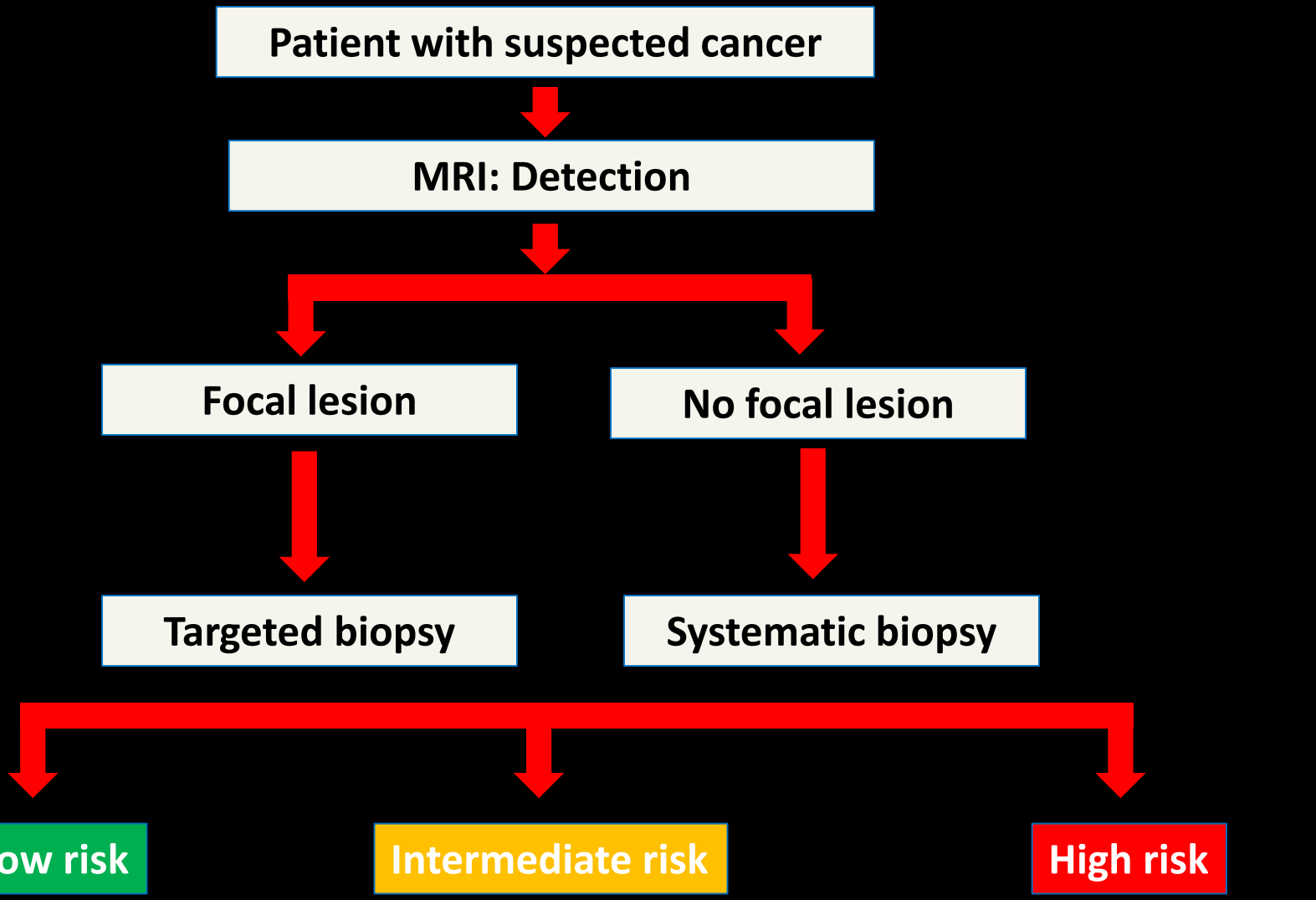
- Miss up to 20-30% of cancers
- Underestimates tumour aggressiveness in >20-30% of cases

Distinguishing aggressive (Rx: Definitive treatment) from indolent tumours (Rx: Surveillance) remains a challenge

The PROMIS study

- 576 men
- MP-MRI followed by TRUS-biopsy (standard practice) & TPM-biopsy (reference standard)
- Clinically significant cancer:
  - MP-MRI versus TRUS-biopsy:
  - Sensitivity: 93% vs 48%
  - Specificity: 41% vs 96%

Ahmed HU et al. PROMIS study group. Lancet 2017;389(10071):815-822
Kapoor J et al. Eur Urol. 2017 Feb 23. pii: S0302-2838(17)30103-3.



Stage	T1-2a
& PSA ng/mL	<10
& Gleason	≤6

Stage	T2b-c
or PSA ng/mL	10-20
or Gleason	7

Stage	≥T3a
or PSA ng/mL	>20
or Gleason	8-10

MRI: Prostate

MRI:

- Assessment of prostate volume
- Presence of focal lesion:
  Yes/No
- Localization for targeted biopsy
- Guidance for biopsy
- Staging & treatment planning

Multi-parametric MRI

MRI	Biological Correlate	Measure
Anatomical T2/T1 MRI	Anatomical structure	Morphology descriptors
Diffusion weighted MRI	Cell density	Signal intensity Apparent Diffusion Coefficient
Dynamic contrast enhanced MRI	Vascularisation	Present/absent Curve type K^{trans}, k_{ep}, V_e
MR Spectroscopy	Cell membrane turnover Replacement of normal glandular tissues	Spectra Choline-Creatine to Citrate ratio

MRI Acquisition

1.5 or 3-Tesla

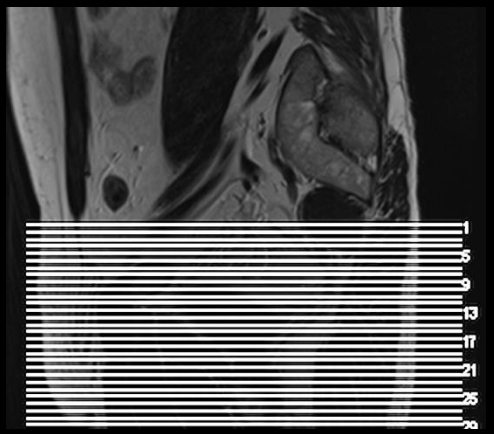
Region	Sequence
Pelvis	T1 TSE axial
	T2 TSE axial
Tumour	T2 TSE sagittal
	T2 TSE coronal*
	T2 TSE axial*
	Diffusion
	Dynamic contrast enhanced

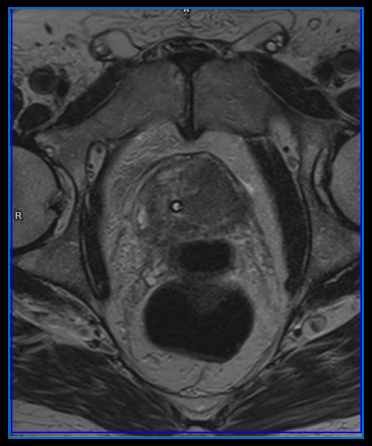
TSE: Turbo spin echo

Patient preparation:

- No prior patient preparation
- Normal renal function: IV contrast administration
- Emptying the bladder prior to MRI & anti-peristaltic (Buscopan IM) may improve imaging by reducing artefact

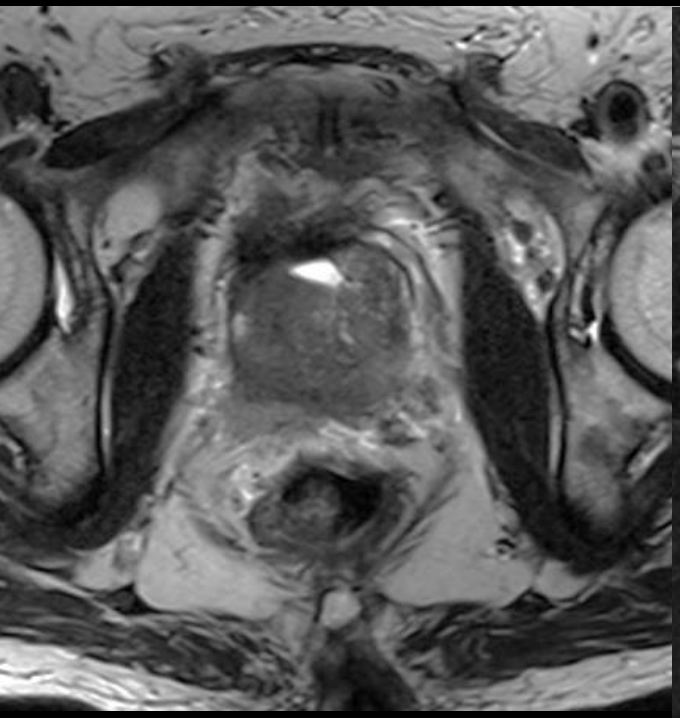
MRI Acquisition



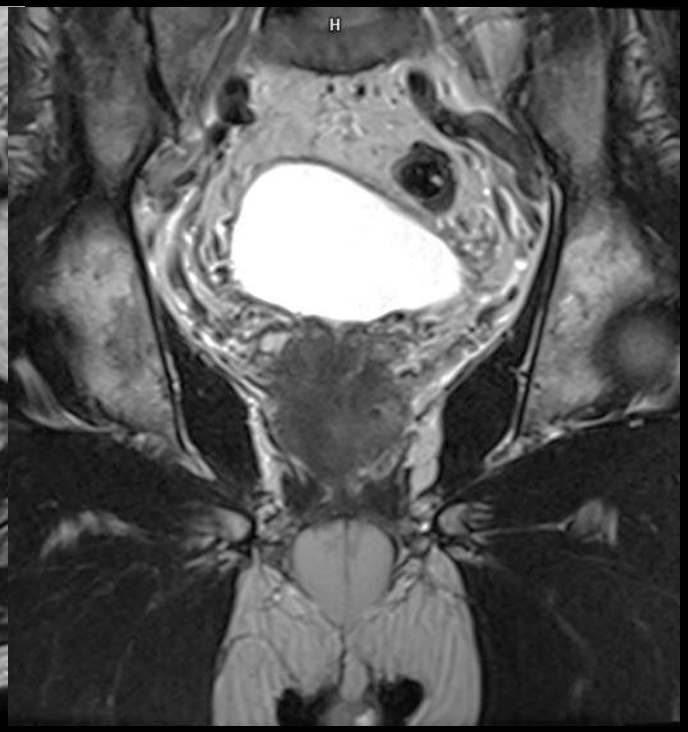


T2: Tumour High resolution TSE	**TR**	7000
	TE	105
	NEX	2
	FOV Matrix	163*200 216*512
	ST	3mm

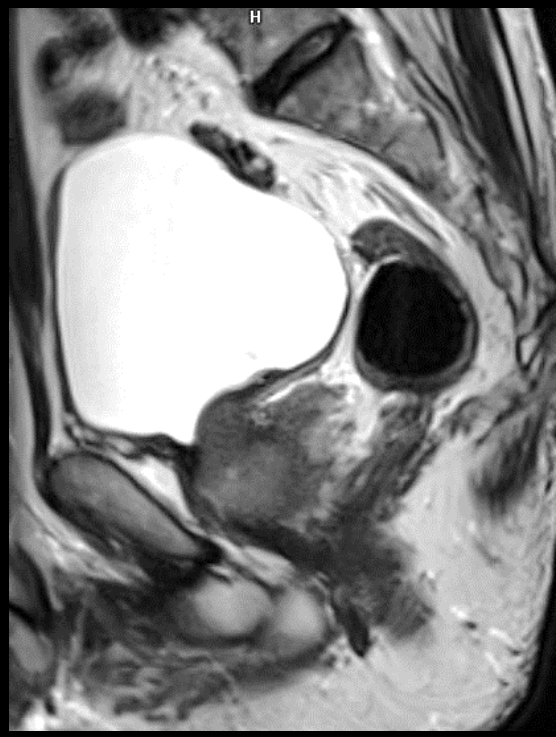
- Phased surface array coils centred for good SNR at prostate level
- Pelvic coverage: Sacral promontary to below symphysis pubis
- Endorectal coil: Not necessary



Axial



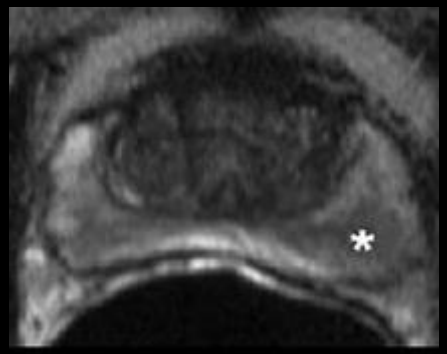
Cor

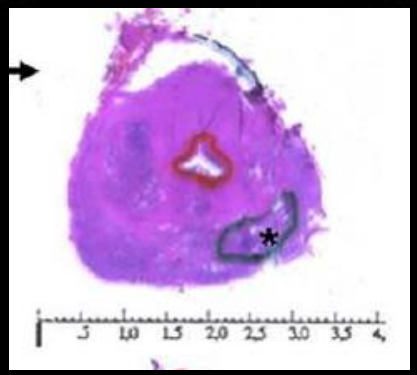


Sagittal

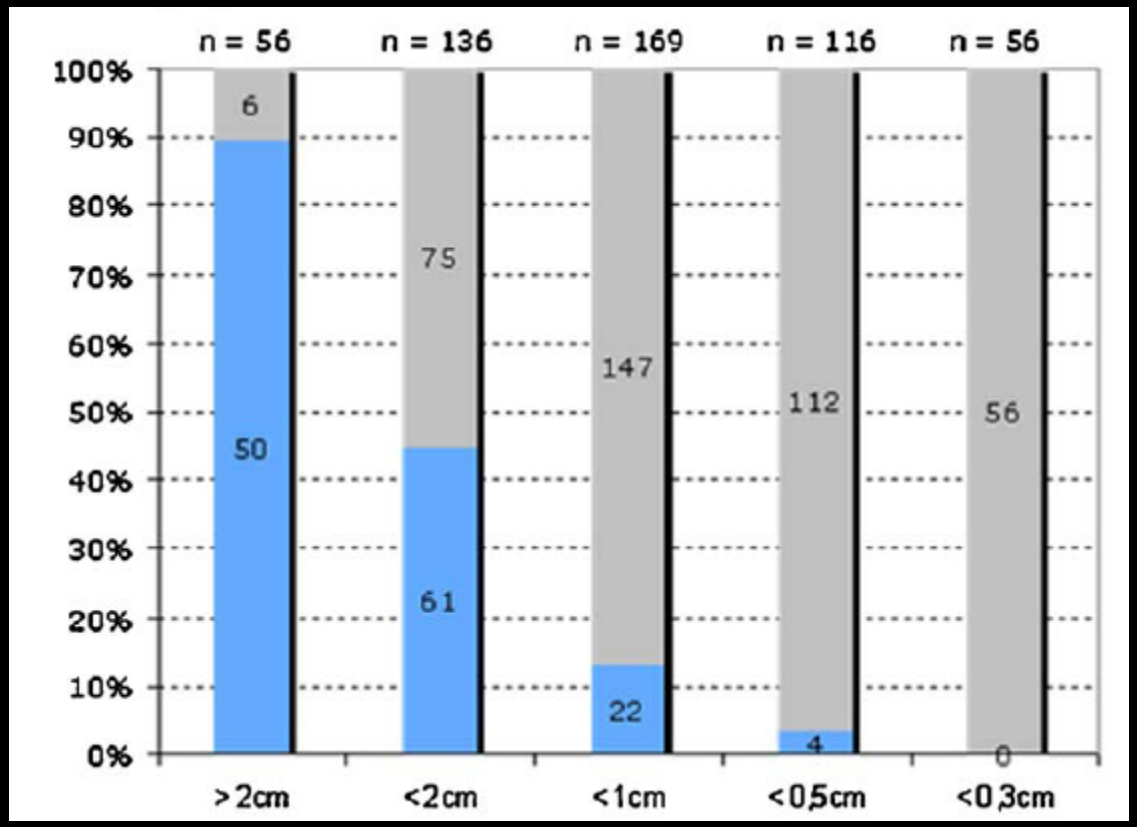
Multiplanar Imaging of the Prostate Gland

Tumour Detection: T2W MRI





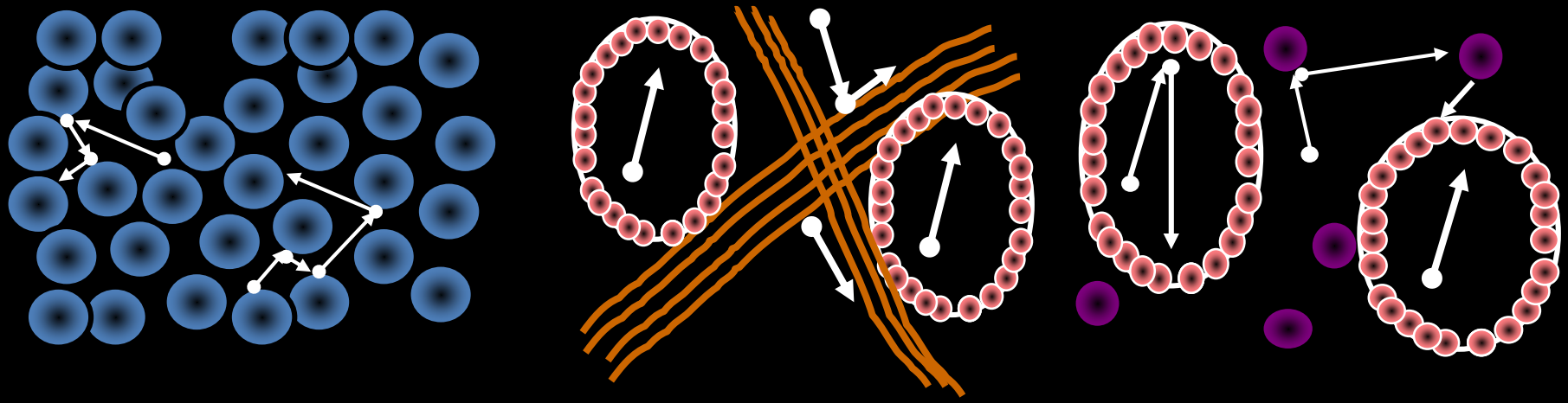
n=70,
Endorectal coil
Total tumour foci: 553



Detected by MRI (%)	89	45	13	3	0

Roethke MC et al. Eur J Radiol 2011; 79(2): 189-95

Diffusion Weighted MRI



Tightly packed cellular tumour

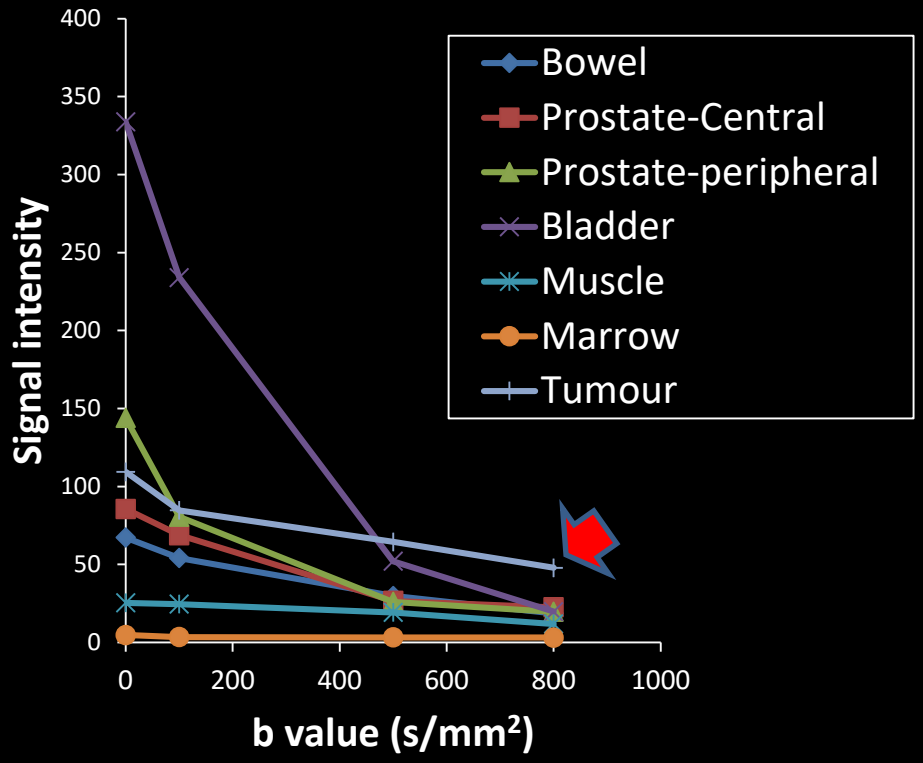
Fibroglandular BPH

Glandular tissue

Courtesy: AR Padhani

Increasing restriction of water diffusion

Diffusion Weighted MRI

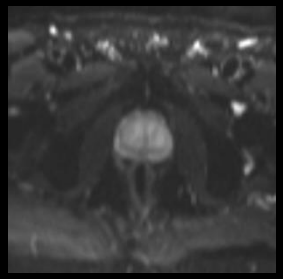


$$\frac{S}{S_0} = e^{-bD}$$

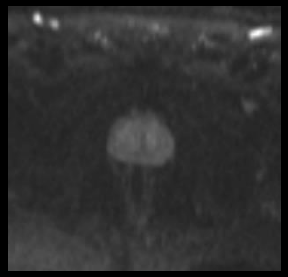
S = DW signal
S_0 = signal without DW
b=diffusion factor
D = diffusion coefficient

Normal prostate

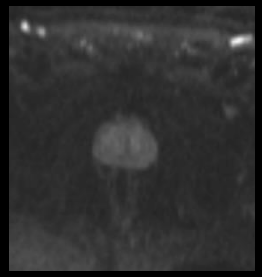
b0



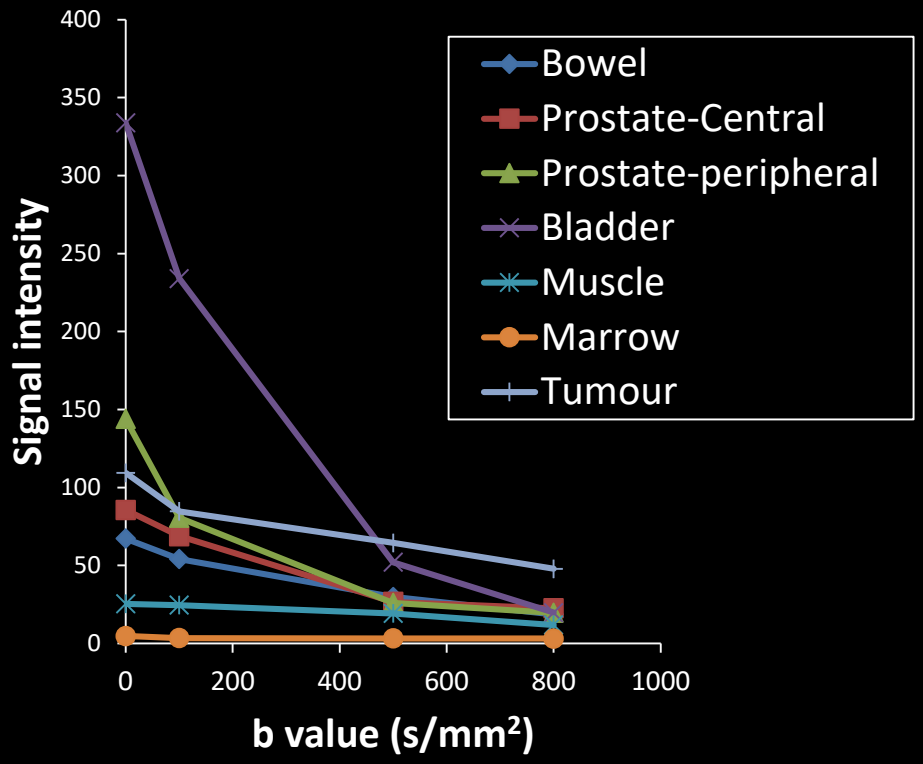
b100



b800



Diffusion Weighted MRI



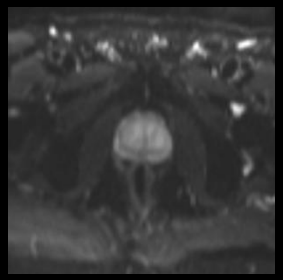
$$ADC = -\frac{1}{bi} x \ln\left(\frac{Si}{S0}\right)$$

Apparent Diffusion Coefficient

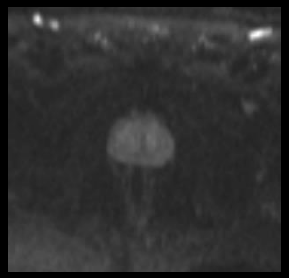
Gradient of $_{ln}$SI change (mm^2/s)

Normal prostate

b0



b100



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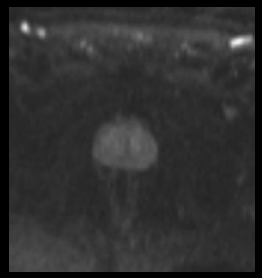
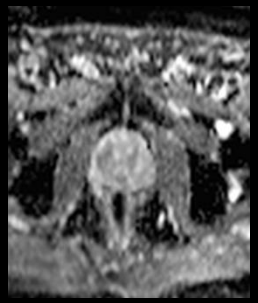
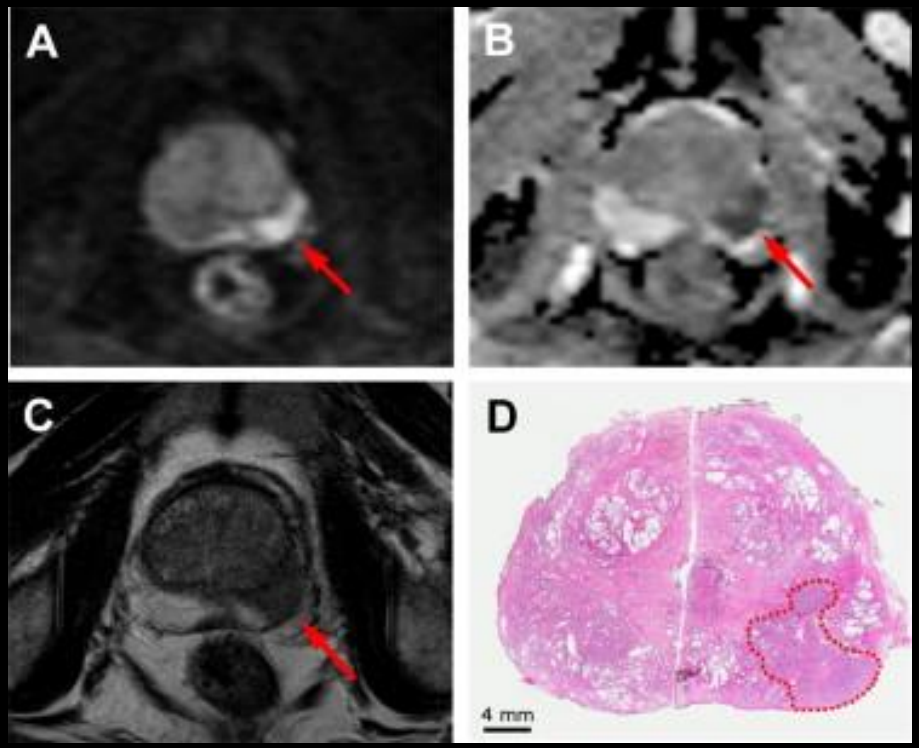


ADC



Diffusion Weighted MRI



Bains LJ et al. J Urol 2014; 192(3):737-42

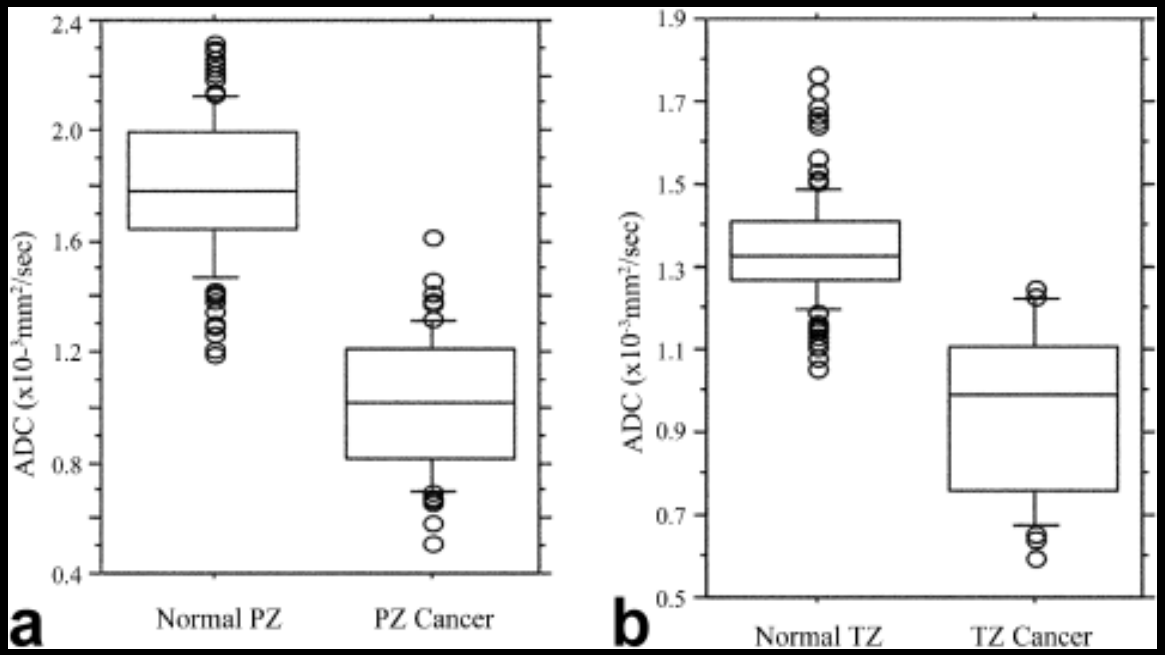
3T-MRI with b: 0, 500,1000 s/mm²

DWI	Sensitivity (%)	Specificity (%)
Reader 1	89	77
Reader 2	90	81
Reader 3	91	77

N=111: 93 with prostate cancer

Diffusion Weighted MRI

Lower ADC in cellular tumours:



- ADCs associated with different Gleason scores in the whole prostate

Caveat:
Overlapping ADCs

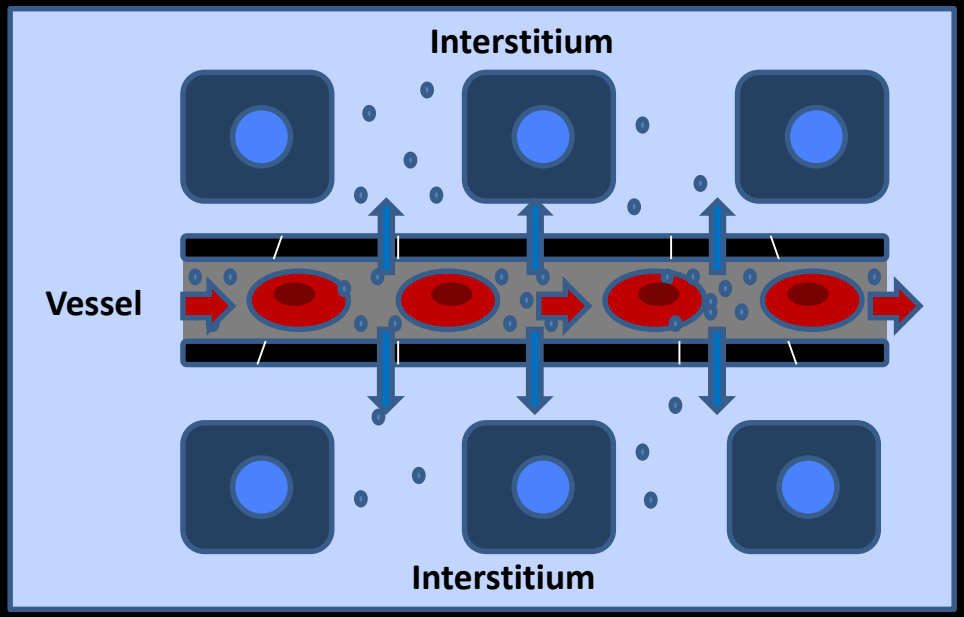
- Low-mod differentiated
- Benign Hyperplasia

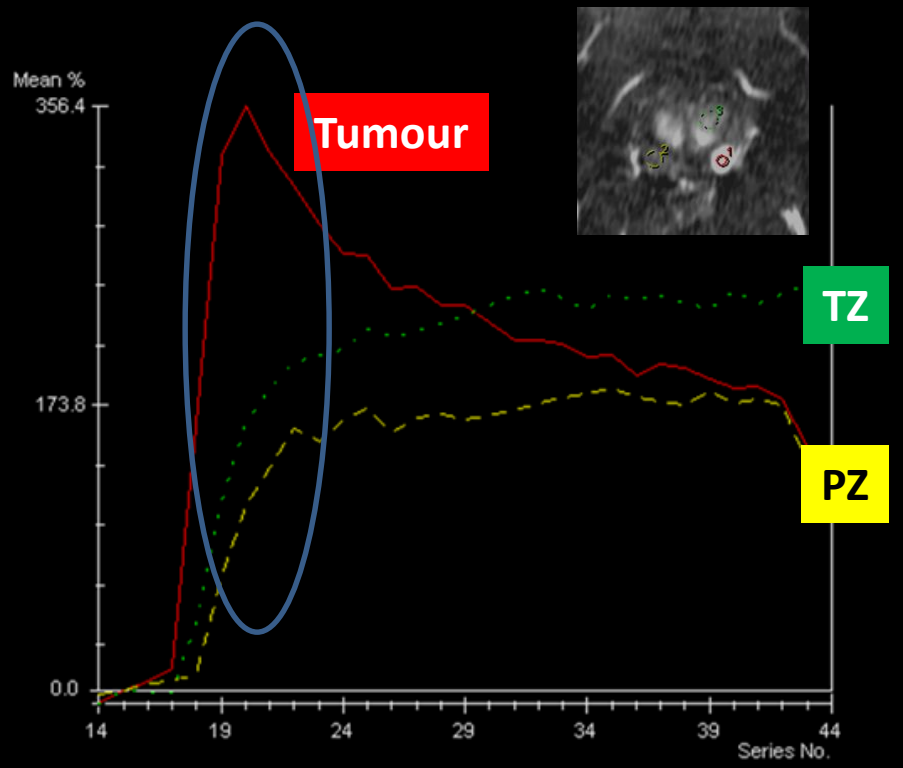
Tamada T et al. J Magn Reson Imaging 2008; 28(3): 720-6

Zelhof B et al. BJU Int 2009; 103: 883-8

Turkbey B et al. Radiology 2011;258:488-495

Dynamic Contrast Enhanced MRI

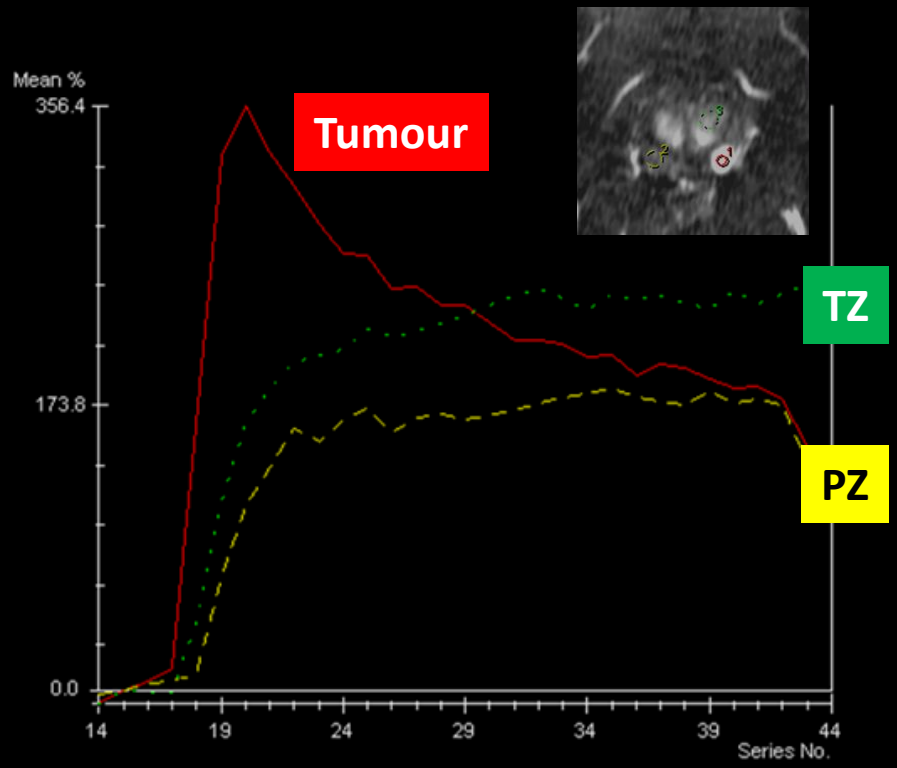




Contrast agent kinetics may differ between tumour & normal prostate

Early vascularisation within tumours

Dynamic Contrast Enhanced MRI

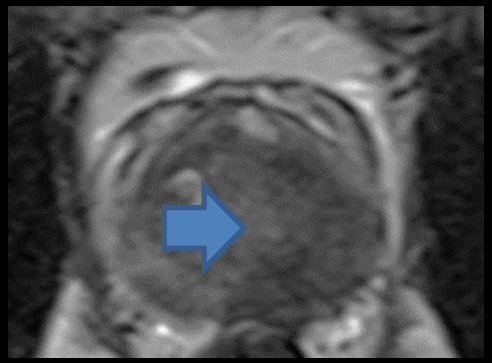


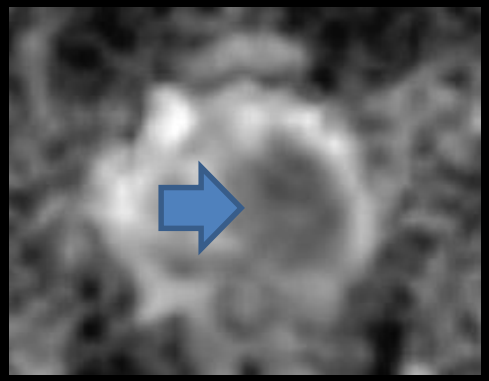
- Can detect clinically important cancer in 93% of cases*
- Role in TRUS biopsy-negative cancers with elevated PSA

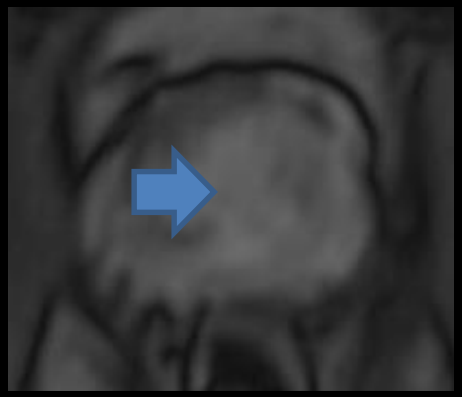
*Hara et al. Prostate 2005; 62: 140-7
Beyersdorff et al. Radiology 2002; 224: 701-6

Multi-parametric MRI: Typical Tumour Appearances

MRI	Appearances
Anatomical	Focal T2 low signal intensity lesion
DWI	Focal high signal on high b value sequence Focal low signal on ADC maps
DCE-MRI	Early enhancement & wash-out







PIRADS v2

Scoring:

- 1: Very low, clinically significant PCa highly unlikely
- 2: Low, clinically significant PCa is unlikely
- 3: Intermediate, equivocal presence of clinically significant PCa
- 4: High, clinically significant PCa likely
- 5: Very high, clinically significant Pca highly likely

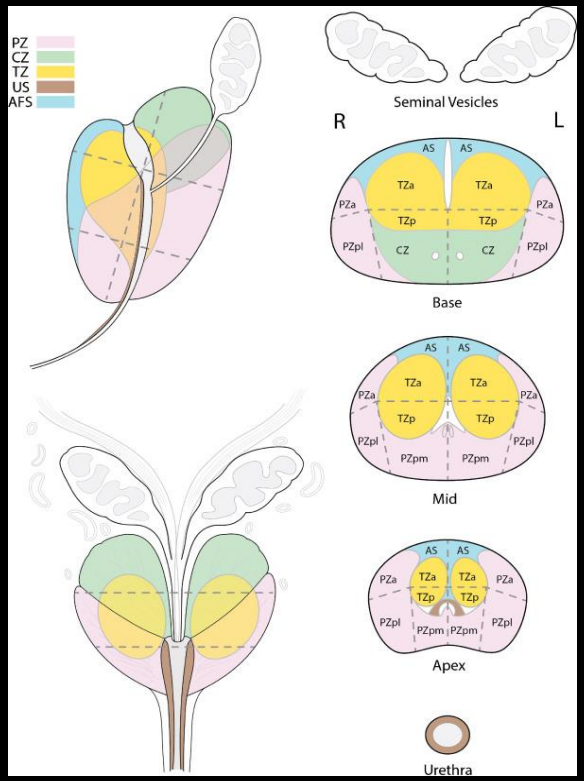
http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS

Barentsz J et al. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. Eur Urol 2016; 69: 41-9.

PIRADS v2

- Overall scores from the T2W, DWI & DCE applied sequentially
- Certain sequences are dominant according to zonal anatomy
- PZ: **DWI** is primary determinant
  - E.g. if the DWI score is 4 & T2W score is 3, the PI-RADS assessment category should be 4
- TZ: **T2W** is the primary determinant
  - E.g. if T2W score is 4 & DWI score is 2, the PI-RADS assessment category should be 4

39 sector map



Barentsz J et al. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. Eur Urol 2016; 69: 41-9.

http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS

PIRADS v2

Peripheral Zone (PZ)

DWI	T2W	DCE	PI-RADS
1	Any*	Any	1
2	Any	Any	2
3	Any	–	3
		+	4
4	Any	Any	4
5	Any	Any	5

* "Any" indicates 1-5

Transition Zone (TZ)

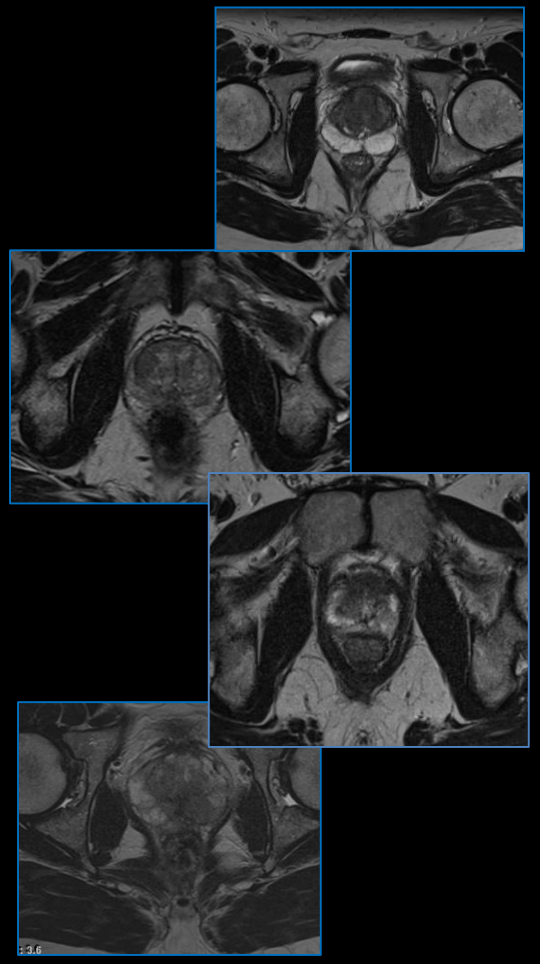
T2W	DWI	DCE	PI-RADS
1	Any*	Any	1
2	Any	Any	2
3	≤4	Any	3
	5	Any	4
4	Any	Any	4
5	Any	Any	5

* "Any" indicates 1-5

T2 Evaluation: PZ

Score	Peripheral Zone (PZ)
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

http://www.acr.org



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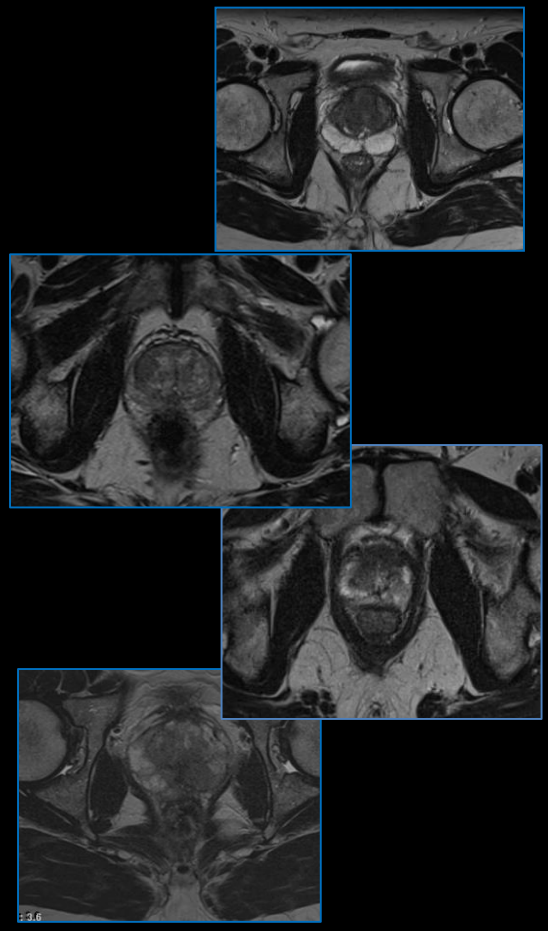
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

http://www.acr.org



T2 Evaluation: PZ

Score	Peripheral Zone (PZ)
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension
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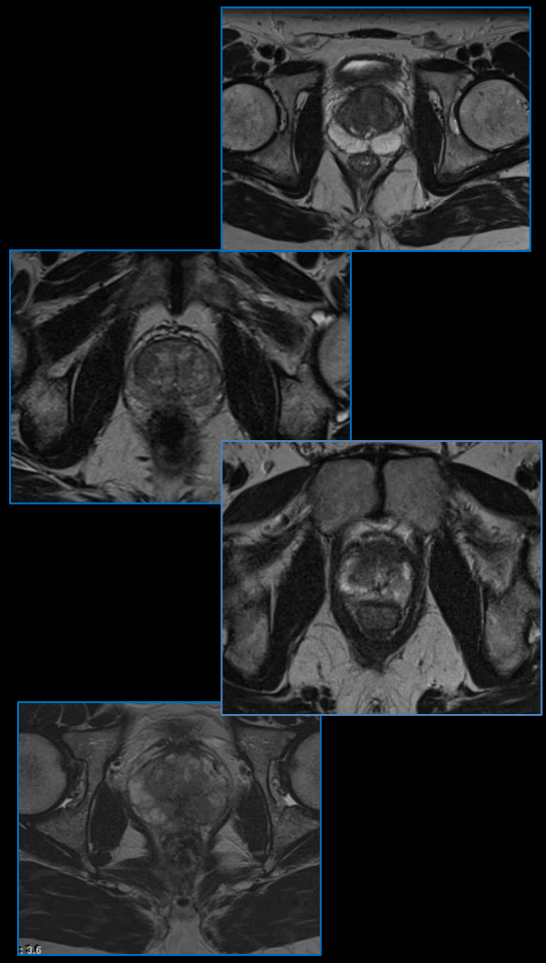

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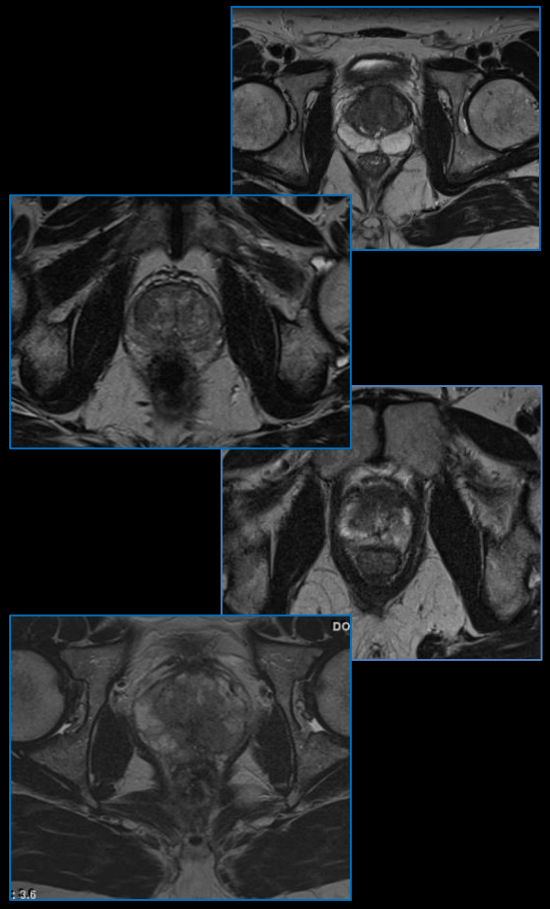
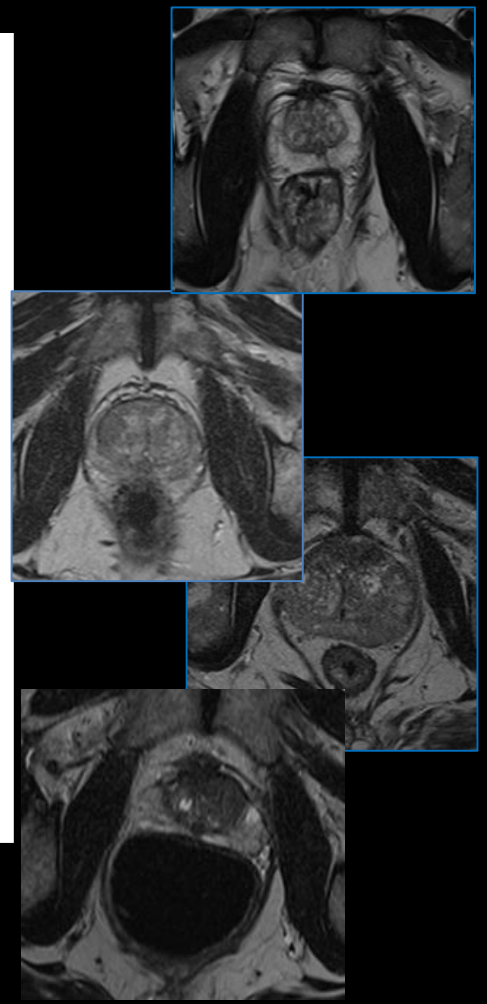


T2 Evaluation: TZ

Score	Transition Zone (TZ)
1	Homogeneous intermediate signal intensity (normal)
2	Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)
3	Heterogeneous signal intensity with obscured margins Includes others that do not qualify as 2, 4, or 5
4	Lenticular or non-circumscribed, homogeneous, moderately hypointense, and <1.5 cm in greatest dimension
5	Same as 4, but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior



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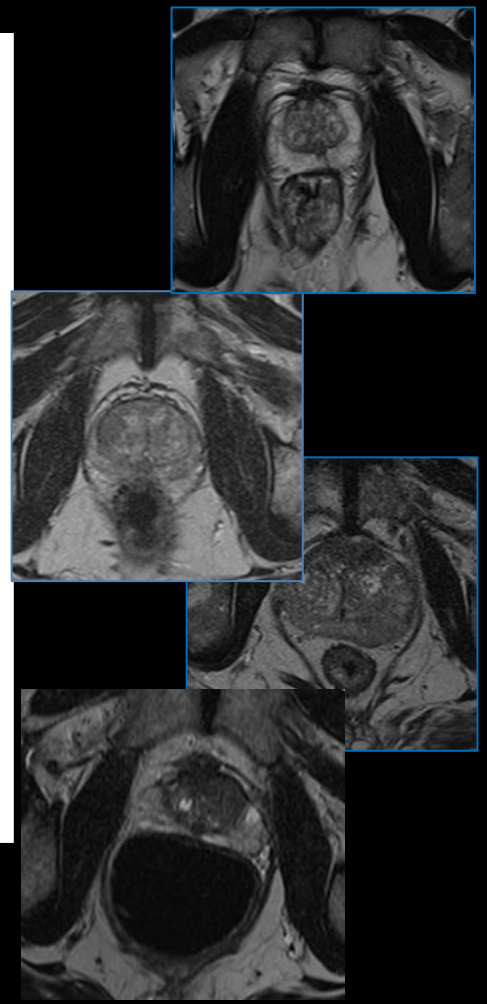

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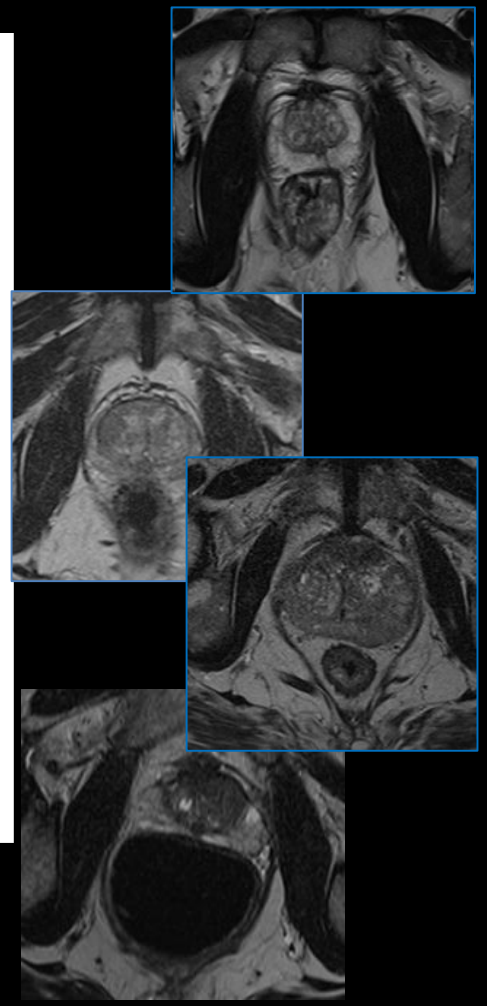

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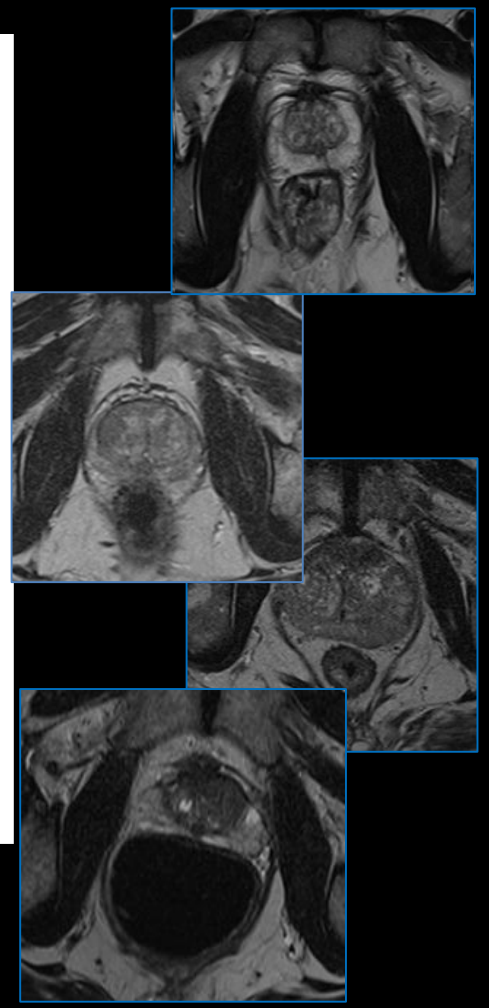
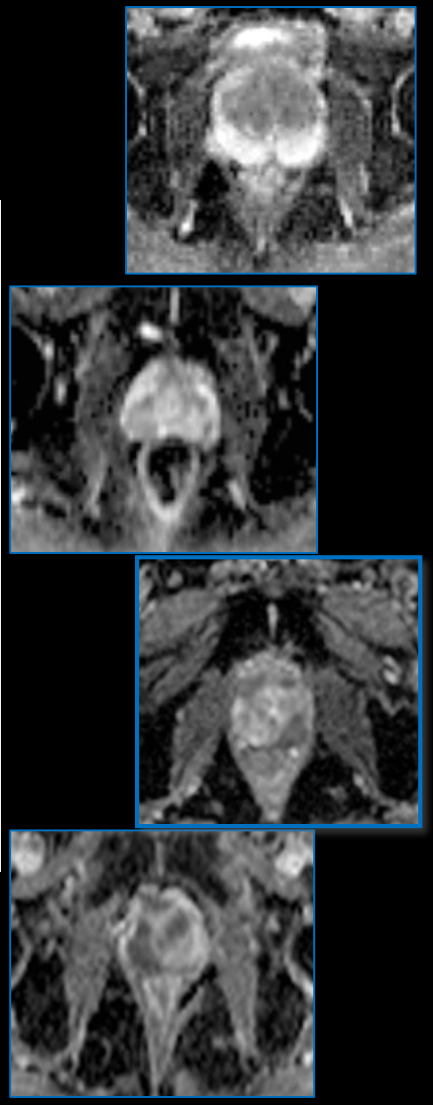


DWI Evaluation

Score	Peripheral Zone (PZ) or Transition Zone (TZ)
1	No abnormality (i.e., normal) on ADC and high b-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI.
4	Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI; <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior



http://www.acr.org

DWI Evaluation

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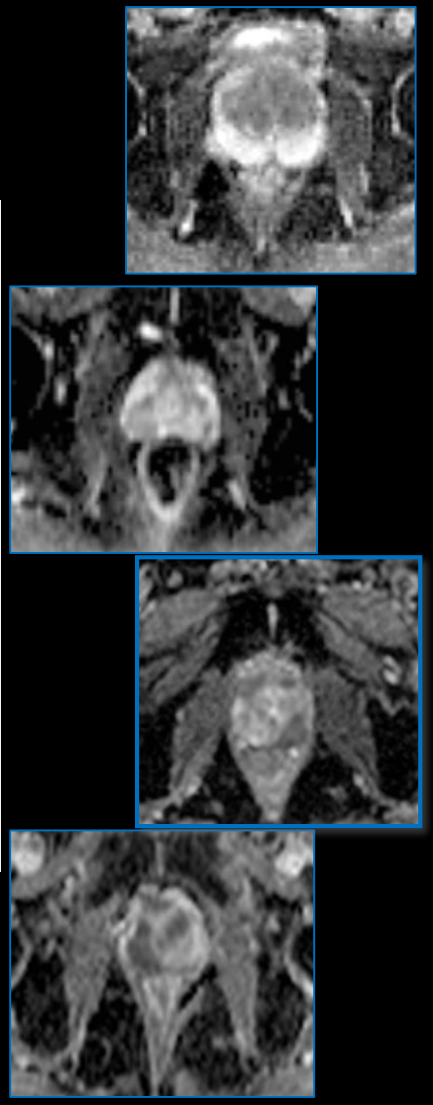

http://www.acr.org

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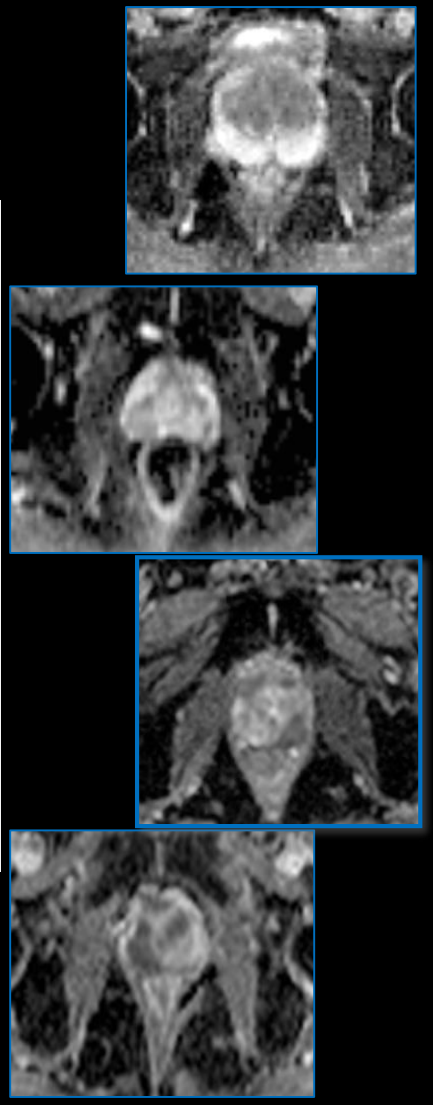

http://www.acr.org

DWI Evaluation

Score	Peripheral Zone (PZ) or Transition Zone (TZ)
1	No abnormality (i.e., normal) on ADC and high b-value DWI
2	Indistinct hypointense on ADC
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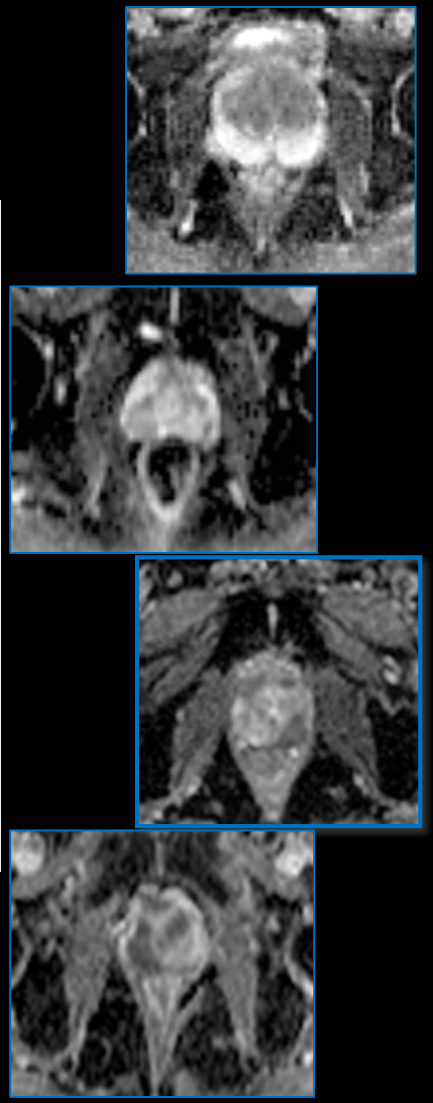
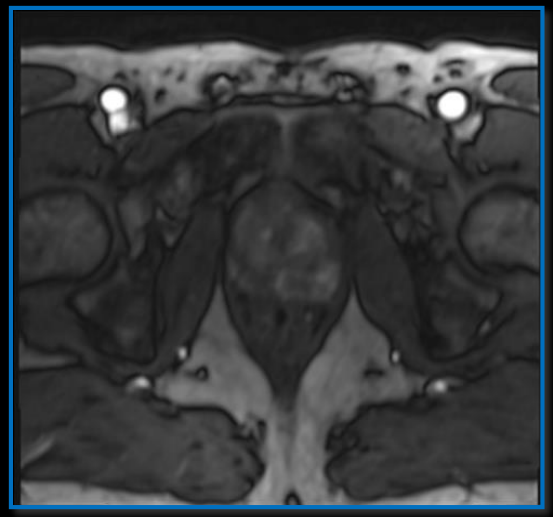


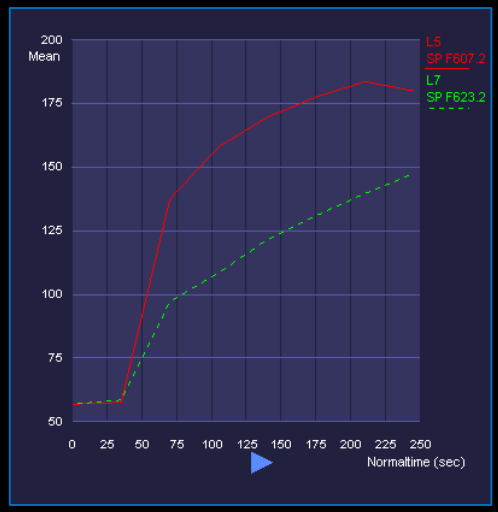
http://www.acr.org

DCE Evaluation

Score	Peripheral Zone (PZ) or Transition Zone (TZ)
(–)	no early enhancement, or diffuse enhancement not corresponding to a focal finding on T2W and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2WI
(+)	focal, and; earlier than or contemporaneously with enhancement of adjacent

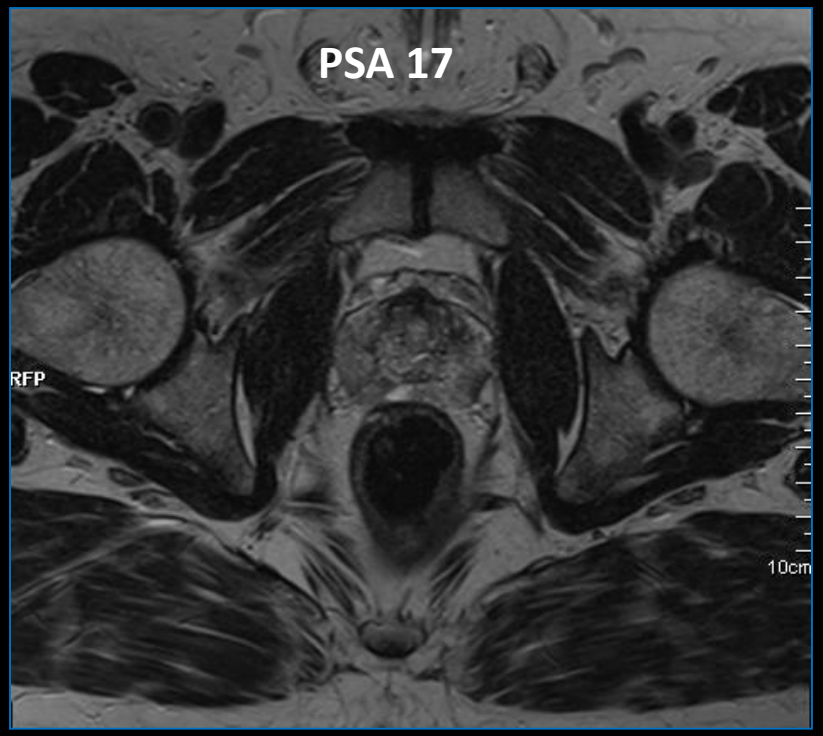
http://www.acr.org





False Positives

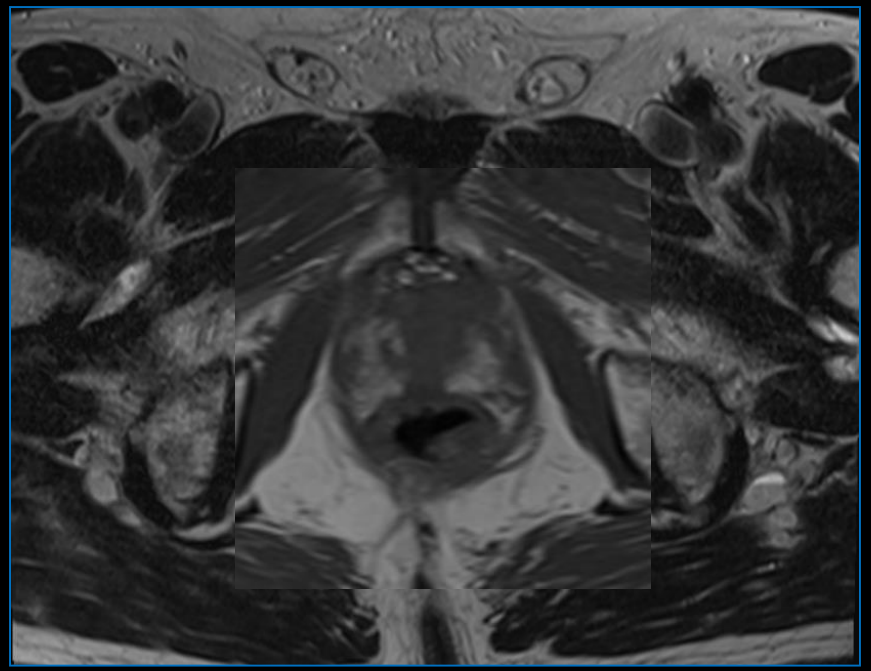
- False positives:
  - Prostatitis
  - Haemorrhage



Prostatitis

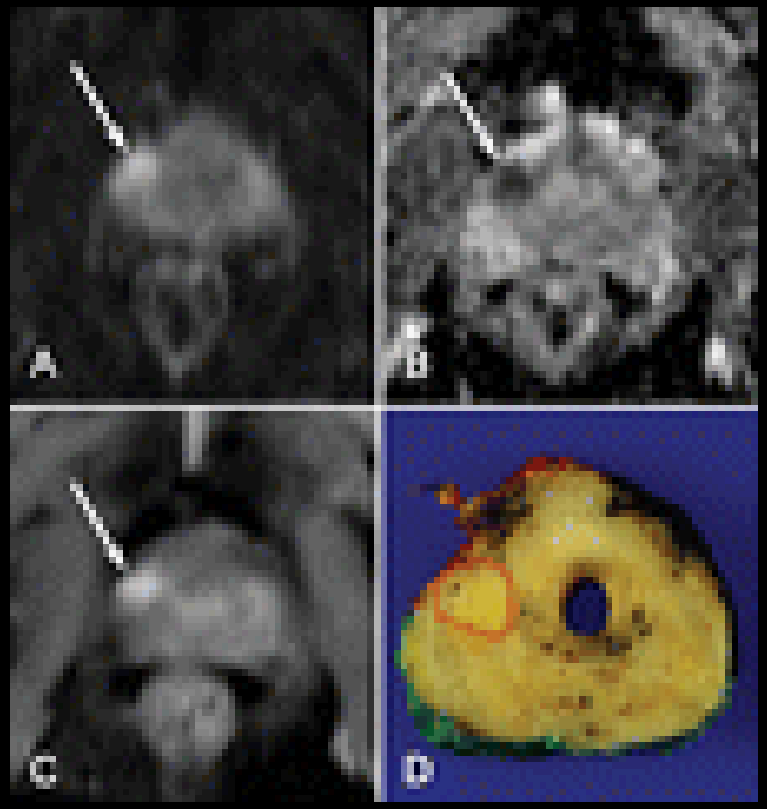
False Positives

- False positives:
  - Prostatitis
  - Haemorrhage
  - Treatment effects



Haemorrhage

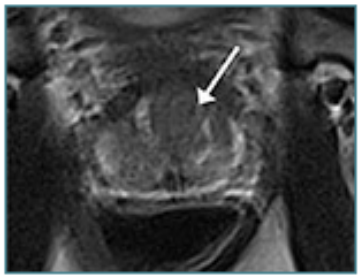
Improved Diagnosis



- PIRADS v2.0 predicts clinically significant cancer
- 425 patients with prostate cancer who had radical prostatectomy
- Defined by: (a) Gleason score of 7 or greater, (b) tumour volume of 0.5 cm3 or greater, or a (c) positive extracapsular extension or seminal vesicle invasion
- ROC AUC: 0.79-0.81

Park SY et al. Radiology 2016;280(1): 108-116

Interobserver Agreement: PIRADS v2.0



Interobserver Reproducibility of PI-RADS Version 2 Lexicon Was Moderate among Experienced Radiologists

Six experienced radiologists achieved moderate reproducibility for Prostate Imaging Reporting and Data System (PI-RADS) version 2 and neither required nor benefitted from a training session. In a study of six radiologists who assessed prostate MR imaging examinations by using the PI-RADS lexicon, Rosenkrantz et al found agreement tended to be better in the peripheral zone (PZ) than the transition zone (TZ), although it was weak for dynamic contrast-enhanced imaging in the PZ. Despite considerable variation in reproducibility for individual features within the PI-RADS version 2 lexicon, the system achieved moderate interreader reproducibility among experienced radiologists for PI-RADS score of 4 or greater in both the PZ and TZ; further studies are needed to evaluate reproducibility and the influence of training interventions among less experienced radiologists.

Inter-observer agreement

PI-RADS score of ≥4 :

κ = 0.593 in peripheral zone

κ = 0.509 in transition zone

Diffusion-weighted imaging

κ = 0.535–0.619

Dynamic contrast enhanced

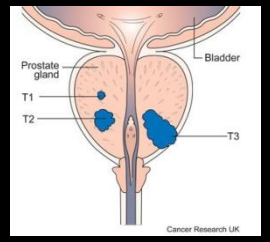
κ = 0.266–0.439

Definite T2-w extraprostatic extension

κ = 0.289

Rosenkrantz AB et al. Radiology 2016; 280(3): 793-804

Staging



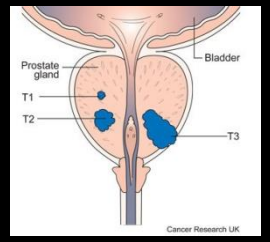
Not visible on MRI

- T1: Clinically inapparent
- Tumour neither palpable nor visible by imaging
  - T1a: incidental histologic finding in ≤5% of resected tissue
  - T1b: incidental histologic finding in >5% of resected tissue
  - T1c: identified by needle biopsy

Visible on MRI

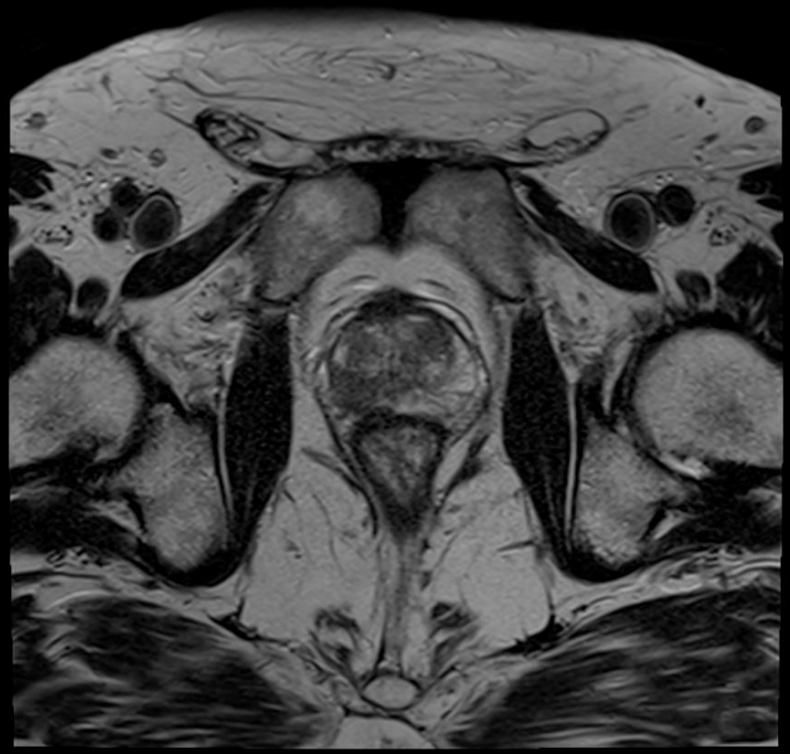
- T2: Confined to prostate
  - T2a: ≤ one half of one lobe
  - T2b : >one half of one lobe
  - T2c: involves both lobes

T Staging



Visible on MRI

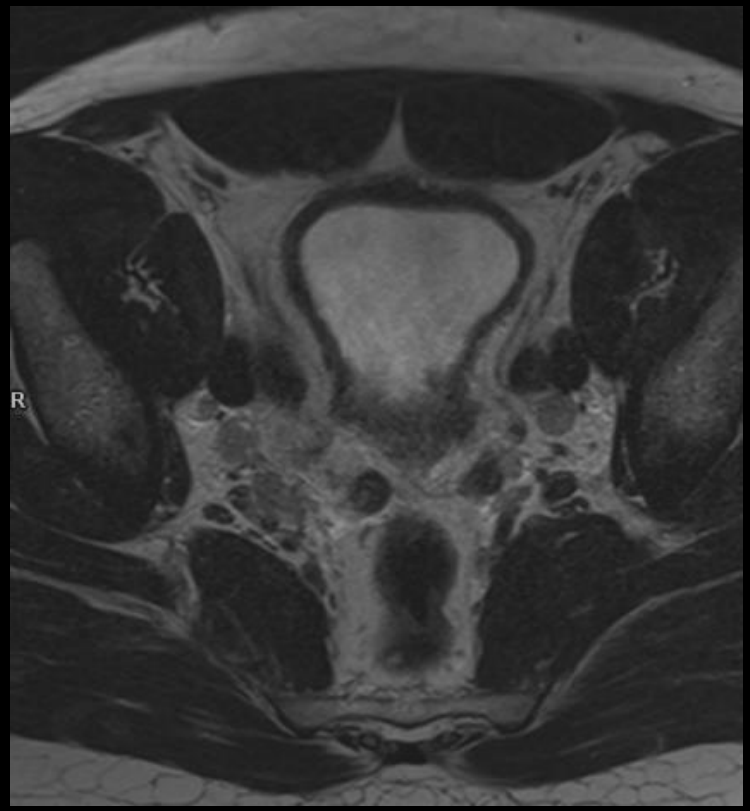
- T3: Extension through capsule
  - T3a: Extracapsular extensions
  - T3b: Invades seminal vesicles
- T4: Tumour is fixed or invades adjacent structures e.g. rectum, bladder, levator &/or pelvic wall



N Staging

N Staging

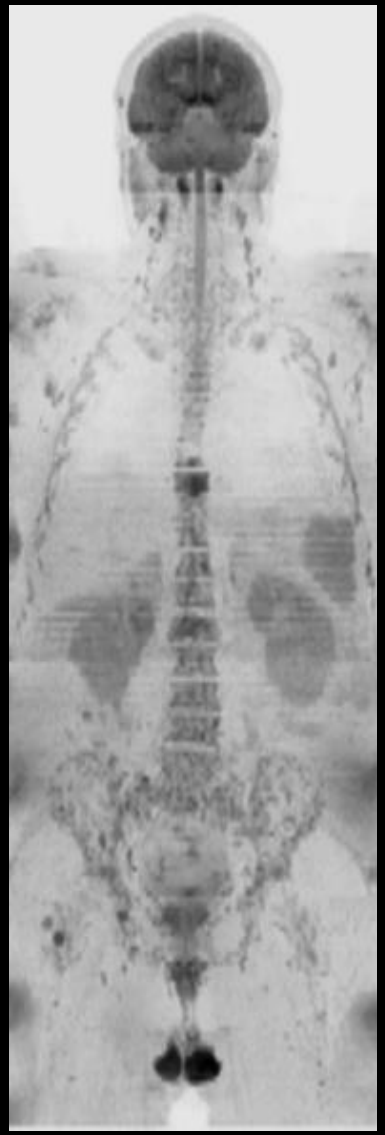
- Locoregional nodes:
  - N0: No nodes involved
  - N1: Locoregional nodes involved



N & M Staging

M Staging

- M0: No metastases
- M1a: Metastatic nodes
- M1b: Bones metastases
- M1c: Other distant metastases



WB-DWI

Limitations of MRI for Staging

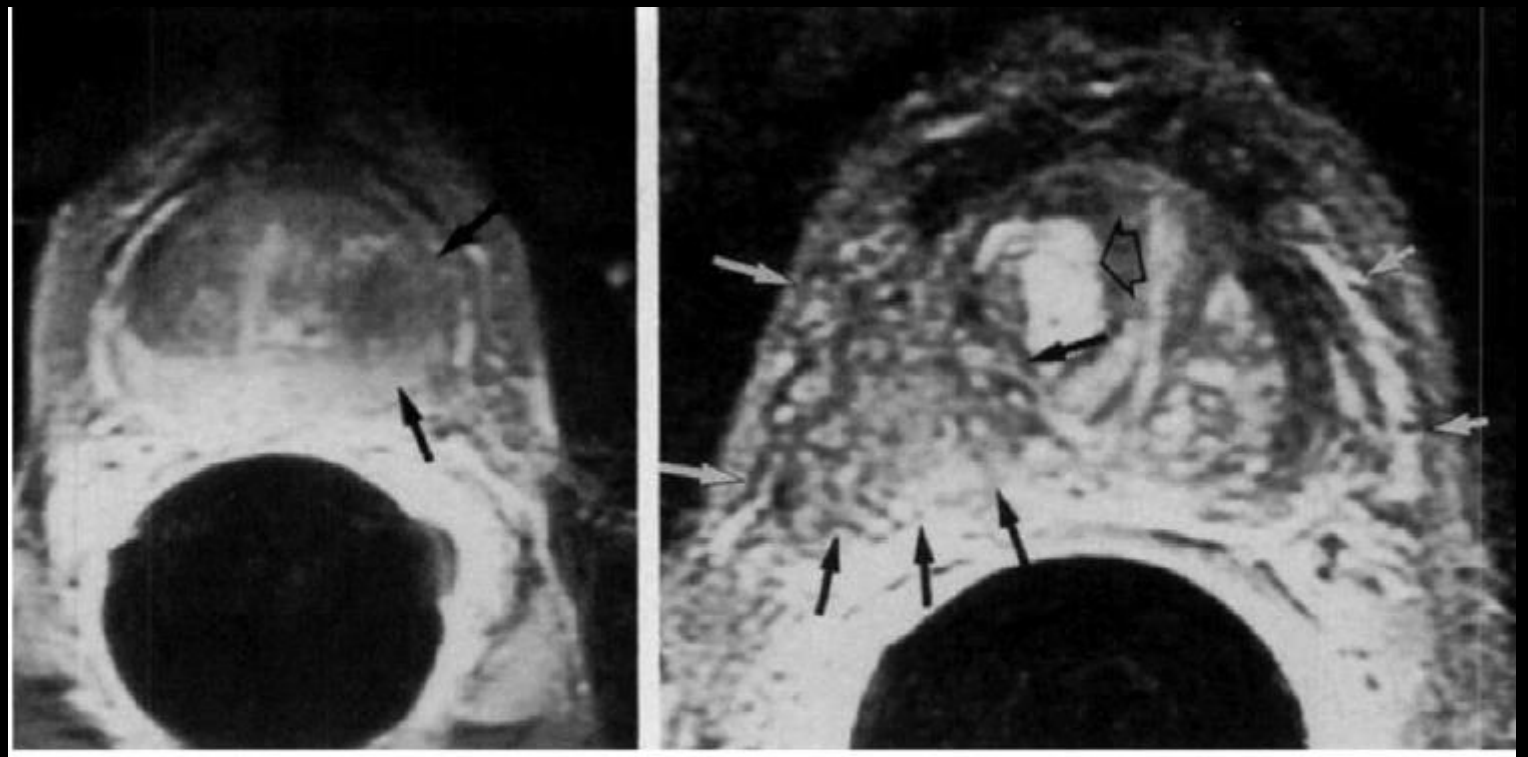
Nodal staging:

- Tumour may be present in normal sized nodes
- High incidence of enlarged reactive pelvic nodes
- High incidence of microscopic nodal spread to surgically non-sampled sites

Tumour staging:

- Varying ability to distinguish T2 (localised) from T3 (extracapsular) disease
- Sensitivity of T2-weighted MRI : 37-96% *
- DCE-MRI may improve tumour staging: Increased specificity for extracapsular extension+

*Kirkham A et al. Eur Urol 2006; 50 (6): 1163-74
+ Bloch B et al. Eur Radiol 2012; 22(10):2201-10



a. b.

Figure 4: MR images in two patients with prostatic carcinoma. **(a)** Low-intensity lesion in left peripheral zone is in region with positive biopsy findings (arrows). **(b)** Low-intensity lesion in right side of the prostate extends into the periprostatic fat (large solid arrows). High-signal-intensity glandular benign prostatic hypertrophy is seen in the central gland (open arrow) (images from reference 30).

Schnall MD et al. Prostate: MR imaging with an endorectal surface coil. Radiology 1989;172: 570-4

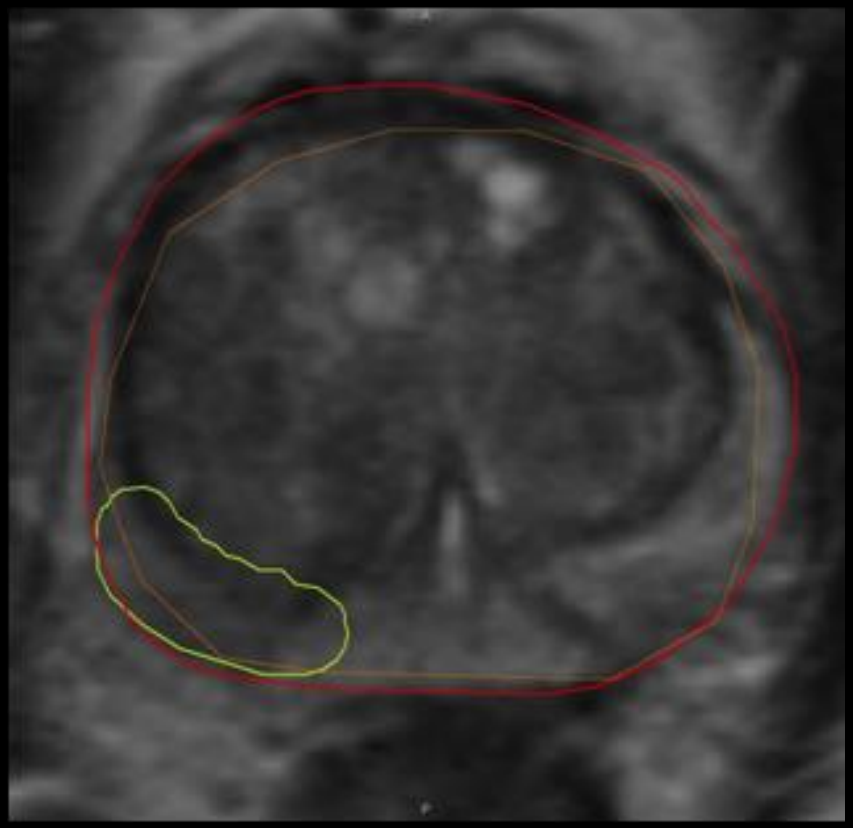
MR-Guided Biopsy & Treatment

Urol Clin North Am. 2014; 41(2): 315–326

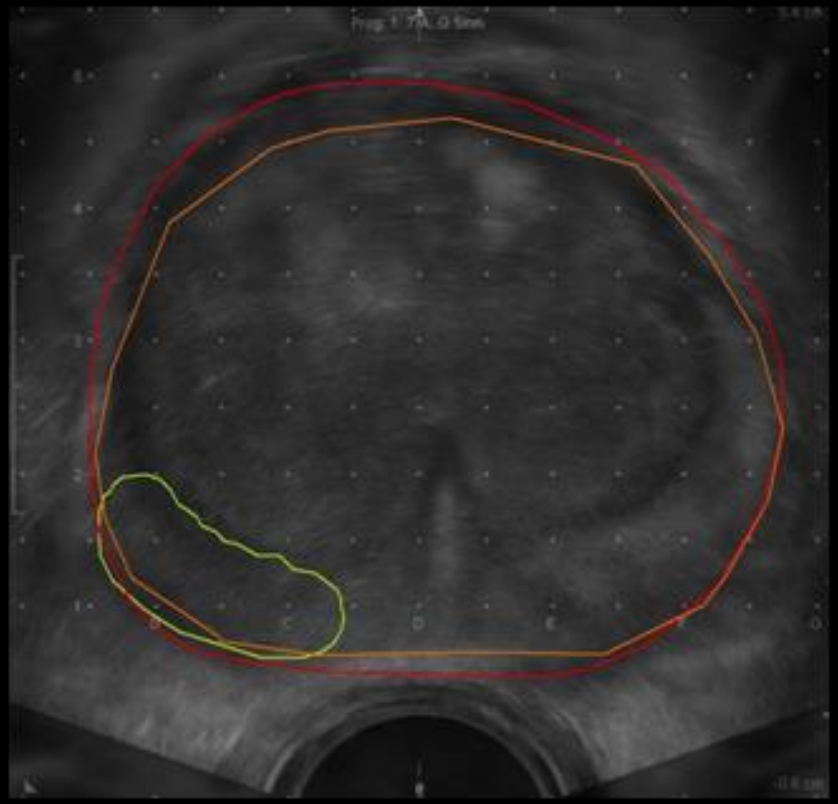
- MR guided biopsy possible of suspicious areas
- MR-US fusion allow biopsy to be performed in OP setting

Bayersdorff D et al. Radiology 2005; 234 (2): 576-81
Anastasiadis AG et al. Eur Urol; 50(4): 738-48
Engelhard K et al. Eur Radiol; 16(6): 1237-43

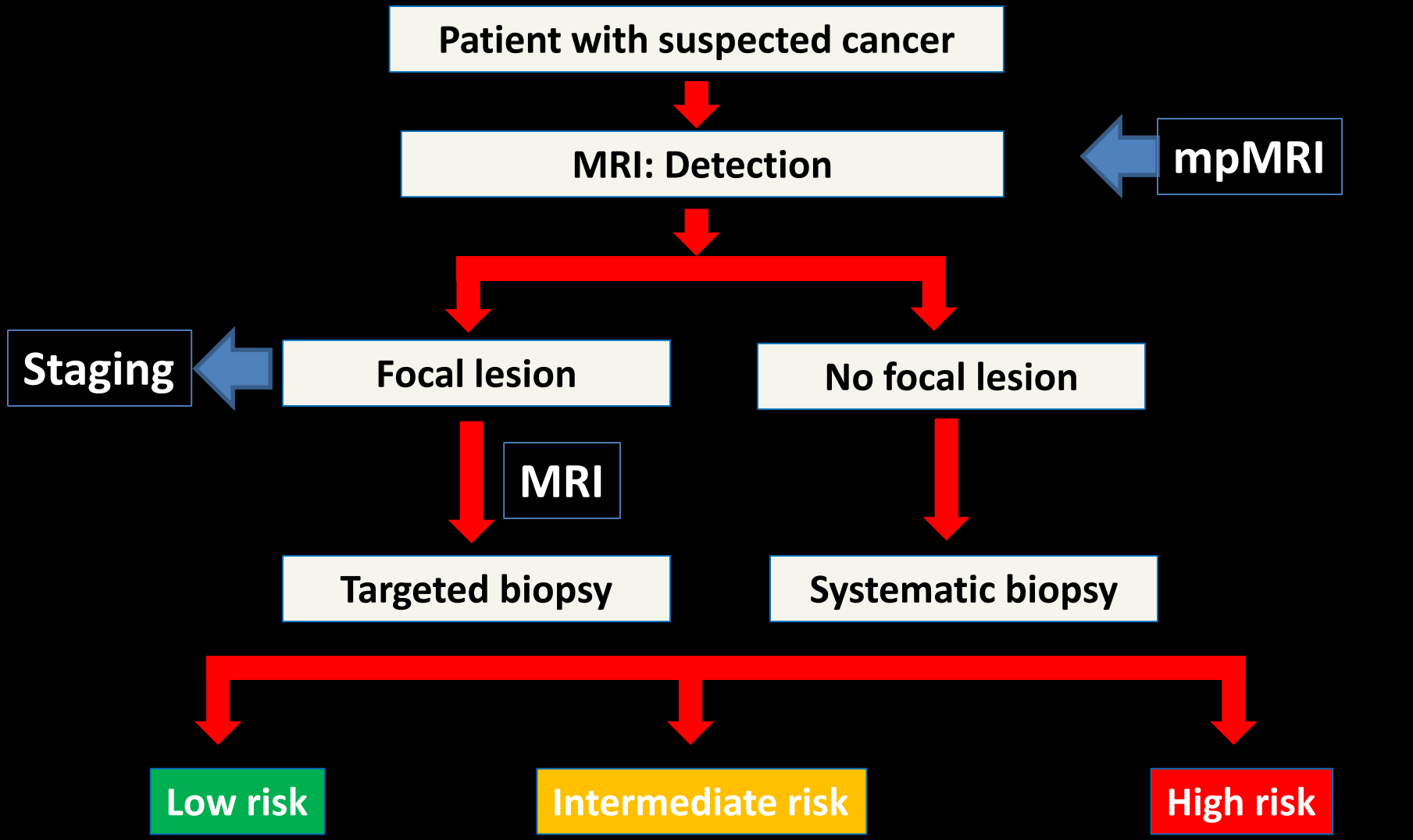
Tumour Delineation: Guided Biopsy



MRI: Tumour is delineated



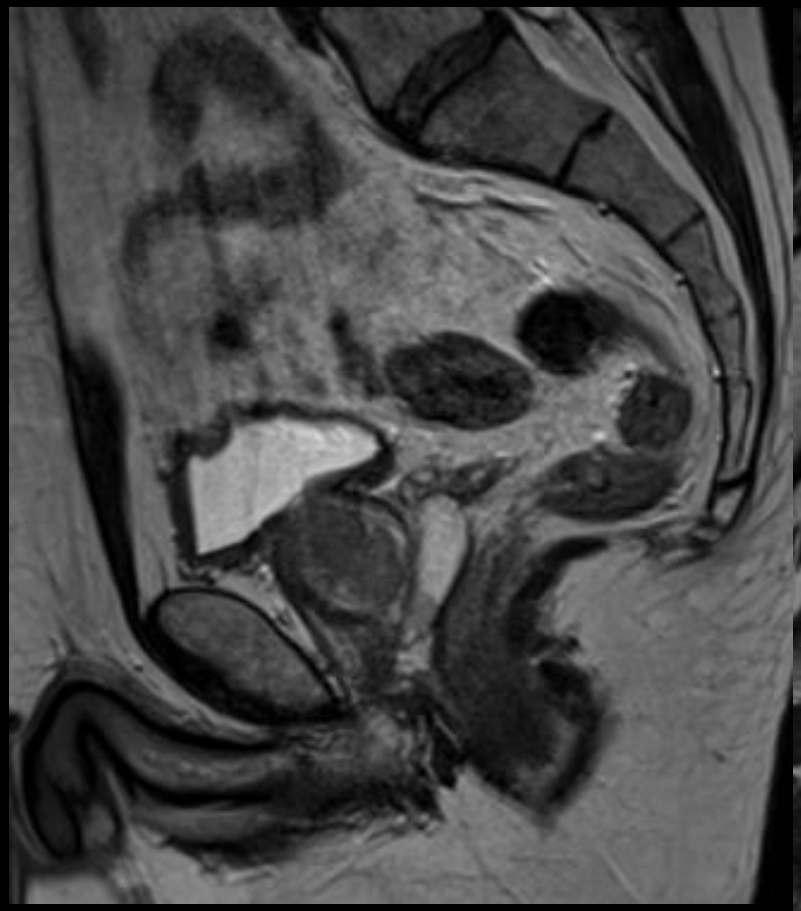
MRI- US fusion

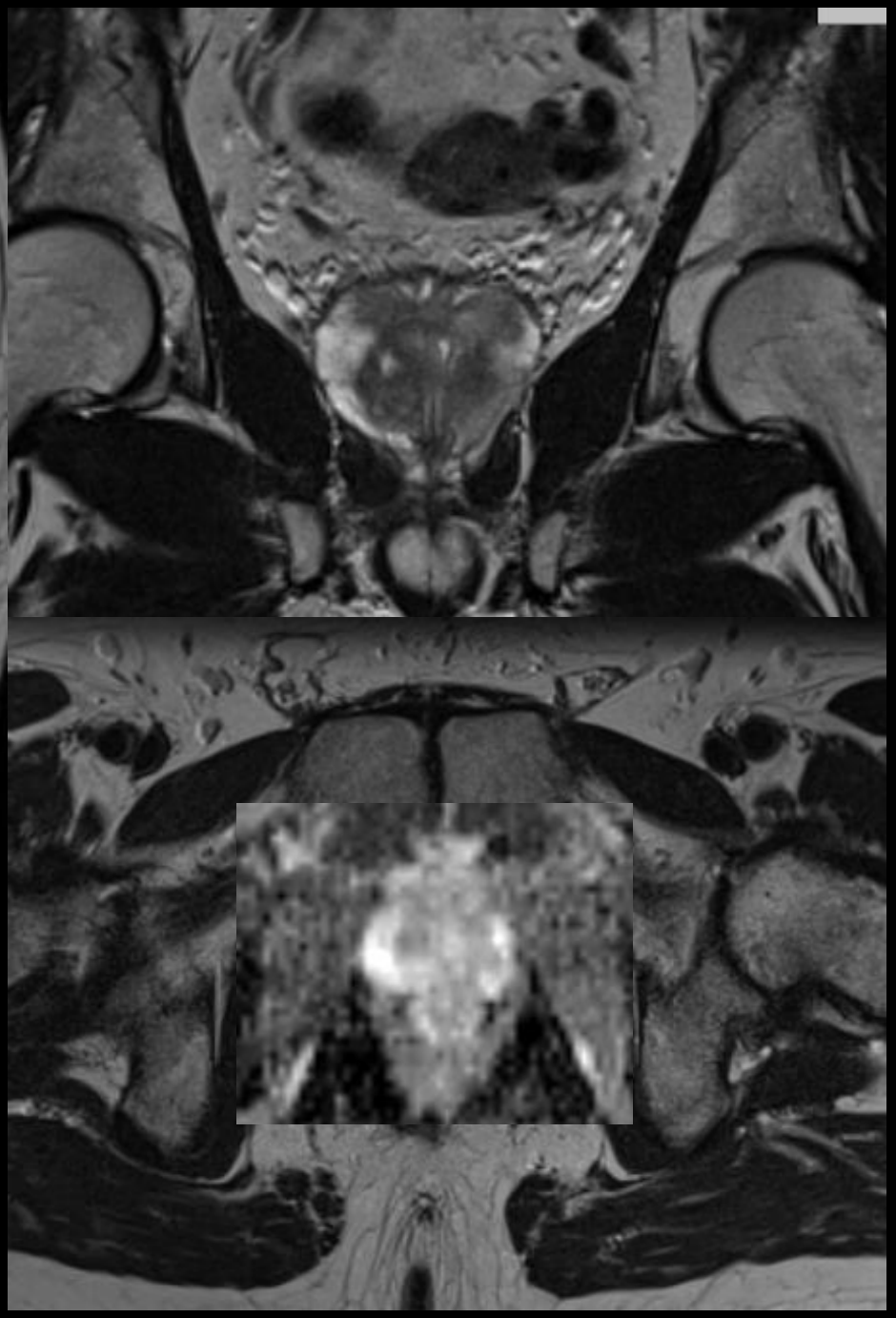


Stage	T1-2a
& PSA ng/mL	<10
& Gleason	≤6

Stage	T2b-c
or PSA ng/mL	10-20
or Gleason	7

Stage	≥T3a
or PSA ng/mL	>20
or Gleason	8-10





Is there a suspicious lesion?

Can you assign a PIRADS score?

What stage is this?

With respect to prostate cancer, which of the following is correct?

A. Its is a multifocal disease with multiple dominant lesions
B. All cancer foci are visible on MRI
C. A high risk cancer is a cT2c cancer, PSA >20ng/dl, Gleason 7+
D. A stage T3a cancer is invading the seminal vesicle
E. A PIRADS score of 4 & above is highly suspicious of cancer

With respect to prostate imaging, which of the following is correct?

A. Ultrasound is the initial modality of choice to diagnose prostate cancer
B. MRI should be performed at 3T
C. Multiparametric MRI (T2-, diffusion & multiphasic contrast enhanced) should be used to diagnose prostate cancer
D. Multiparametric MRI (T2-, diffusion, multiphasic contrast enhanced & spectroscopy) should be used to diagnose prostate cancer
E. Multiparametric MRI is essential for staging

PET/CT
for Prostate Cancer

Maria Picchio, Milan, Italy

Wouter V. Vogel, NKI-AVL, Amsterdam, the Netherlands

ESNM European School of Nuclear Medicine

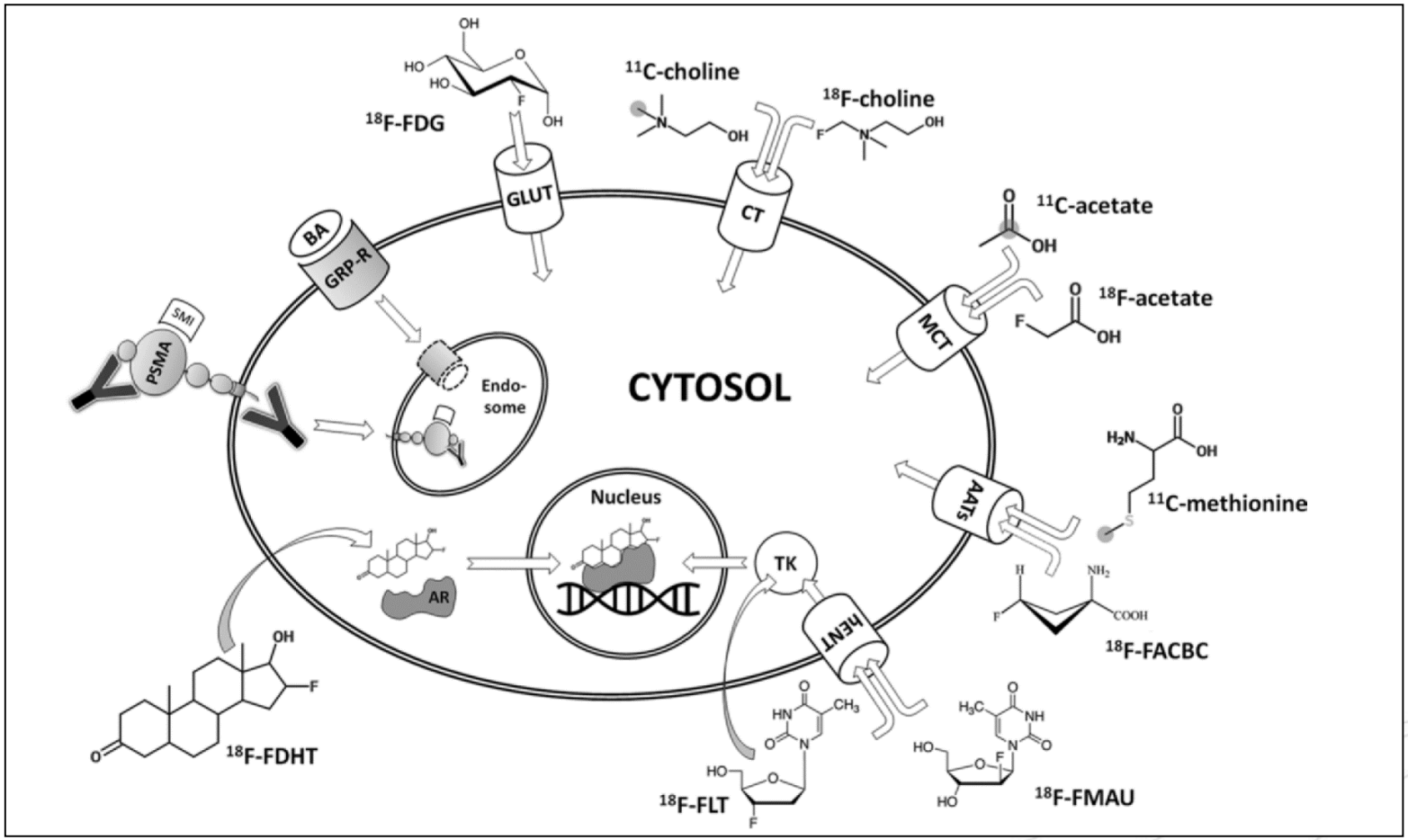
ESTRO School

Prostate Cancer

- **Prostate Cancer** (PCa) is currently the cancer with the highest prevalence in men (417,000 cases, 22.8% of all incidental cases) and the third most common cause of cancer deaths in men (9.5%) in Europe.

- **Imaging**
  - DIAGNOSIS - Detection and Characterization of Primary PCa lesions
  - STAGING – T/N/M
  - RESTAGING - Detection and Localization of relapse

PET Radiotracers in PCa: overview

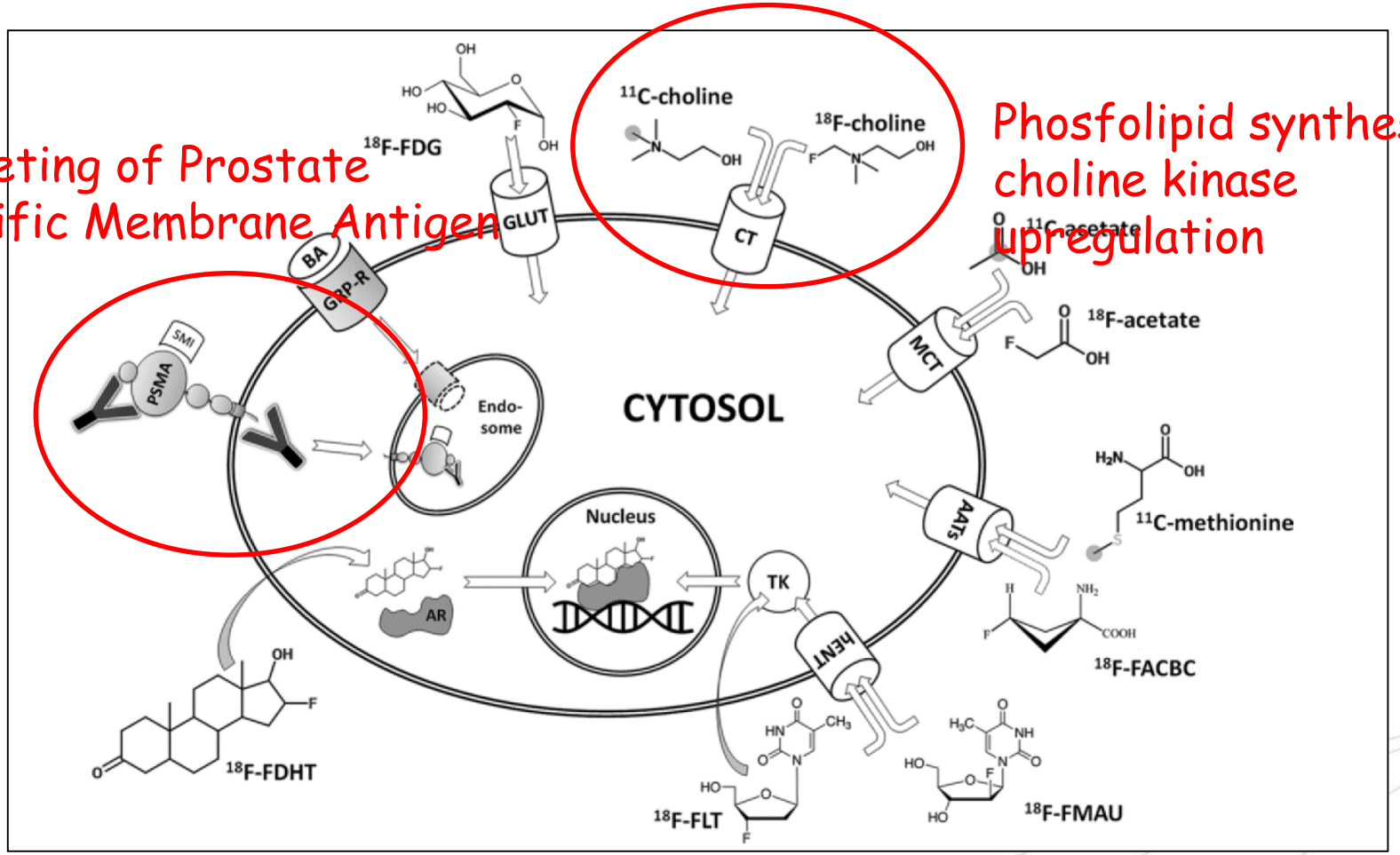


Wibmer et al. Radiographics, 2016

PET Radiotracers in PCa: overview

Targeting of Prostate Specific Membrane Antigen

Phosfolipid synthesis choline kinase upregulation

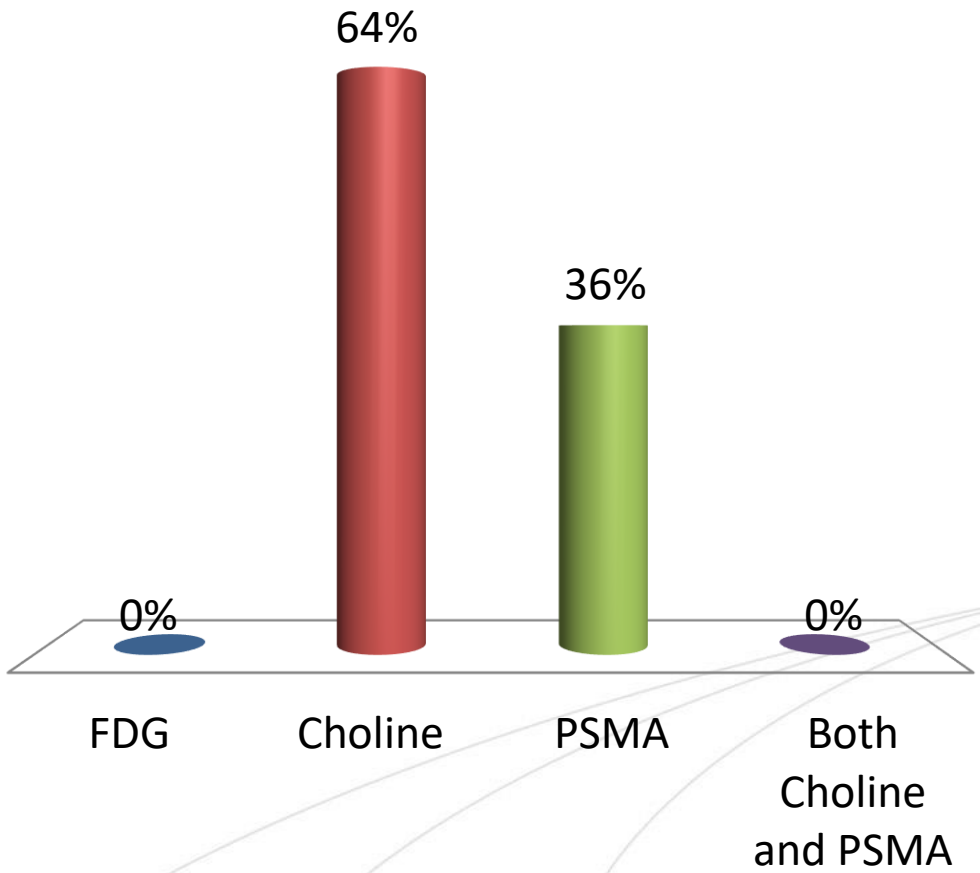


Wibmer et al. Radiographics, 2016

QUESTION 1.

Which PET tracer are you currently using in your Institution for Pca?

A. FDG
B. Choline
C. PSMA
D. Both Choline and PSMA



Choline PET/CT in Radiation Treatment Planning

- **Primary Treatment**: detection of intraprostatic lesions (Diagnosis) and patient selection for treatment (Staging)

- **Treatment of Relapse**: detection of recurrences (Restaging) and treatment monitoring

Choline PET/CT in Radiation Treatment Planning

- **Primary Treatment**: detection of intraprostatic lesions (Diagnosis) and patient selection for treatment (Staging)

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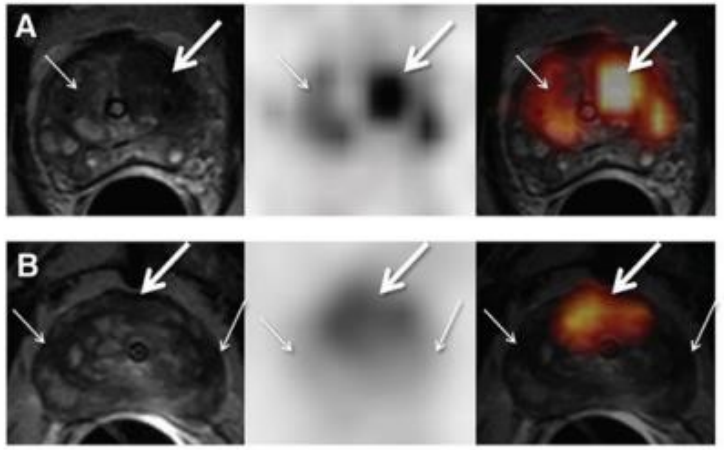
Choline PET – Primary Prostate Cancer

Study	n	Choline-PET–CT	
		Sensitivity (%)	Specificity (%)
Tumour			
Van den Bergh *et al.*[12]	49	77.4	44.9
Testa *et al.*[22]	50	55.0	86.0
Watanabe *et al.*[23]	43	73.0	59.0



	Primary Tumor
Sensitivity	54-100%
Specificity	43-86%

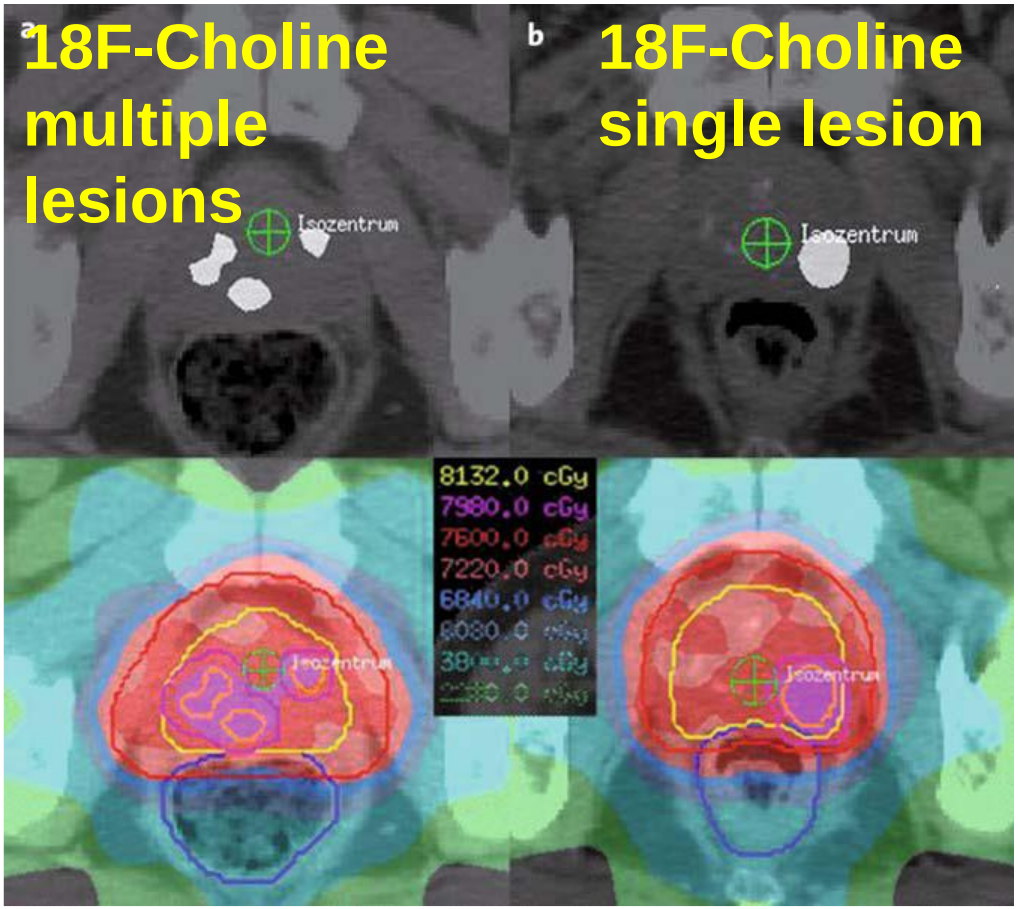
Mapelli and Picchio, Nat Rev Urol 2015

Hartenbach et al, CCR 2014

Brogsitter et al, Nucl Med Mol Imaging. 2013

Watanabe et al, JMRI 2010

Choline PET/CT for Pca Primary Treatment



66 prostate cancer pts

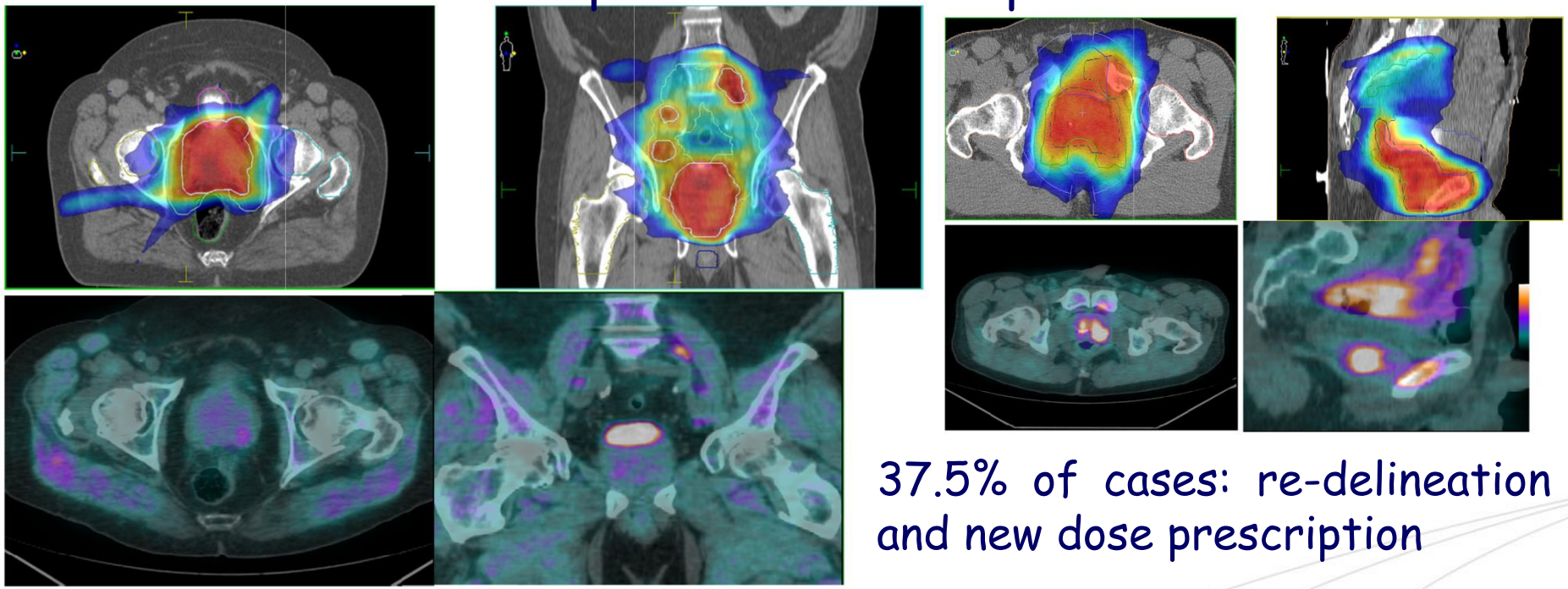
Treatment planning with Choline allows the definition of an integrated boost

GTV_{PET} and SUV are dependent on prognostic risk factors

Pinkawa et al. Strahlentherapie und Onkologie, 2011

Influence of ^{11}C-choline PET/CT on radiotherapy planning in prostate cancer

AIM: to analyse RT planning modification based on 11C-Choline PET/CT in 16 prostate cancer patients

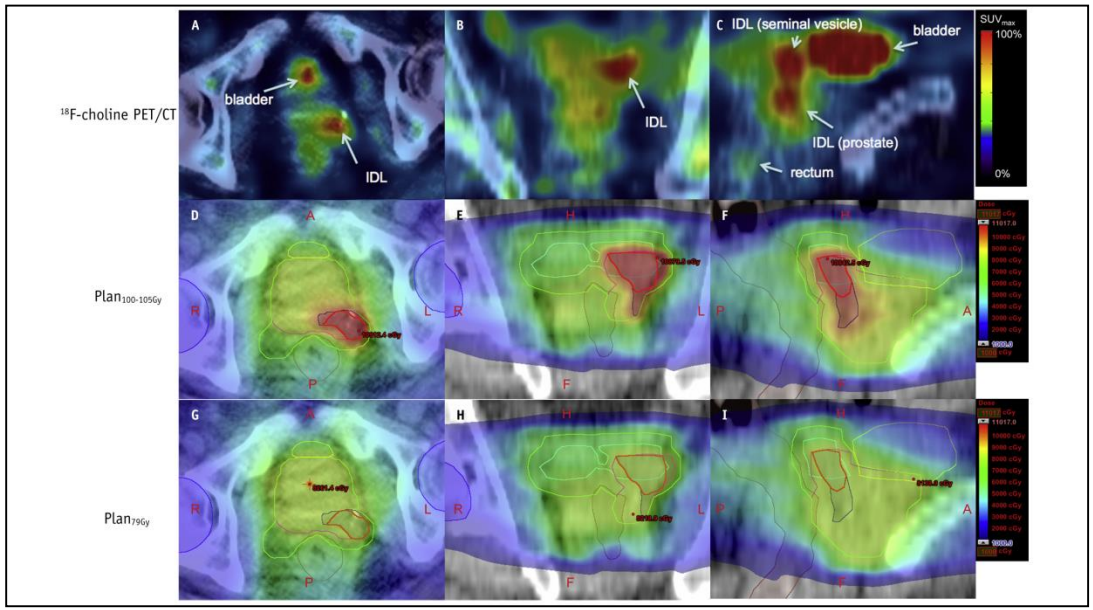


37.5% of cases: re-delineation and new dose prescription

Data show good preliminary clinical results in terms of biochemical control and toxicity. Lopez et al. Rep Pract Onc Radiot, 2015

Volumetric Modulated Arc Therapy Planning for Primary Prostate Cancer With Selective Intraprostatic Boost Determined by ^{18}F-Choline PET/CT

30 pts with localized Pca; 18F-choline PET/CT before treatment. Two VMAT plans for each pt: 79Gy vs 79Gy and 100-105Gy on intraprostatic dominant lesion (IDL)

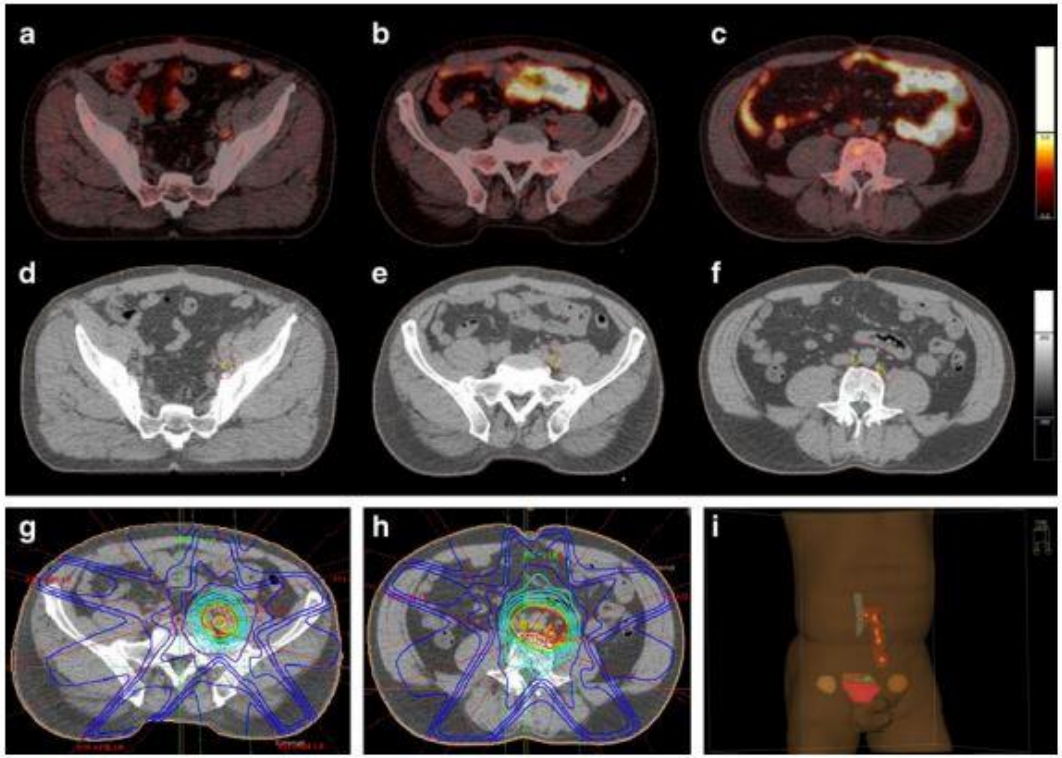


Kuang et al. Int J Rad Onc, 2015

Plan 100-105 Gy had significantly higher tumor control probability than plan 79 Gy across all prostate regions → increasing likelihood of tumor control in primary PCa

Choline PET/CT for Pca Primary Treatment

Choline PET/CT prior to RT might be useful in high-risk prostate cancer **to detect lymph node metastases** which might be included in the conventional irradiation field (instead of irradiation of single lymph nodes) influencing conventional PTV and surgery.



Eur J Nucl Med Mol Imaging (2013) 40 (Suppl 1):S28–S35
DOI 10.1007/s00259-013-2404-0

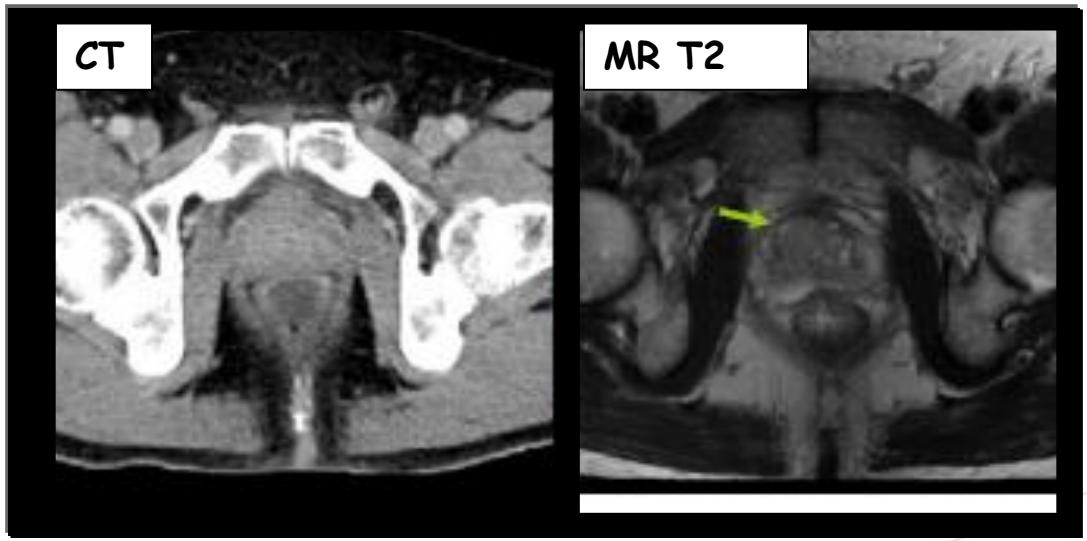
REVIEW ARTICLE

Role of choline PET/CT in guiding target volume delineation for irradiation of prostate cancer

S. M. Schwarzenböck · J. Kurth · Ch. Gocke · T. Kuhnt · G. Hildebrandt · B. J. Krause

MRI – Primary Prostate Cancer

- High spatial resolution - excellent soft tissue contrast
- Distinguish changes in the prostatic parenchyma
- Assess small structures in the small pelvis



Souvatzoglou M. et al. EJNMMI, 2013

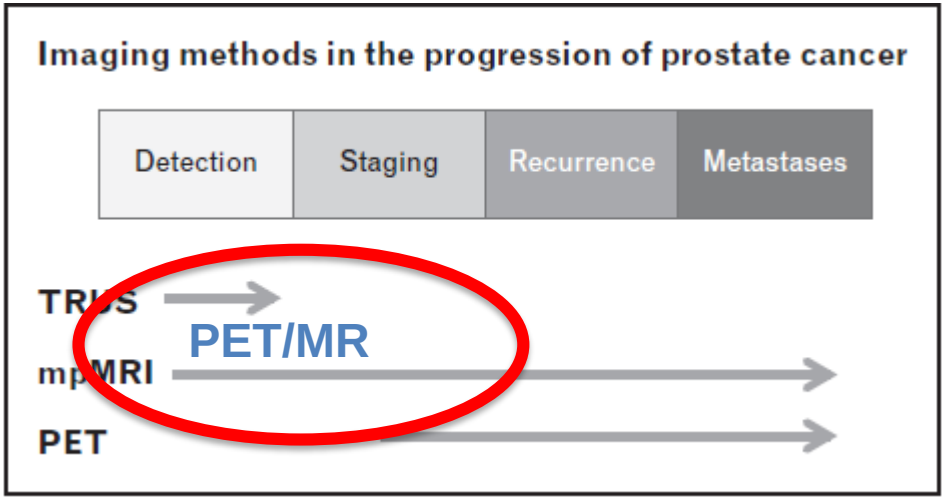
Diagnosis and Staging

Future directions

PET/CT

?

PET/MR

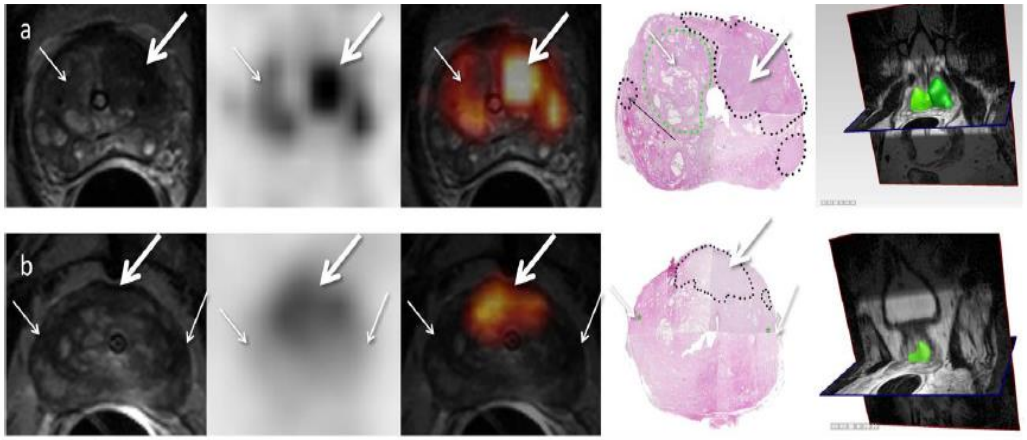


Bouchelouche et al. Curr Opin Oncol, 2015

PET/MRI – Primary Prostate Cancer

N=98 Lesions >5 mm

Modality	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
MR (T2)	67	35	59	44	54
PET (18F-Chol)	85	45	68	69	68
PET/MR	**84**	**80**	**85**	**78**	**82**



Hartenbach et al. Clin Cancer Res., 2014

PET/MRI – Primary Prostate Cancer

Gleason >6 vs <6	Sens	Spec	PPV	NPV	Acc
Biopsy	56	71	60	68	67
PET/MR	**63**	**90**	**83**	**76**	**81**

- **Enhance the success rate of needle biopsies**
- **Potential role in pt selection for active surveillance and watchful waiting**

Hartenbach et al. Clin Cancer Res., 2014

Choline PET – Primary Prostate Cancer

Choline PET

- Not recommended for primary staging
- Not recommended for RT dose painting
- Any attempts should be limited to controlled trials
- Possible role of PET/MRI

Choline PET - N in newly diagnosed PCa

Intermediate and high risk	Sensitivity	Specificity	NPV	PPV	Accuracy
Patient-based analyses	19-60%	95-97%	59-87%	63-90%	75-80%
Region-based analyses	9-41%	99.7%	91-97%	50-94%	NA

Change therapeutical approach in almost 15-20% of pts

Heck et al, Eur J Nucl Med Mol Imaging 2014
Schiavina et al, Eur Urol 2008
Van Der Bergh et al, Urol Oncol 2015

Influence of ^{11}C-choline PET/CT on radiotherapy planning in prostate cancer

Table 3 – Planning modification after ^{11}C-choline PET/CT.[a]

Patient	PET findings	CTV prior to PET	CTV after PET	Dose prescribed prior to PET	Dose prescribed after PET
1	Positive bone metastases	Prostate plus seminal vesicles	Pelvic lymph nodes, seminal vesicles, prostate, pubic bone	66 Gy[b]	70 Gy[c]
2	Negative bone metastases	Pelvic lymph nodes, seminal vesicles, prostate, vertebral bone	Prostate plus proximal seminal vesicles	No RT or 70 Gy[c]	66 Gy[b]
3	Positive lymph nodes	Prostate plus proximal seminal vesicles	Retroperitoneal and pelvis lymph nodes, seminal vesicles, prostate	66 Gy[b]	70 Gy[c] (64.4 Gy, 2.3 Gy to retroperi-toneal positive lymph nodes)
4	Positive lymph nodes	Prostate plus proximal seminal vesicles	Pelvic lymph nodes, seminal vesicles, prostate	66 Gy[b]	70 Gy[c]
5	Positive tumour bed and lymph nodes	Tumour bed	Pelvic lymph nodes, tumour bed	60 Gy[b]	70 Gy[c]
6	Positive tumour bed and lymph nodes	Tumour bed	Pelvic lymph nodes, tumour bed	60 Gy	70 Gy[c]

[a] PET/CT: positron emission tomography/computed tomography.
[b] 3 Gy/fraction.
[c] 2.5 Gy/fraction.

Lopez et al. Rep Pract Onc Radiot, 2015

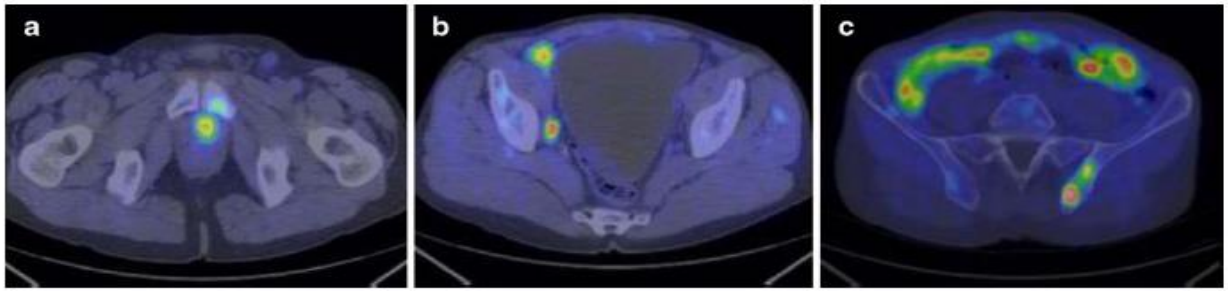
Choline PET/CT in Radiation Treatment Planning

- Primary Treatment: detection of intraprostatic lesions (Diagnosis) and patient selection for treatment (Staging)

- **Treatment of Relapse**: detection of recurrences (Restaging) and treatment monitoring

Choline PET – Recurrent disease

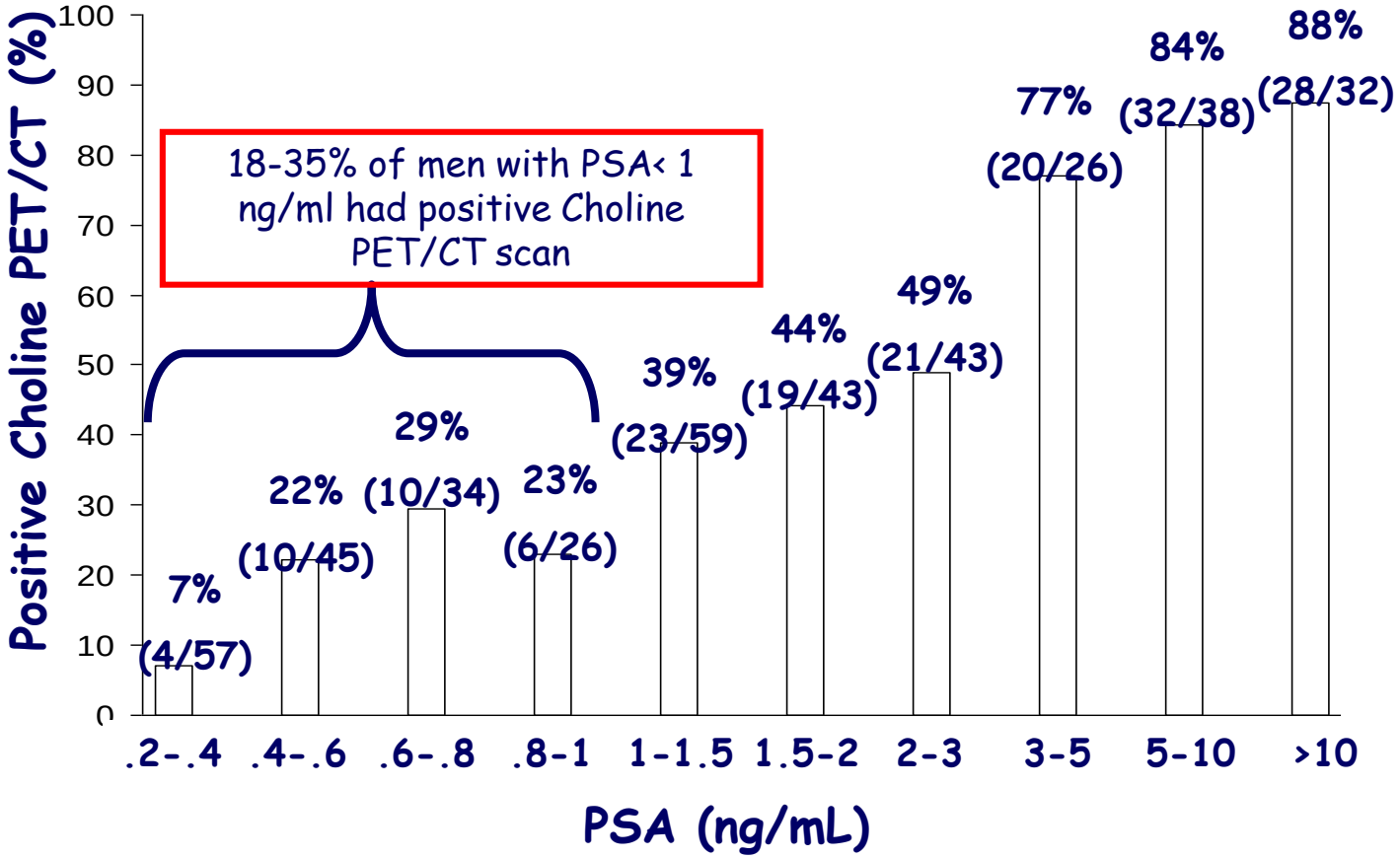
	Patient-based analyses 12 studies, 1055 pts
Sensitivity	85% (95% CI, 89-89%)
Specificity	88% (95% CI, 73-95%)



Umbehr et al, Eur Urol, 2013

Giovacchini et al, EJNMMI, 2010

Choline PET – PSA Dependency



Giovacchini et al. Eur J Nucl Med Mol Imaging, 2010

Picchio et al. Eur Urol, 2011

Choline PET – PSA Dependency

IS IT POSSIBLE TO SOLVE THIS ISSUE?

The best predictors of positive imaging at low PSA level (<1/1.5 ng/ml) are PSA kinetics (PSA doubling time)

	Imaging approach	Patient population	Detection rates
Castellucci et al	11C-choline PET/CT	PSA<1.5 ng/ml	Overall: 28% PSA DT <7 months: 58%
Giovacchini et al	11C-choline PET/CT	PSA<1.5 ng/ml (n=75)	Overall 21% PSADT<6 months: 50%

Castellucci et al, Eur J Nucl Med Mol Imaging, 2011

Giovacchini et al, J Urol, 2013

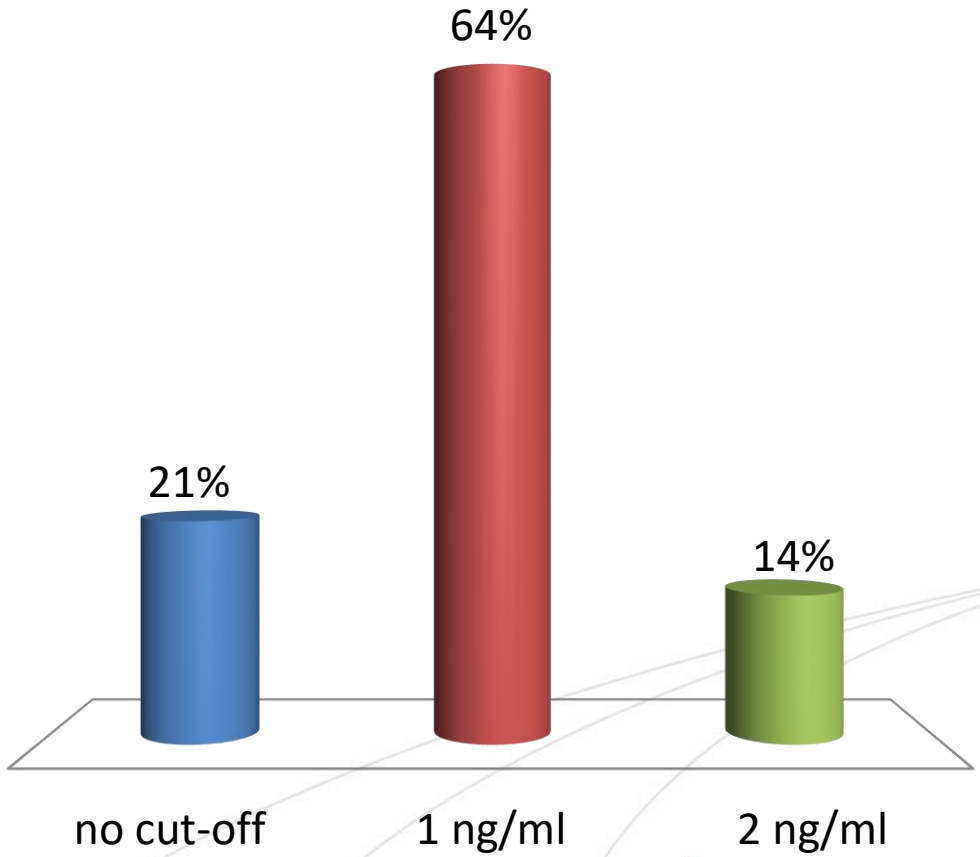
Castellucci and Picchio, Eur J Nucl Med Mol Imaging, 2013

Evangelista L. Clin Nuc Med., 2013

QUESTION 2.

Which cut-off PSA value are you using to perform Choline PET study?

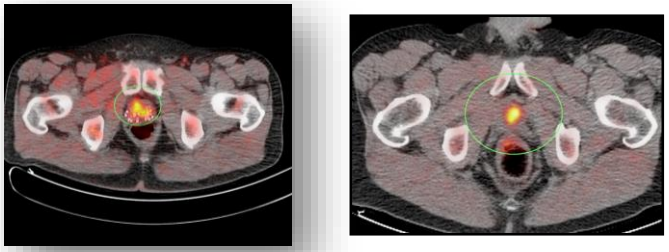
A. no cut-off
B. 1 ng/ml
C. 2 ng/ml

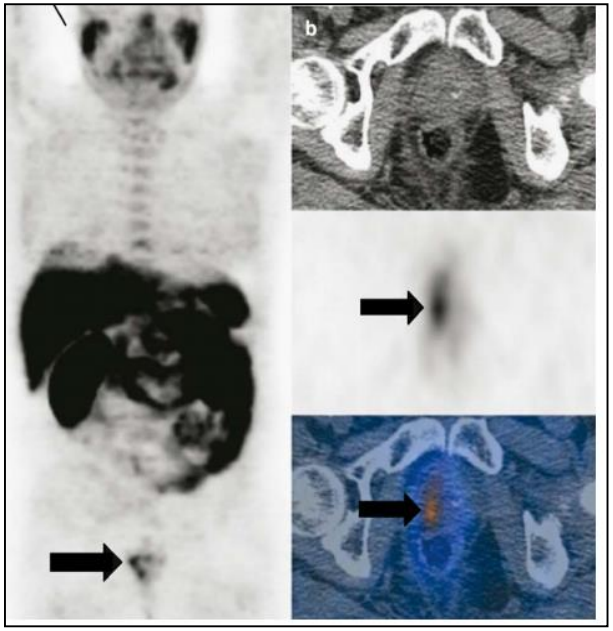


Choline PET – Local Recurrence

	Prostatic Fossa Relapse
	Pooled Value (95% CI)
Sensitivity	75.4% (66.9–82.6)
Specificity	82.0% (68.6–91.4)
Positive likelihood ratio	2.35 (1.03–5.39)
Negative likelihood ratio	0.44 (0.26–0.74)
Diagnostic odds ratio	5.86 (1.81–18.94)

Evangelista et al. Clin Nuc Med, 2013





Husarik et al. EJNMMI, 2008

Main limitations:
- microscopic diseases (beyond spatial resolution)
- inflammatory uptake in the prostatic site

Choline PET/CT in Radiation Treatment of local recurrence

60 pts with biochemical progression after radical prostatectomy. Median PSA before RT: 0.9 ng/mL

High-dose salvage radiation therapy delivered up to total dose of 80Gy to choline PET/CT-positive area.

Mean follow-up: 31.2 months, 76.6% pts free of recurrence.

3-year biochemical progression-free survival rate: 72.5%.

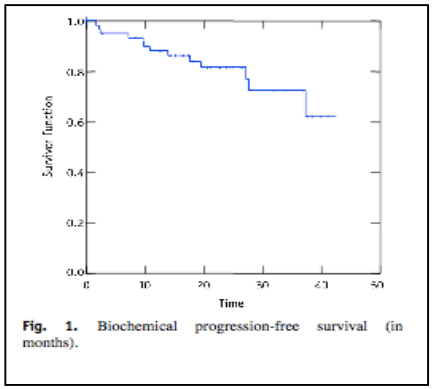


Fig. 1. Biochemical progression-free survival (in months).

18F-choline PET/CT-driven high-dose salvage radiation therapy seems to be feasible and well tolerated, with a low rate of toxicity.

D'angelillo et al. Int J Rad Onc, 2014

Choline PET – N Recurrence

Table 1 Comparison of PET/CT reliability based on the results from different authors

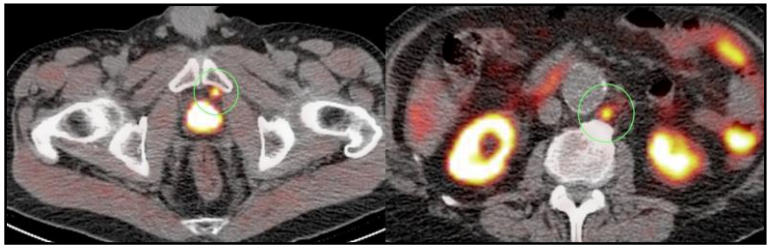
	Sensitivity	Specificity	PPV	NPV
(Farsad et al. 2005)	66.0%	81.0%	87.0%	55.0%
(Castellucci et al. 2011)	93.0%	74.0%	60.0%	96.0%
(Schiavina et al. 2008)	41.4%	99.8%	94.4%	97.2%
(Budiharto et al. 2011)	9.4%	99.7%	75.0%	91.0%
(Kjölhede et al. 2013)	33.0%	92.0%	76.0%	65.0%

Osmonov et al. Springerplus, 2014

Choline PET – N Recurrence

11C-Choline PET/CT After RP – lesion based analysis

	Lymph node metastases
Sensitivity	40-64%
Specificity	90-96%
PPV	75-86%
NPV	72-83%
Accuracy	72-82%
MEDIAN PSA: 1.9-6 ng/ml	



Scattoni et al, Eur Urol, 2007

Scattoni et al, Eur Urol, 2007

Hovels et al, Clin Radiol, 2008

Picchio et al, Eur J Nucl Med Mol Imaging, 2012

Evangelista et al, Clin Nucl Med, 2013

Tilki et al, Eur Urol, 2013

Choline PET/CT: MDT

Study	No. of patients	Site of metastasis: node/bone/visceral	Median PSA at time of metastasis	Staging method	Type of MDT	Median follow-up, mo	Median PFS
Casamassima et al. [23]	25	25/0/0	5.65	Choline PET/CT	SBRT	29	24 mo
Muacevic et al. [24]	40	0/40/0	5.4	Choline PET/CT	SBRT	14*	NR
Würschmidt et al. [25]	15	15/0/0	1.79	Choline PET/CT	NRT	28	Median not reached: 3-yr PFS: 75%
Ahmed et al. [26]	17	1/15/1	2.1	Choline PET/CT ($n = 9$), MRI ($n = 6$), CT ($n = 1$), and biopsy ($n = 1$)	SBRT	6	12 mo
Jereczek-Fossa et al. [27]	19	18/1/0	1.77 (pelvic nodes); 10.7 (M1)	Choline PET/CT	SBRT	17	Median not reache 30-mo PFS: 63.5%
Schick et al. [28]	50	33/15/2	6.7	Choline PET/CT and bone scintigraphy	SBRT ($n = 14$) NRT ($n = 36$)	31	Median not reache 3-yr PFS: 58.6%
Decaestecker et al. [29]	50	27/22/1	3.8	Choline ($n = 18$) or FDG ($n = 32$) PET/CT	SBRT	25	19 mo
Picchio et al. [30]	83	83/0/0	2.6	Choline PET/CT	HRT	22	NR
Rinnab et al. [31]	15	15/0/0	1.98	Choline PET/CT	LND	13.7*	NR
Schilling et al. [32]	10	10/0/0	8.75	Choline PET/CT	LND	11*	NR
Winter et al. [33]	6	6/0/0	2.04	Choline PET/CT	LND	24 mo	NR
Busch et al. [37]	6	6/0/0	37.6*	Choline ($n = 3$), MRI ($n = 1$), CT ($n = 2$)	LND	NR	15.5 mo
Jilg et al. [34]	47	47/0/0	11.1*	Choline PET/CT	LND	35.5	27 mo**
Martini et al. [35]	8	8/0/0	1.62	Choline PET/CT	LND	NR	NR
Suardi et al. [36]	59	59/0/0	2.0	Choline PET/CT	LND	76.6	60 mo**

Ost et al. Eur Urol., 2014

Choline PET/CT: MDT

Study	No. of patients	Site of metastasis: node/bone/visceral	Median PSA at time of metastasis	Staging method	Type of MDT	Median follow-up, mo	Median PFS
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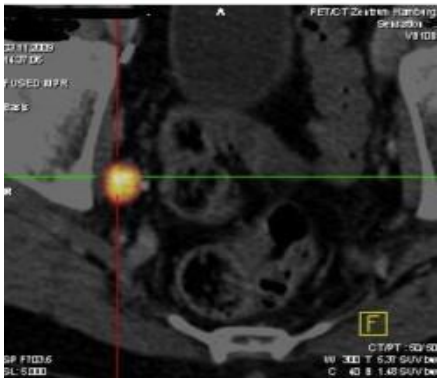
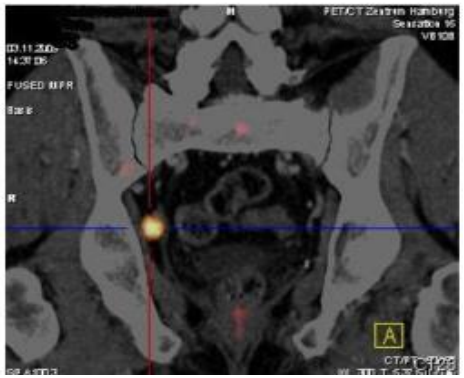
Metastases directed therapy (MDT: Surgery/RT)

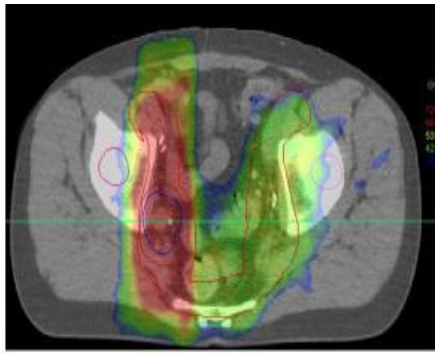
- Reduce toxicity of systemic therapies
- Randomized trails are necessary
- PFS 1-3 yrs in half of pts after treatment

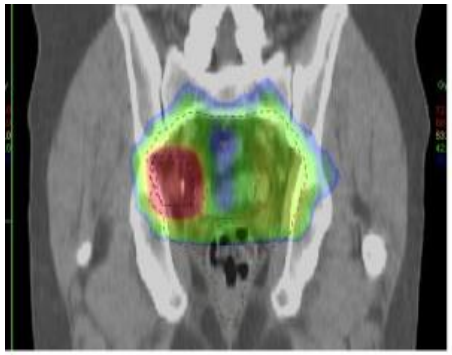
Ost et al. Eur Urol., 2014

PET/CT as guide for MDT









Wurschmidt et al. Radiation Oncology, 2011

19 Pts with recurrent PC

(median PSA: 1.9 ng/ml, range 0.42 - 65)

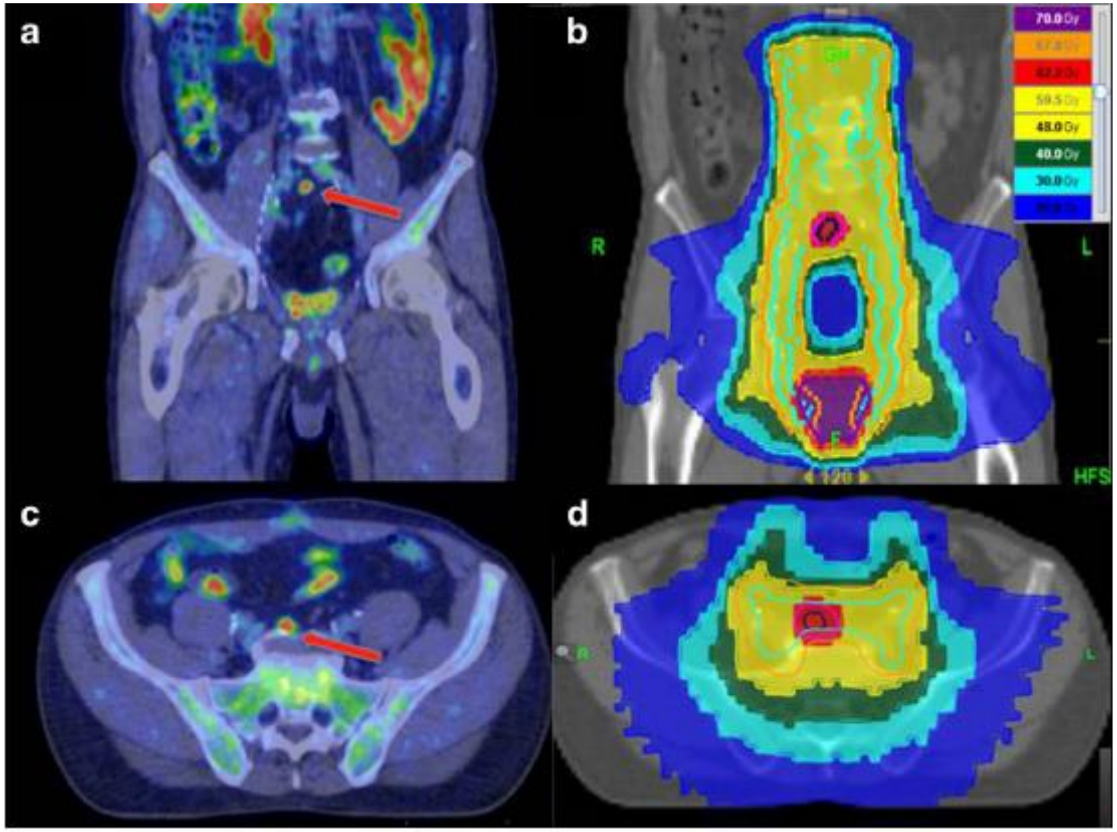
Chol+ at Right Obturatoria LN (SUVmax: 6.0)

IMRT (45 Gy) on pelvic LN

Boost dose (66.6 Gy) on positive LN

- **18F-Choline PET/CT planning could be helpful in dose escalation to lymph nodal sites of prostate cancer**

PET/CT as guide for MDT



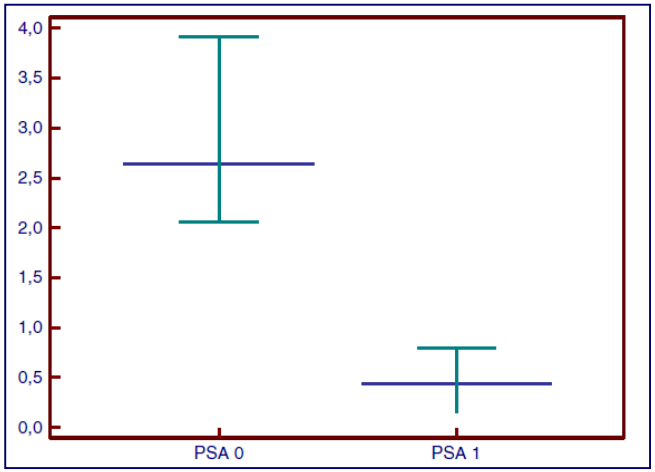
11C-Choline PET/CT is a valuable tool for planning and monitoring HTT in LN relapse after primary treatment.

Well tolerated and associated with a high early biochemical response rate

Picchio et al. EJNMMI, 2014

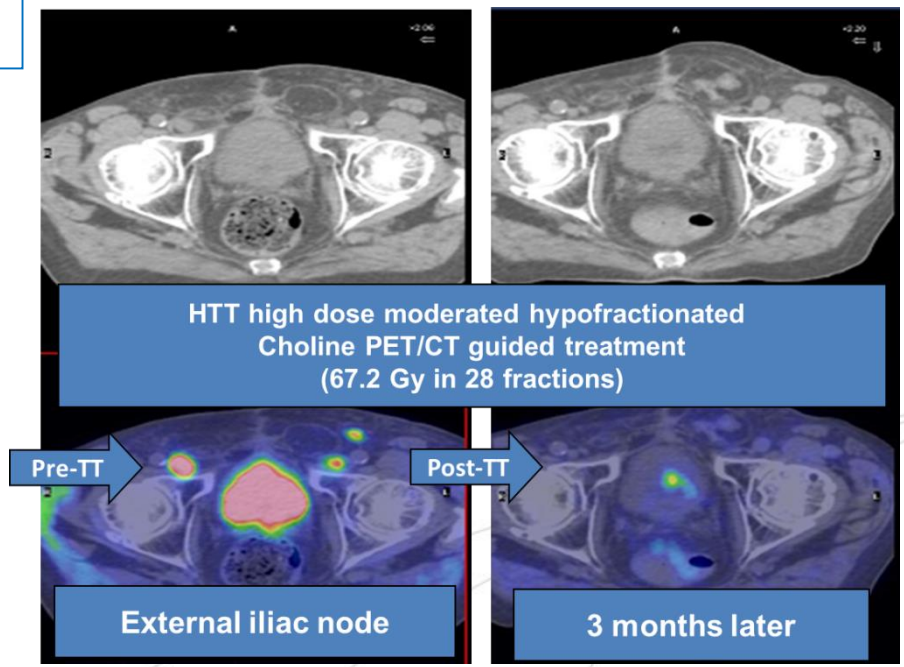
PET/CT to monitor Treatment

Table 3 Biochemical response results (PSA_1 vs. PSA_0)	
Biochemical response	No. (%) of 94 treatments
Complete response	66 (70.2)
Partial response	12 (12.8)
Stable disease	1 (1.0)
Progression of disease	15 (16.0)



PSA_0 and PSA_1 ($p<0.0001$)

83 prostatectomized Pca pts
PSA: 7.6 ng/ml
HTT with SIB of Choline positive LNs



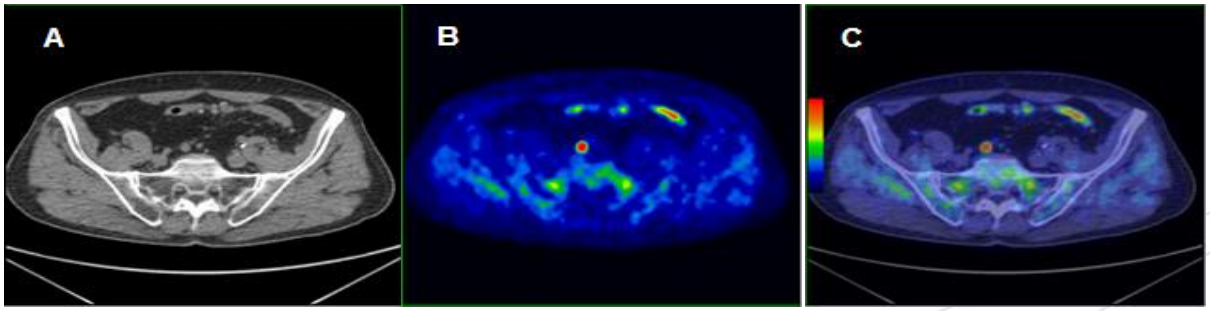
Picchio et al. EJNMMI, 2014

Radiation Treatment of Lymph Node Recurrence from Prostate Cancer: Is ^{11}C-Choline PET/CT Predictive of Survival Outcomes?

Elena Incerti[1], Andrei Fodor[2], Paola Mapelli[1], Claudio Fiorino[3], Pierpaolo Alongi[1], Margarita Kirienko[4], Giampiero Giovacchini[5], Elena Busnardo[1], Luigi Gianolli[1], Nadia Di Muzio[2], and Maria Picchio[1]

Choline-PET/CT-guided HTT - 68 PCa pts with biochemical recurrence after primary treatment (median PSA: 2.42 ng/ml)

MTV60>0.64 and extra-pelvic disease are independently correlated with cRFS (MTV60> 0.64: HR= 4.1, *p*: 0.010 and extra-pelvic disease: HR= 7.3, *p*: 0.0005)

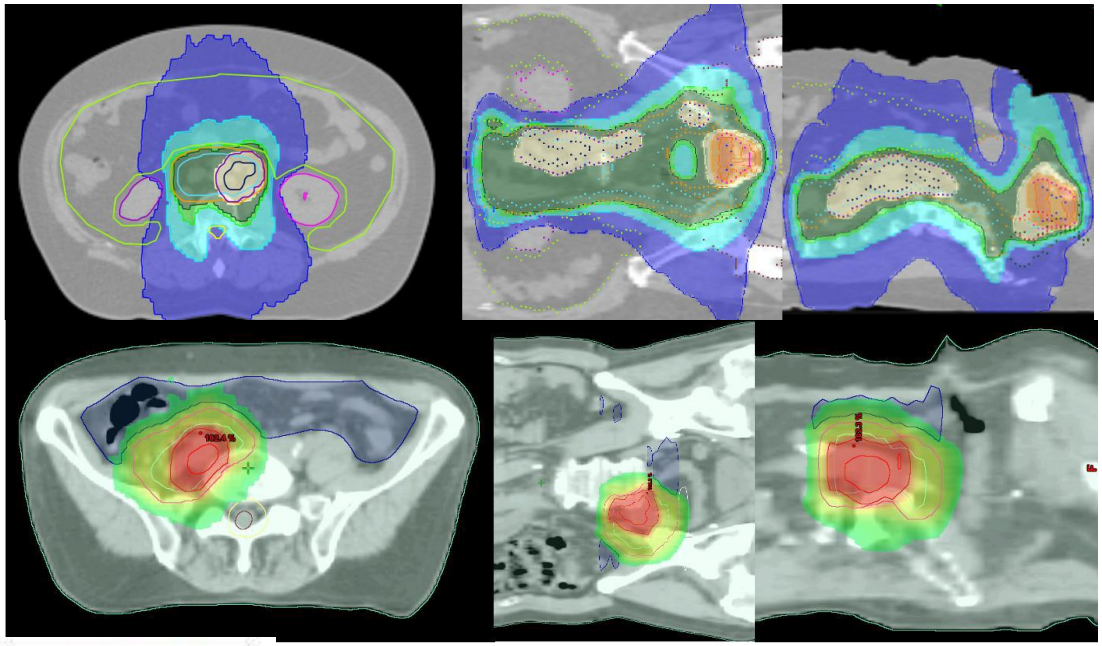


JNM, 2015 – Alavi-Mandell Award 2016

Choline PET/CT for RT of Recurrence PCa

81 recurrence patients after surgery±RT.

The 3 year overall, local-relapse-free and clinical-relapse-free survival were 80.0%, 89.8% and 61.8%, respectively.



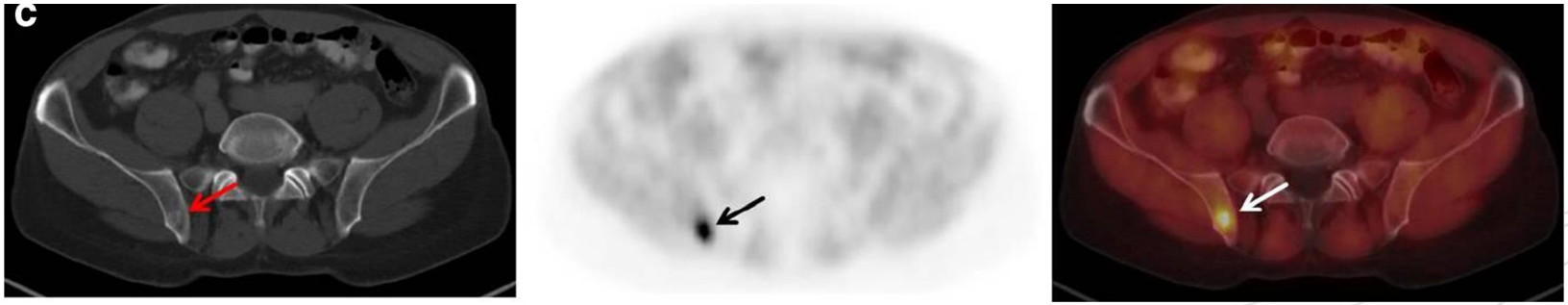
Toxicity	Small bowel	Rectal	Genito-urinary
G1	31.7% (25/79)	22.8% (18/79)	6.4% (5/79)
G2	2.5% (2/79)	3.8% (3/79)	3.8% (3/79)
G3	0	0	2.5% (2/79)

11C-Ch-PET/CT-guided HTT is safe and effective in the treatment of LN relapses of previously treated prostate cancer patients.

Fodor et al, BJU International, 2016

Choline PET – Bone Recurrence

	Sensitivity	Specificity
Fuccio et al. Ann Nucl med 2010	86%	100%
Picchio et al. EJNMMI 2012	89%	98%
Langsteger et al. QJNMMI 2011	90%	96%



Ceci et al, Eur J Nucl Med Mol Imaging, 2014

SBRT to oligometastatic bone metastasis

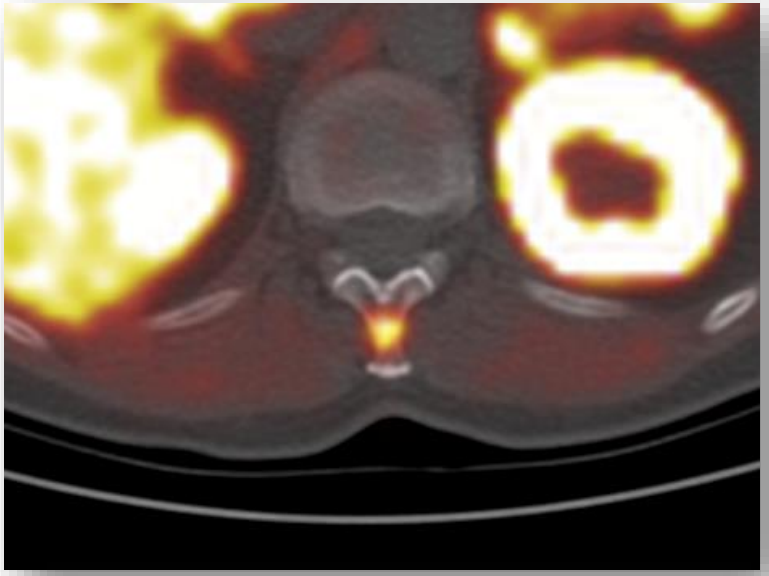
Methods

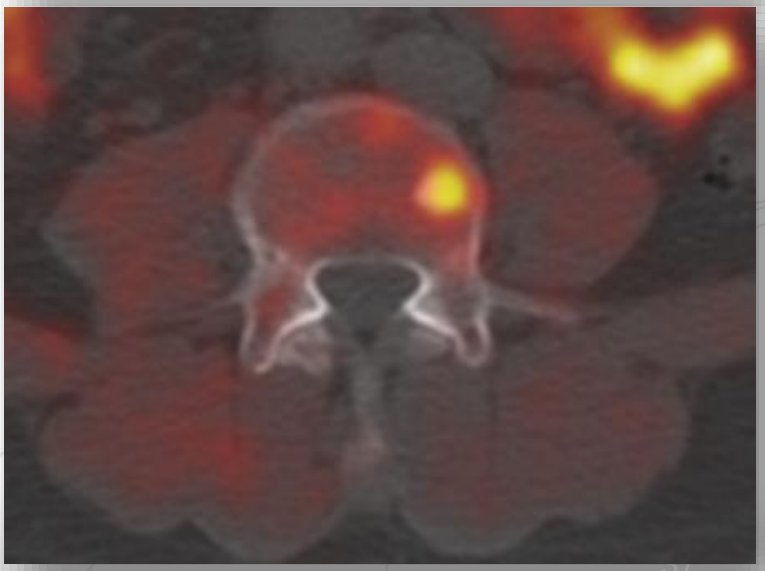
- 40 patients, 64 lesions
- SBRT 1x20Gy to PET lesion
- Follow-up 14 months

Results

- Local control 95%
- PSA reduction average 50%

Muacevic A et al., Urol Oncol., 2011





[^{11}C]Choline PET/CT Impacts Treatment Decision Making in Patients With Prostate Cancer Referred for Radiotherapy

Barbara Alicja Jereczek-Fossa,[1,6] Marcello Rodari,[4] Maria Bonora,[1,6] Paola Fanti,[1,6] Cristiana Fodor,[1] Giovanna Pepe,[4] Egesta Lopci,[4] Dario Zerini,[1] Barbara Vischioni,[3] Guido Baroni,[3,5] Deliu Victor Matei,[2] Ottavio De Cobelli,[2,6] Arturo Chiti,[4] Roberto Orecchia[1,3,6]

74 Pca pts referred for first radiotherapy (primary or recurrent tumor)

Cho-PET/CT changed the treatment approach in 27% of cases compared with standard treatment that would have been adopted without cho-PET/CT.

Cho-PET/CT is valuable in defining the extent of disease and supporting therapeutic decisions in the management of prostate cancer.

Clinical Genitourinary Cancer, Vol. 12, No. 3, 155-9 © 2014

Prostate cancer
Choline PET- Radiation therapy
Conclusions

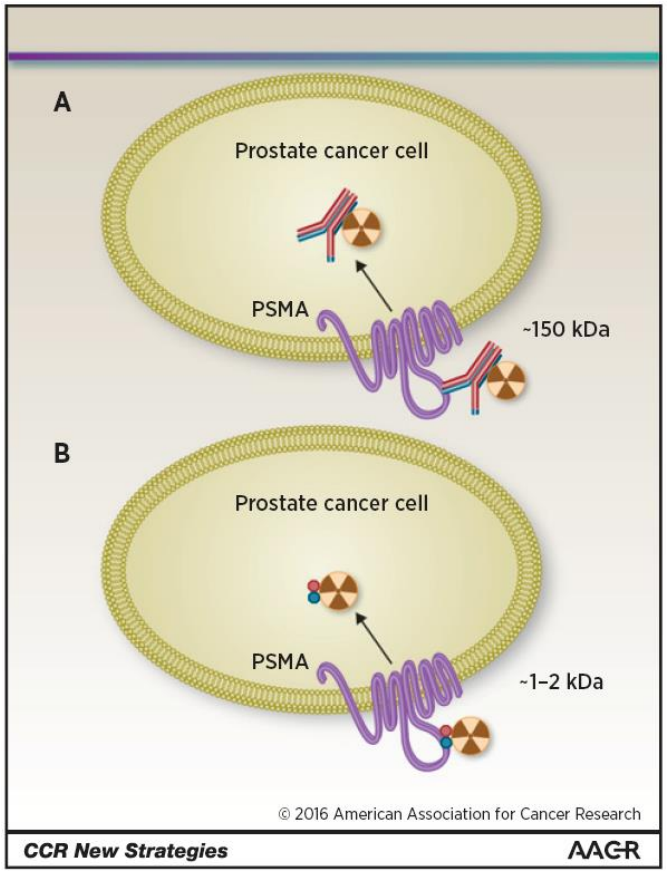
Primary Treatment:

- Limited role→ possible improvement with PET/MRI

Treatment of Relapse:

- Accurate for N and M → Role in guiding and monitoring MDT
- Predictive role

Prostate-Specific Membrane Antigen (PSMA)



- PSMA, also known as **Glutamate carboxypeptidase II**, is a type II transmembrane glycoprotein (Upon ligand binding PSMA is internalized with bound molecules)
- PSMA is expressed in a number of tissues including prostate, kidney, and both the central and peripheral nervous systems.
- PSMA is an established cancer marker. In particular, it is upregulated in prostate cancer and has proven to be an effective diagnostic and prognostic indicator of cancer.
- Ideal for developing targeted radiopharmaceuticals (fast blood clearance and low background activity)

PSMA PET/CT guidelines

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3670-z

GUIDELINES

^{68}Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0

Wolfgang P. Fendler[1,2] · Matthias Eiber[1,3] · Mohsen Beheshti[4] · Jamshed Bomanji[5] · Francesco Ceci[6] · Steven Cho[7] · Frederik Giesel[8] · Uwe Haberkorn[8] · Thomas A. Hope[9] · Klaus Kopka[10] · Bernd J. Krause[11] · Felix M. Mottaghy[12,13] · Heiko Schöder[14] · John Sunderland[15] · Simon Wan[5] · Hans-Jürgen Wester[16] · Stefano Fanti[6] · Ken Herrmann[1,17]

68Ga PSMA-HBED-CC
Normal biodistribution

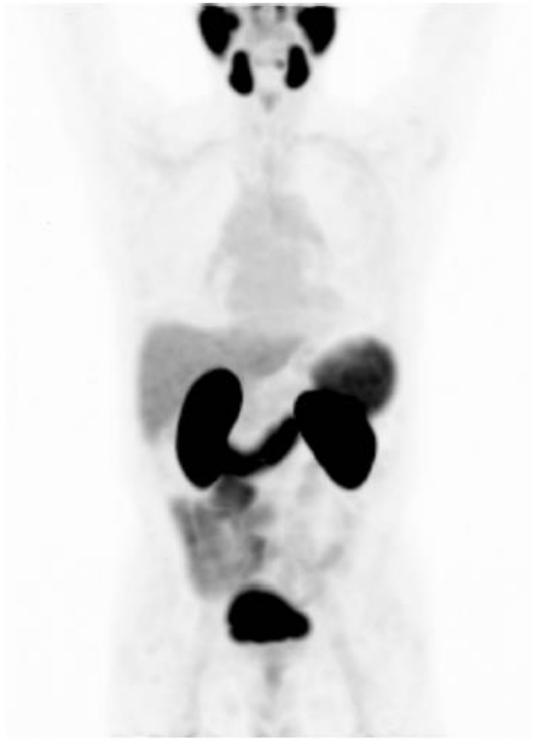


Fig. 2 Normal body distribution of ^{68}Ga-PSMA-11. Maximum intensity projection of a 78-year-old male patient after injection of 217 MBq ^{68}Ga-PSMA-11

- Parotis and salivary glands
- Spleen
- Liver
- Kidneys
- Duodenum
- Bladder

Fendler et al. EJNMMI 2017

PSMA PET/CT - Indications

- Localisation of tumor tissue in recurrent Pca

- Primary staging in high-risk disease before surgical procedures or planning external beam radiation

Fendler et al. EJNMMI 2017

PSMA PET/CT - Indications

- **Localisation of tumor tissue in recurrent Pca**

- Primary staging in high-risk disease before surgical procedures or planning external beam radiation

Fendler et al. EJNMMI 2017

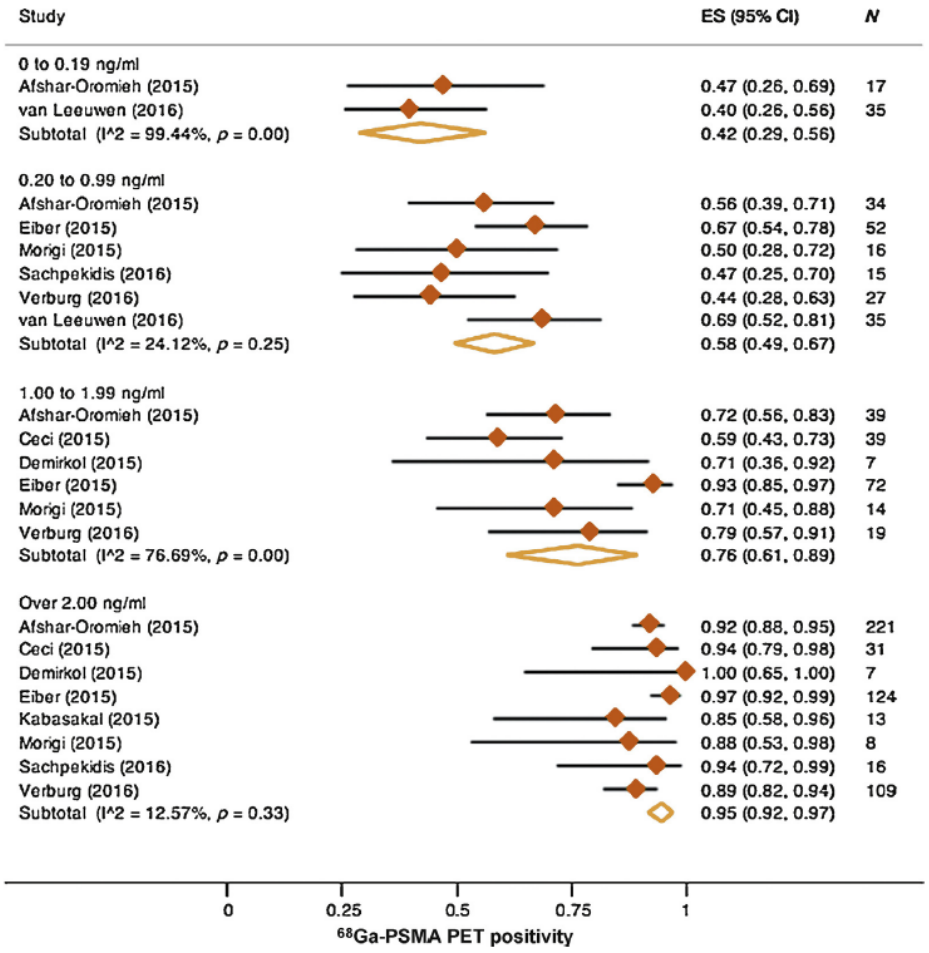
PSMA PET/CT - Indications

Localization of tumour tissue in recurrent prostate cancer

Most studies, mainly retrospective data, are available on the use of ^{68}Ga-PSMA PET/CT for localization of prostate cancer in the setting of biochemical recurrence [8, 9, 15–21]. Here, the use is especially recommended in patients with low PSA values between 0.2 and 10 ng/mL to identify the site of recurrence and to potentially guide salvage therapy. Higher sensitivities are noted in patients with shorter PSA doubling times and those with higher initial Gleason scores [21].

Fendler et al. EJNMMI 2017

PSMA – ReStaging Prostate Cancer

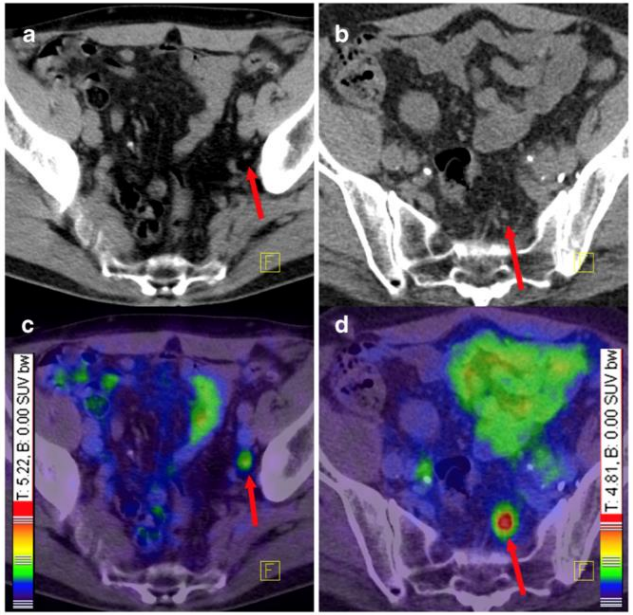


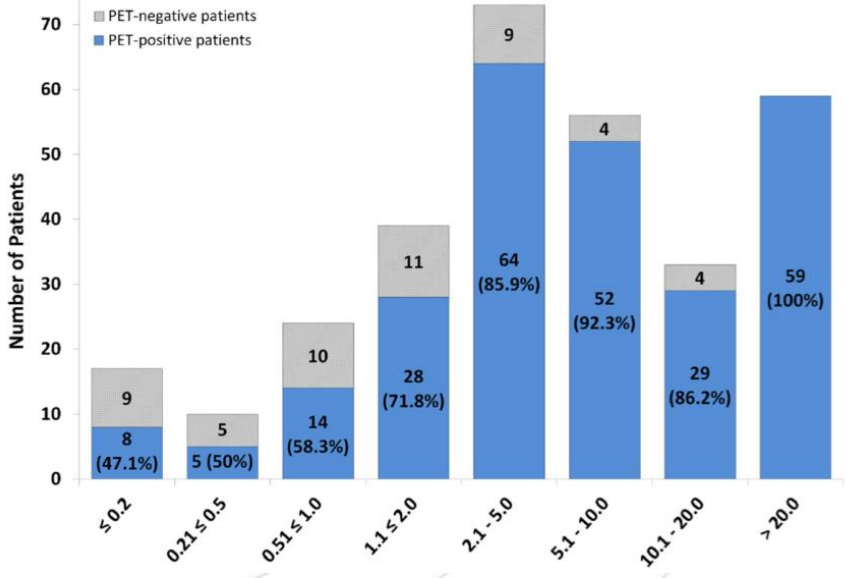
12 studies
736 pts in BCR
DR: 76%

Perera et al. Eur Urol 2016

The diagnostic value of PET/CT imaging with the ^{68}Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer

- ✓ Retrospective analysis in **319 patients** who underwent 68Ga-PSMA-ligand PET/CT from 2011 to 2014 for recurrent PCa (90% of the cases after treatment with curative intent)
- ✓ In 82.8% of the patients at least one lesion indicative of PCa was detected





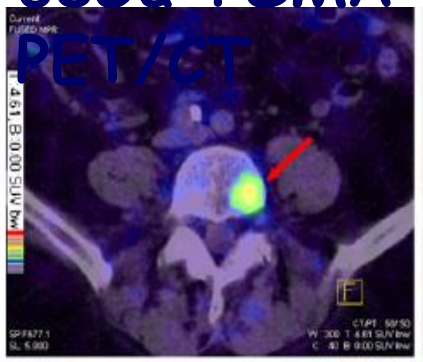
ESNM European School of Nuclear Medicine

ESTRO School

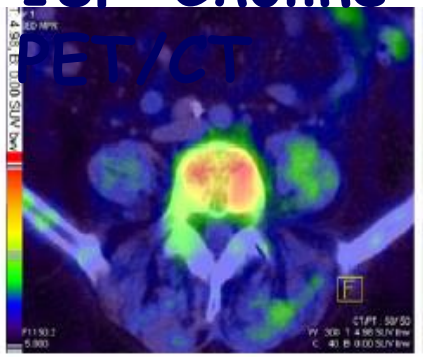
Afshar-Oromieh et al. Eur J Nucl Mol Imaging, 2015

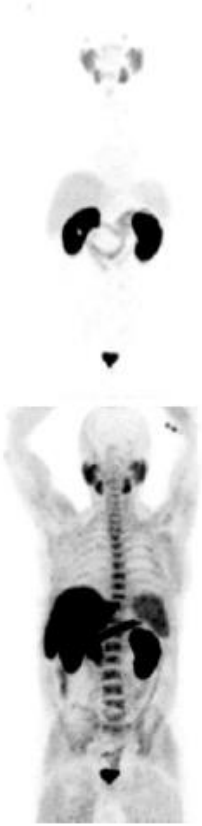
Comparison of PET imaging with a ^{68}Ga-labelled PSMA ligand and ^{18}F-choline-based PET/CT for the diagnosis of recurrent prostate cancer

68Ga-PSMA PET/CT



18F-Choline PET/CT

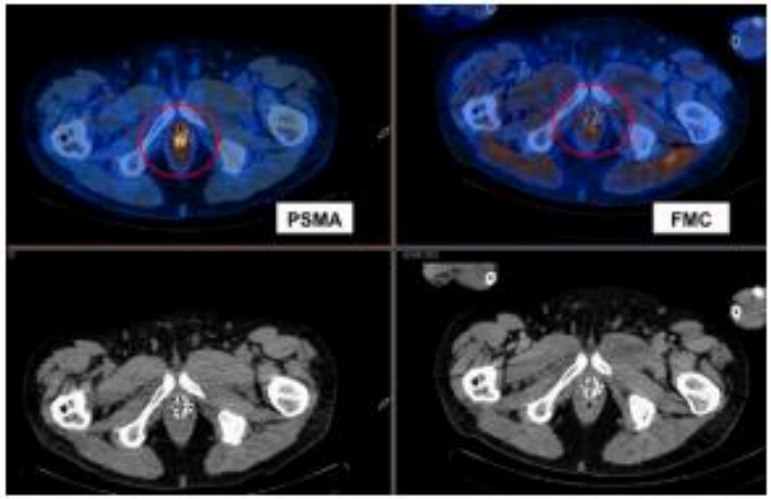




- 37 patients with biochemical relapse of Pca were retrospectively analysed
- 18F-fluoromethylcholine and 68Ga-PSMA PET/CT within a time window of 30 days
- 68Ga-PSMA PET/CT **improved contrast when compared to choline-based PET/CT**

Afshar-Oromieh et al. Eur J Nucl Mol Imaging, 2014

Prospective Comparison of ^{18}F-Fluoromethylcholine Versus ^{68}Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy



38 pts with biochemically recurrent PCa

PSMA detected more lesions

than FCH (59 and 29)

Morigi et al. JNM, 2015

	PSMA PET/CT DR	Choline PET/CT DR
PSA ≤ 0.5 ng/ml	50%	12.5%
PSA 0.5-2.0 ng/ml	69%	31%
PSA > 2.0 ng/ml	86%	57%

PSMA PET/CT - Indications

- Localisation of tumor tissue in recurrent Pca

- **Primary staging in high-risk disease before surgical procedures or planning external beam radiation**

Fendler et al. EJNMMI 2017

Primary staging in high-risk disease before surgical procedures or planning external beam radiation

In patients with high-risk disease (Gleason score >7, PSA >20 ng/mL, clinical stage T2c – 3a) the likelihood of lymph node and bone metastases is increased. Several studies demonstrate the superiority of ^{68}Ga-PSMA PET/CT as compared to CT, magnetic resonance imaging (MRI) or bone scan for detection of metastases for initial staging at primary diagnosis [22–25]. The detection of radiologically occult lymph node metastases can significantly influence patient management, although the impact on overall survival of improved sensitivity by ^{68}Ga-PSMA PET/CT remains unanswered. A contrast-enhanced ^{68}Ga-PSMA PET/CT can replace abdomino-pelvic CT for the detection of lymph node metastases. In addition, preliminary data show that ^{68}Ga-PSMA PET/CT is also more accurate for detection of bone metastases [25]. Nevertheless, for local tumour delineation (if requested by the urological surgeon), pelvic MRI cannot be replaced. It is still under investigation and discussion whether additional functional imaging with bone0seeking agents (e.g. bone scintigraphy, ^{18}F-NaF PET/CT) has relevant additional value after performance of ^{68}Ga-PSMA PET/CT, e.g. in patients with PSMA-negative tumours or densely sclerotic bone lesions.

Fendler et al. EJNMMI 2017

ESTRO School

PSMA – Primary Prostate Cancer

	AUC (95% CI)	Youden-selected threshold	Sensitivity, %, at threshold (95% CI)	Specificity, %, at threshold (95% CI)
mpMRI	0.73[*,†] (0.66–0.80)	4[§]	43 (33–53)	98 (94–100)
		3	58 (49–66)	82 (69–90)
PET	0.83[*,#] (0.78–0.87)	4	64 (56–72)	94 (86–98)
PET/MRI	0.88[#,†] (0.84–0.92)	4	76 (68–82)	97 (90–99)

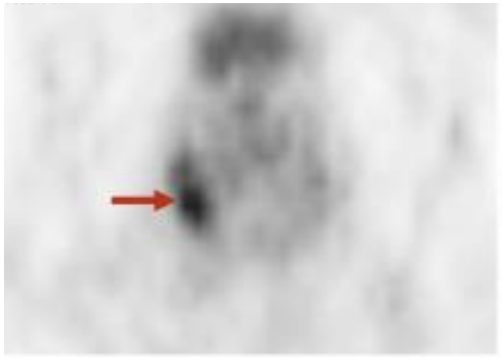
AUC = area under the curve; CI, confidence interval; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PET = positron emission tomography.

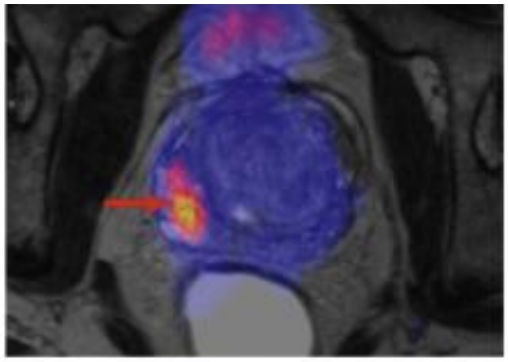
[*] mpMRI versus PET, $p = 0.003$.

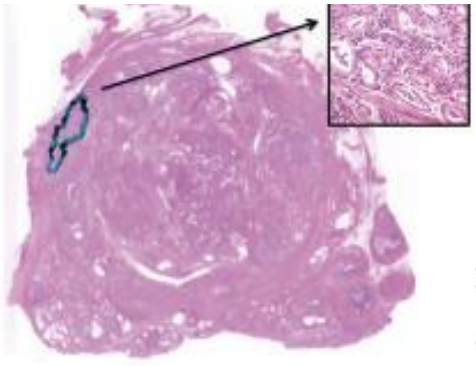
[†] mpMRI versus PET/MRI, $p < 0.001$.

[§] The threshold of 4 for mpMRI is presented to show data with the same threshold for all imaging methods; the threshold of 3 is the calculated optimal cut-off as described in the Material and methods section.

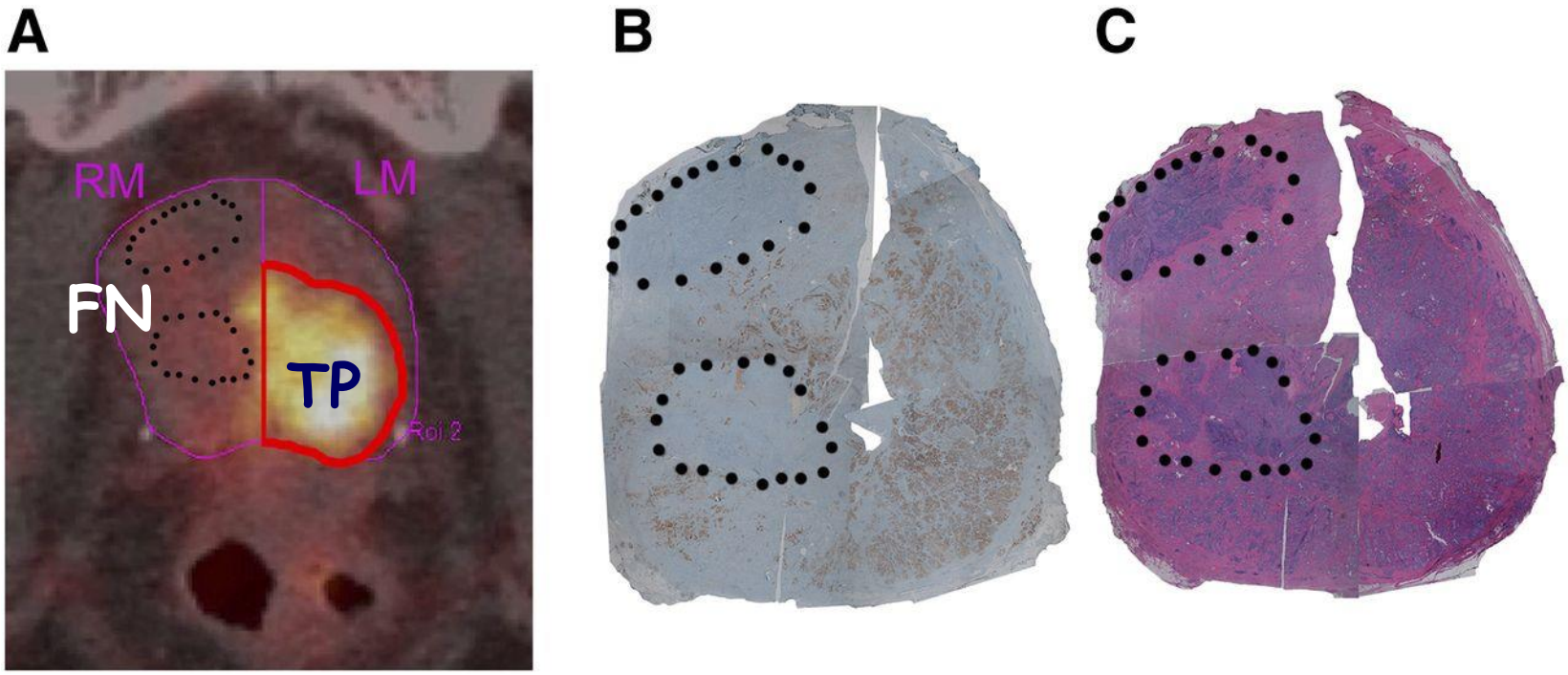
[#] PET versus PET/MRI, $p = 0.002$.







Eiber et al. Eur Urol 2016



False-negative PET finding for acinar adenocarcinoma with partial neuroendocrine differentiation. 68Ga-PSMA PET/CT image (A), PSMA-stained slice (B), and hematoxylin-stained slice (C) for left mid (LM) and right mid (RM) segments are shown. Wolfgang P. Fendler et al. J Nucl Med 2016;57:1720-1725

PSMA – Primary Prostate Cancer

Accuracy of ^{68}Ga-PSMA PET for Detection of Tumor Tissue per Segment

PET result	HP+ (n = 100)	HP− (n = 26)	Accuracy
PET+ (n = 69)	67	2	Positive predictive value, 97%
PET− (n = 57)	33	24	Negative predictive value, 42%
	Sensitivity, 67%	Specificity, 92%	Accuracy, 72%

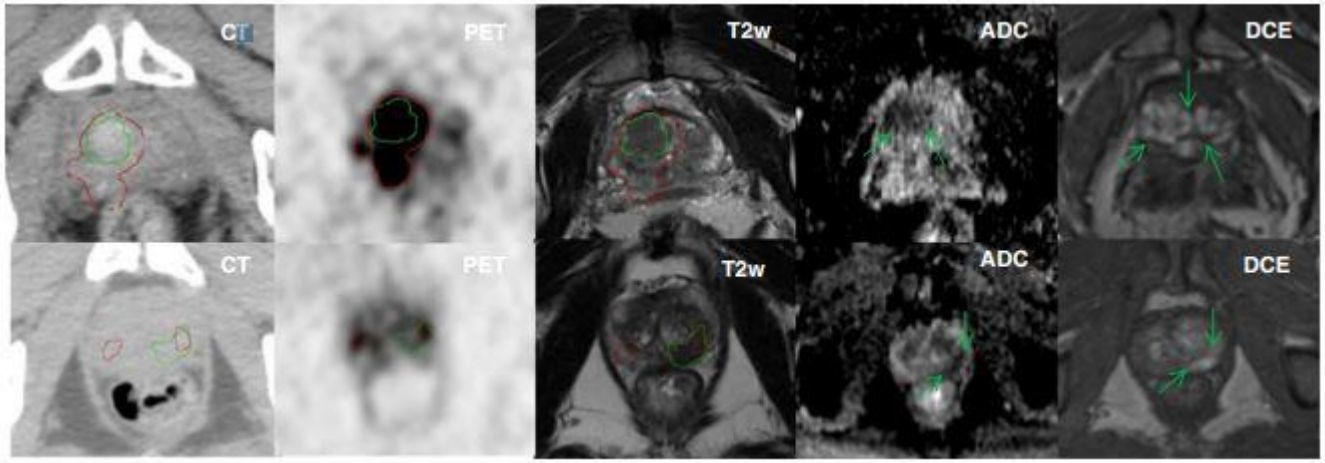
HP = histopathology.
Six segments from 21 patients were analyzed.

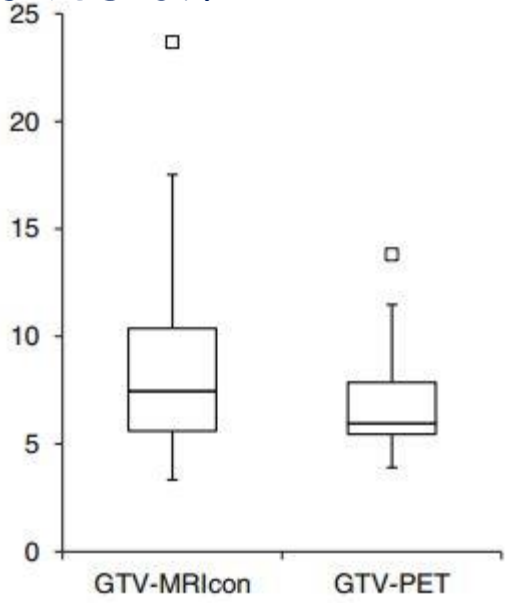
Fendler et al. EJNMMI 2017

PSMA PET and MR – RT primary PCa

22 patients with primary Pca - 68Ga-PSMA PET/CT and mpMRI

GTV-PET was significantly larger than GTV-MRI. 68Ga-PSMA PET/CT may have a role in radiation treatment planning for focal radiation to the dominant intraprostatic lesion





Zamboglou et al. Eur J Nucl Mol Imaging, 2016

PSMA – Staging Prostate Cancer

Table 6 – Guidelines for staging of prostate cancer

Risk group	LE	GR
Any risk group staging		
Do not use CT and TRUS for local staging	2a	A
Low-risk localised PCa		
Do not use additional imaging for staging purposes	2a	A
Intermediate-risk PCa		
Use prostate mpMRI for local staging	2b	A
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan	2a	A

CT = computed tomography; GR = grade of recommendation; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PCa = prostate cancer; TRUS = transrectal ultrasound.

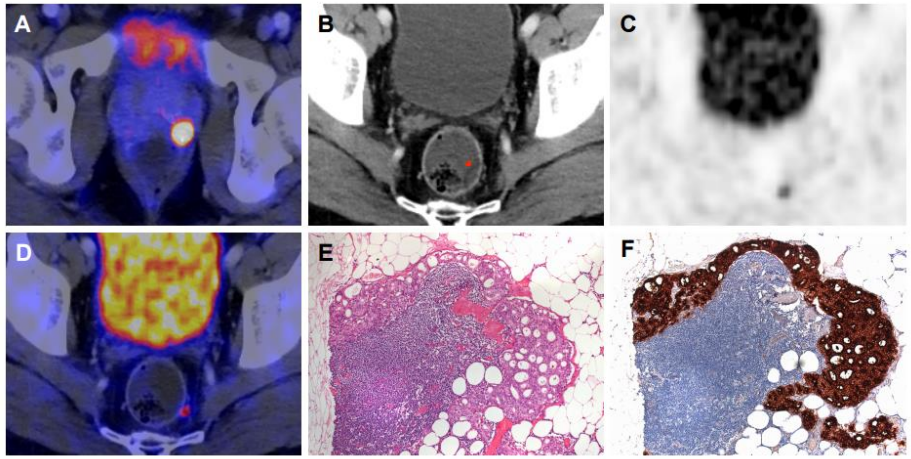
Therefore, choline PET/CT has no place for up-front staging in nodal metastasis. Currently, prostate-specific membrane antigen-PET CT (PSMA PET/CT) remains investigational.

Magnetic resonance imaging sensitivity is low for lymph node metastases and similar [245, 246] or inferior [247] to that of choline PET/CT.

Mottet et al Eur Urol 2017

PSMA PET – Pre-operative LN staging

	Number of patients	Sensitivity	Specificity
Budaus et al	*30 (ePLND)*	*33%*	*100%*
Maurer et al	*130 (ePLND)*	*66%*	*99%*



Budaus L, Eur Urol, 2016
Maurer et al, J Urol, 2016

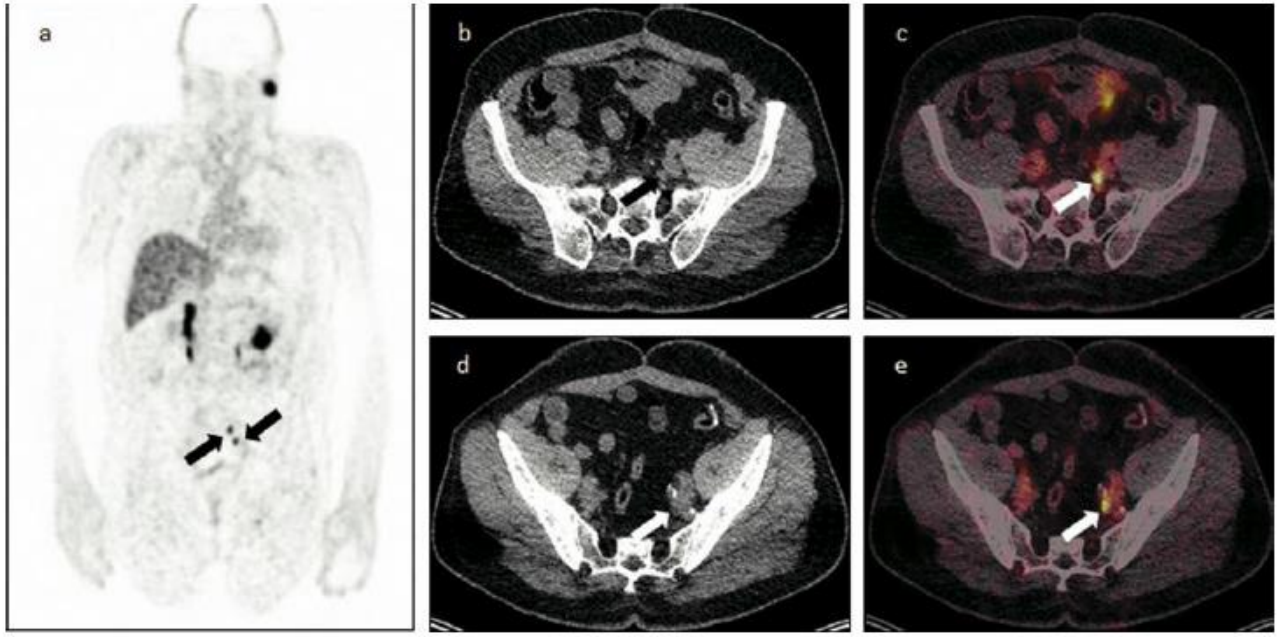
PSMA PET/CT – Emerging Indications

- Staging before and during PSMA-directed radiotherapy (mainly in metastatic castration-resistant prostate cancer)
- Targeted biopsy after previous negative biopsy in patients with high suspicion of prostate cancer
- Monitoring of systemic treatment in metastatic prostate cancer

ANTICANCER RESEARCH *37*: 1273-1280 (2017)
doi:10.21873/anticanres.11444

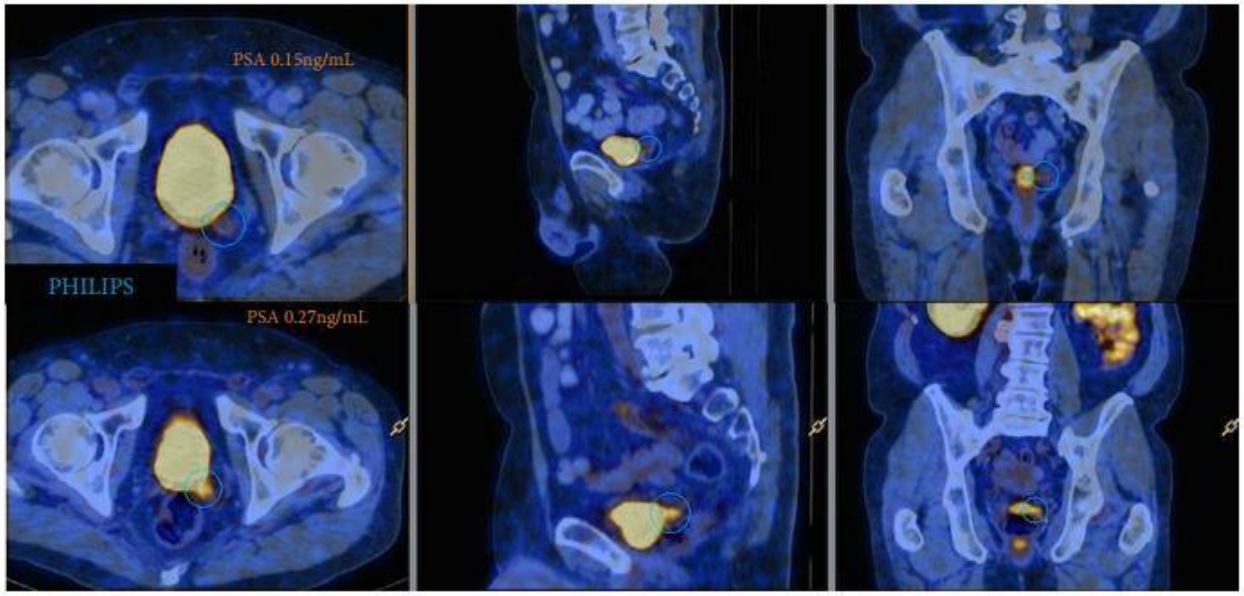
^{68}Ga-PSMA Ligand PET/CT-based Radiotherapy for Lymph Node Relapse of Prostate Cancer After Primary Therapy Delays Initiation of Systemic Therapy

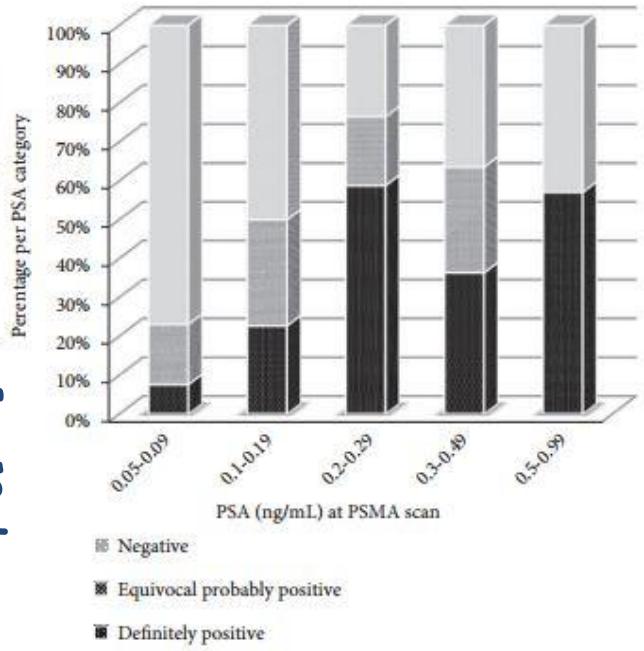
CHRISTOPH HENKENBERENS[1], CHRISTOPH A. VON KLOT[2], TOBIAS L. ROSS[3], FRANK M. BENGEL[3], HANS-JÜRGEN WESTER[4], KATJA HÜPER[5], HANS CHRISTIANSEN[1] and THORSTEN DERLIN[3]



PSMA PET– RT recurrent PCa

300 patients with with biochemical recurrence underwent 68Ga-PSMA-PET/CT, PSA level ≥0.05 and <1.0 ng/mL





68Ga-PSMA appears to be useful for re-staging PCa pts with rising PSA levels who are being considered for salvage RT even at PSA levels <0.5 ng/mL

van Leeuwen et al. BJU international, 2016

PSMA PET– RT PCa

54 Pca referred to PSMA-PET imaging

Table 2 Effect of PSMA PET on disease status outcomes and radiation oncologist decision-making

PSMA vs Conventional scans	PSMA-/CS-	17 (31.5 %)
	PSMA+/CS-	25 (46.3 %)
	PSMA-/CS+	7 (13.0 %)
	PSMA+/CS+	5 (9.3 %)
Change in RT management	No	29 (53.7 %)
	Yes	25 (46.3 %)
Change in ADT management	No	36 (66.7 %)
	Yes	18 (33.3 %)
Any change in management	No	25 (46.3 %)
	Yes	29 (53.7 %)

CS = conventional scans (CT, bone scan, MRI)
- = Negative
+ = Equivocal
RT = radiotherapy
ADT = androgen deprivation therapy

Table 3 Treatment plan before and after PSMA PET

Treatment plan	Pre-PET (%)	Post-PET (%)
Observe	50.0	18.5
Radical radiotherapy (to prostate or prostate bed)	31.5	27.8
Radical radiotherapy including nodes	1.9	0
Palliative radiotherapy to oligometastases	9.3	37.0
Systemic therapy alone	7.4	16.7

PSMA PET changed RT management in 46% of cases with an overall change in decision-making in 54% of pts.

Shakespeare TP. Radiat Oncol., 2015

Prostate Cancer
PSMA PET-Conclusions

- Promising role for staging and re-staging of PCa patients even with low PSA level
- Potential role to guide RT (primary and recurrent disease)
- Potential role for decision-making of radiation oncologists
- PET/MRI as new promising imaging tool

ESNM/ESTRO COURSE
MOLECULAR IMAGING & RADIATION ONCOLOGY
10-13 APRIL BORDEAUX

Magnetic Resonance Imaging: Prostate Cancer

Professor Vicky Goh
Division of Imaging Sciences & Biomedical Engineering, Kings College London
Department of Radiology, Guy's & St Thomas' NHS Trust
London, UK

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KING'S College LONDON

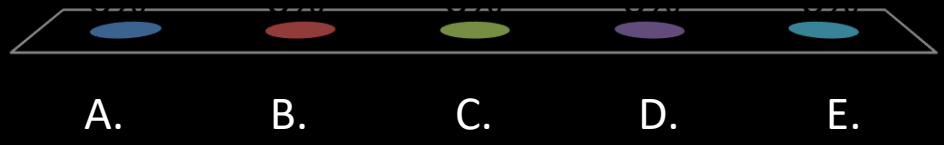
KING'S HEALTH PARTNERS

Learning Objectives

- To understand how MRI is performed and analysed for assessing prostate cancer:
  - Detection
  - Staging
- To appreciate the limitations & challenges of MRI

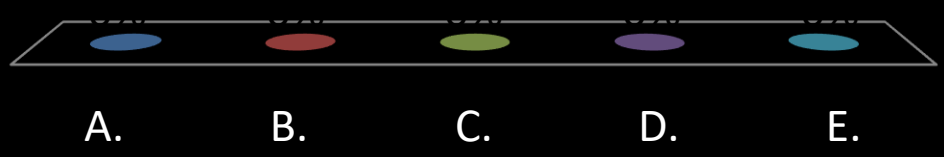
Test: Where are we?

A. Lisbon
B. Bordeaux
C. Barcelona
D. London
E. Paris



With respect to prostate cancer, which of the following is correct?

A. Its is a multifocal disease with multiple dominant lesions
B. All cancer foci are visible on MRI
C. A high risk cancer is a cT2c cancer, PSA >20ng/dl, Gleason 7+
D. A stage T3a cancer is invading the seminal vesicle
E. A PIRADS score of 4 & above is highly suspicious of cancer

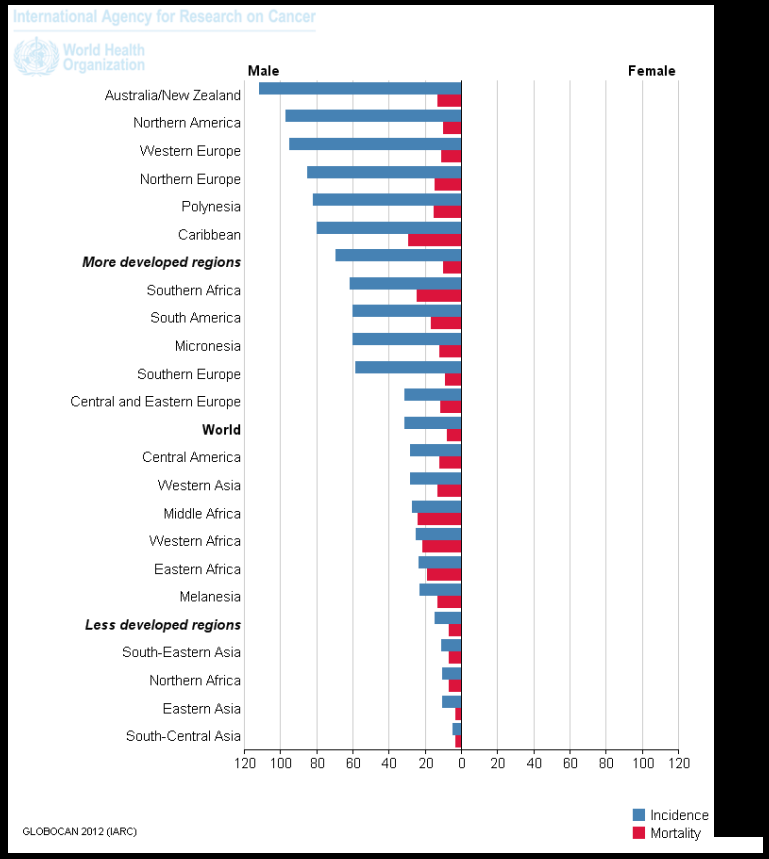


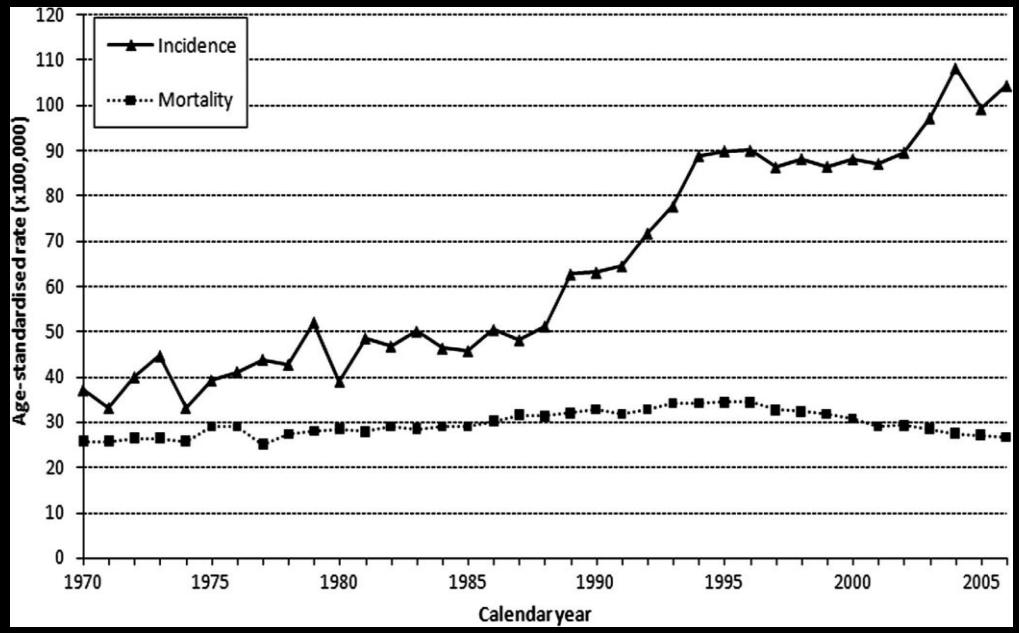
With respect to prostate imaging, which of the following is correct?

A. Ultrasound is the initial modality of choice to diagnose prostate cancer
B. MRI should be performed at 3T
C. Multiparametric MRI (T2-, diffusion & multiphasic contrast enhanced) should be used to diagnose prostate cancer
D. Multiparametric MRI (T2-, diffusion, multiphasic contrast enhanced & spectroscopy) should be used to diagnose prostate cancer
E. Multiparametric MRI is essential for staging

A. B. C. D. E.

Incidence of Prostate Cancer





The Netherlands
Cremers RG et al. Eur J Cancer 2010; 46(11): 2077-87

Source: Globocan 2012

Increasing incidence in Western & Northern Europe

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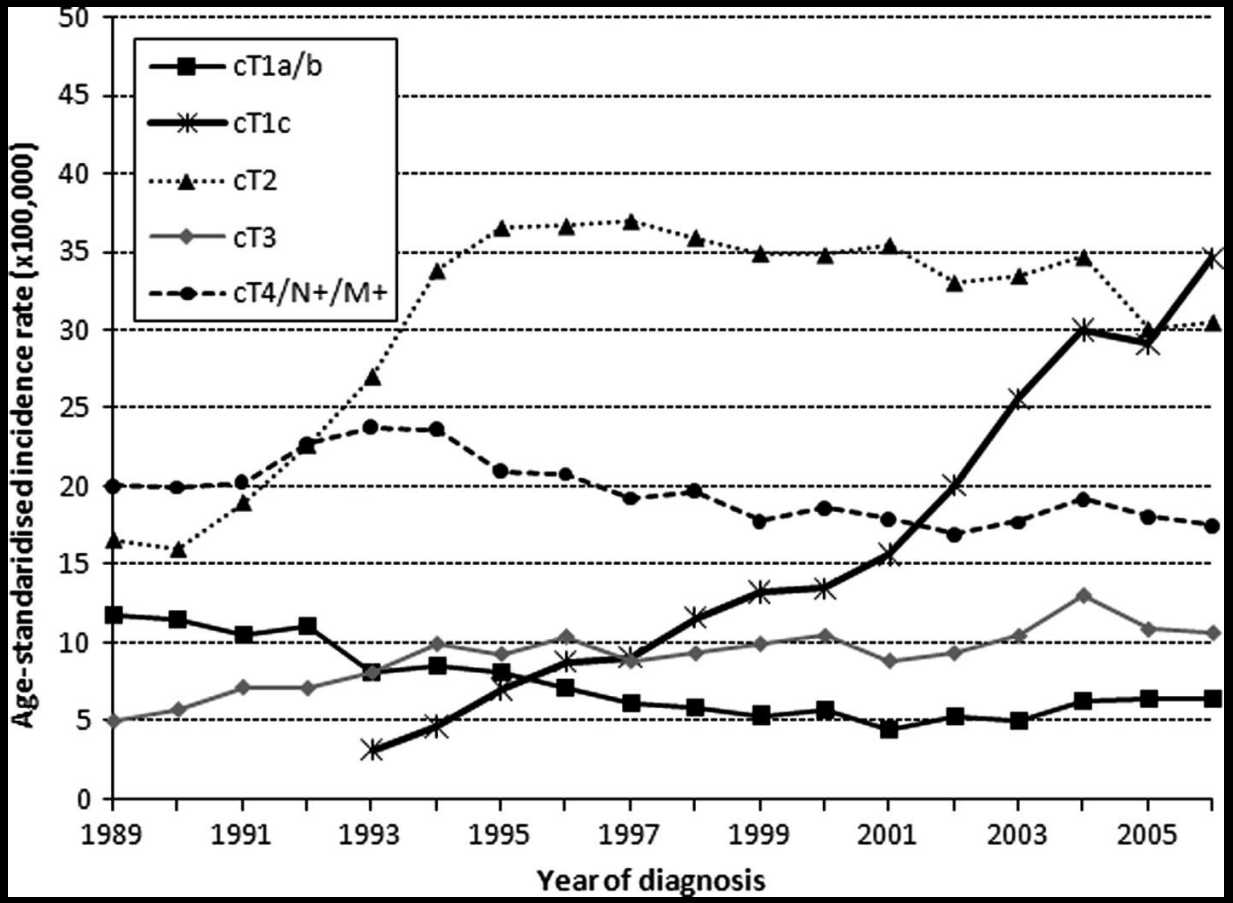
Stage at Initial Diagnosis

The Netherlands



- Downward stage migration
- Increase in cT1c disease
- Introduction of PSA testing

Cremers RG et al. Eur J Cancer 2010; 46(11): 2077-87

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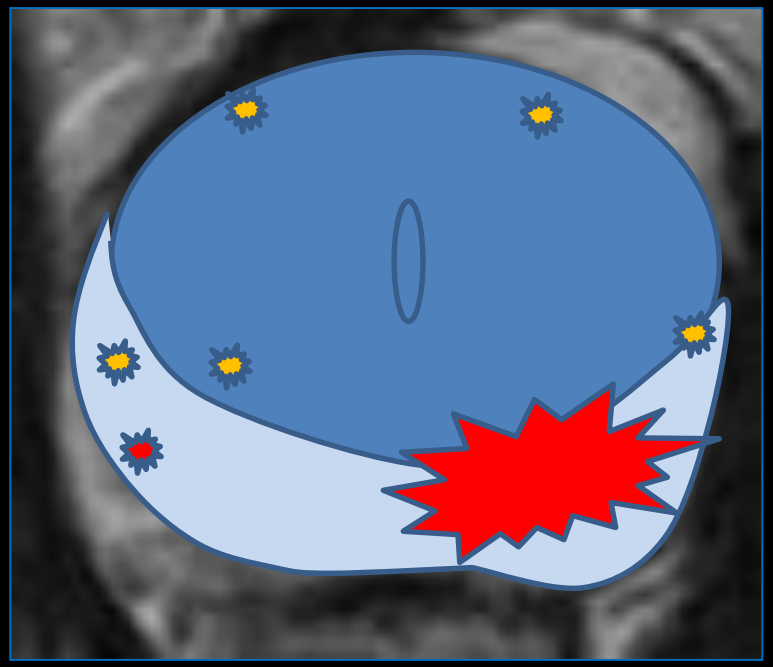
Prostate Cancer: A Multifocal Disease

- 85% of cancers are multifocal
- Index lesion: 90% of total tumor volume
- Other lesions: small (80% <0.5ml; average 0.3ml), similar to cancers found in asymptomatic men



Management of Prostate Cancer

Localised Disease:

Low risk

cStage	T1-2a
& PSA ng/mL	<10
& Gleason	≤6

- Active surveillance
- Offer radical treatment if progression

Intermediate risk

cStage	T2b-c
or PSA ng/mL	10-20
or Gleason	7

- Radical prostatectomy
- Radical radiotherapy
- Active surveillance if patient does not wish to proceed to radical treatment immediately

High risk

cStage	≥T3a
or PSA ng/mL	>20
or Gleason	8-10

- Radical prostatectomy
- Radical radiotherapy ± androgen deprivation therapy ± brachytherapy

Source: NICE UK
Updated Jan 2014

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Challenges for Diagnosis & Characterisation

Serum PSA:

- 15-30% men with prostate cancer have normal PSA
- Abnormal PSA ≠ cancer: 7 of 10 no cancer present

Systematic biopsies:

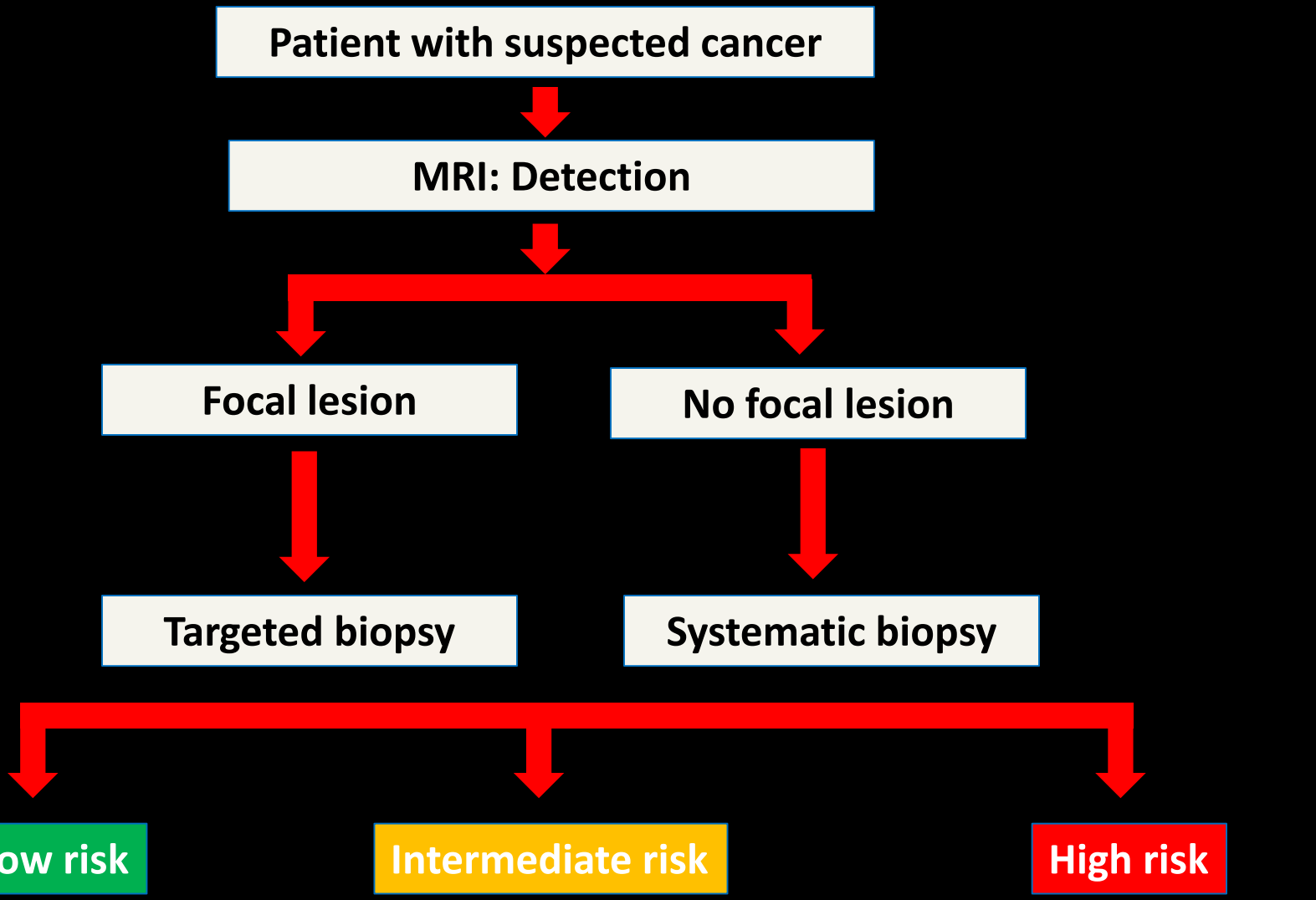
- Miss up to 20-30% of cancers
- Underestimates tumour aggressiveness in >20-30% of cases

Distinguishing aggressive (Rx: Definitive treatment) from indolent tumours (Rx: Surveillance) remains a challenge

The PROMIS study

- 576 men
- MP-MRI followed by TRUS-biopsy (standard practice) & TPM-biopsy (reference standard)
- Clinically significant cancer:
  - MP-MRI versus TRUS-biopsy:
  - Sensitivity: 93% vs 48%
  - Specificity: 41% vs 96%

Ahmed HU et al. PROMIS study group. Lancet 2017;389(10071):815-822
Kapoor J et al. Eur Urol. 2017 Feb 23. pii: S0302-2838(17)30103-3.



Stage	T1-2a
& PSA ng/mL	<10
& Gleason	≤6

Stage	T2b-c
or PSA ng/mL	10-20
or Gleason	7

Stage	≥T3a
or PSA ng/mL	>20
or Gleason	8-10

MRI: Prostate

MRI:

- Assessment of prostate volume
- Presence of focal lesion:
  Yes/No
- Localization for targeted biopsy
- Guidance for biopsy
- Staging & treatment planning

Multi-parametric MRI

MRI	Biological Correlate	Measure
Anatomical T2/T1 MRI	Anatomical structure	Morphology descriptors
Diffusion weighted MRI	Cell density	Signal intensity Apparent Diffusion Coefficient
Dynamic contrast enhanced MRI	Vascularisation	Present/absent Curve type K^{trans}, k_{ep}, V_e
MR Spectroscopy	Cell membrane turnover Replacement of normal glandular tissues	Spectra Choline-Creatine to Citrate ratio

MRI Acquisition

1.5 or 3-Tesla

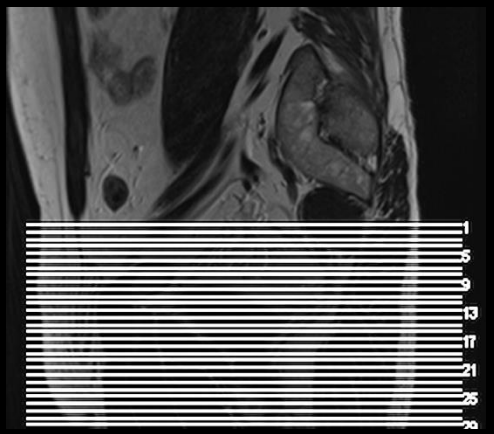
Region	Sequence
Pelvis	T1 TSE axial
	T2 TSE axial
Tumour	T2 TSE sagittal
	T2 TSE coronal*
	T2 TSE axial*
	Diffusion
	Dynamic contrast enhanced

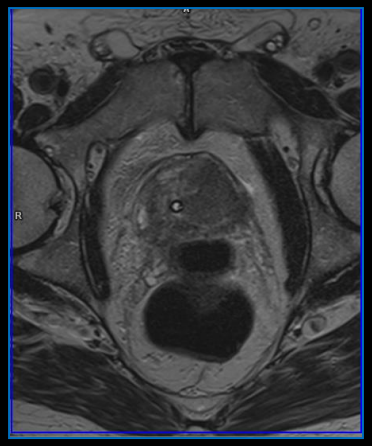
TSE: Turbo spin echo

Patient preparation:

- No prior patient preparation
- Normal renal function: IV contrast administration
- Emptying the bladder prior to MRI & anti-peristaltic (Buscopan IM) may improve imaging by reducing artefact

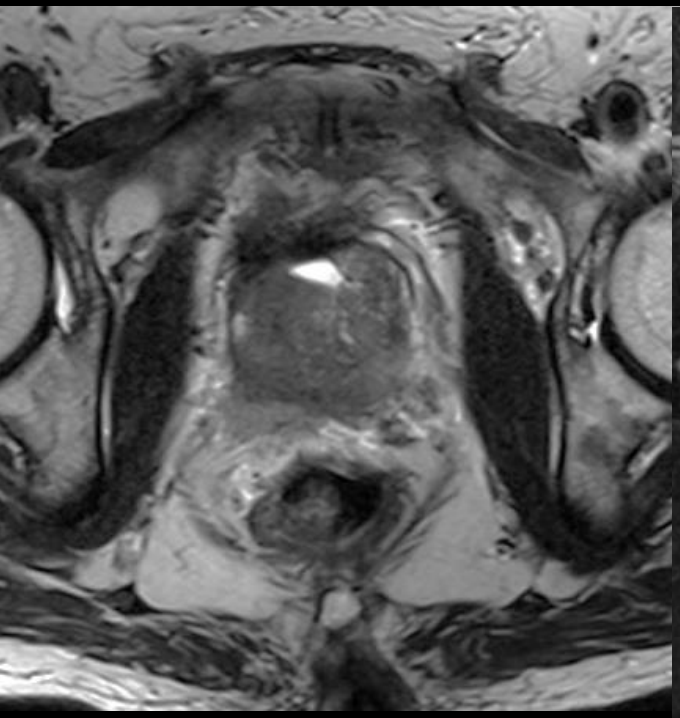
MRI Acquisition



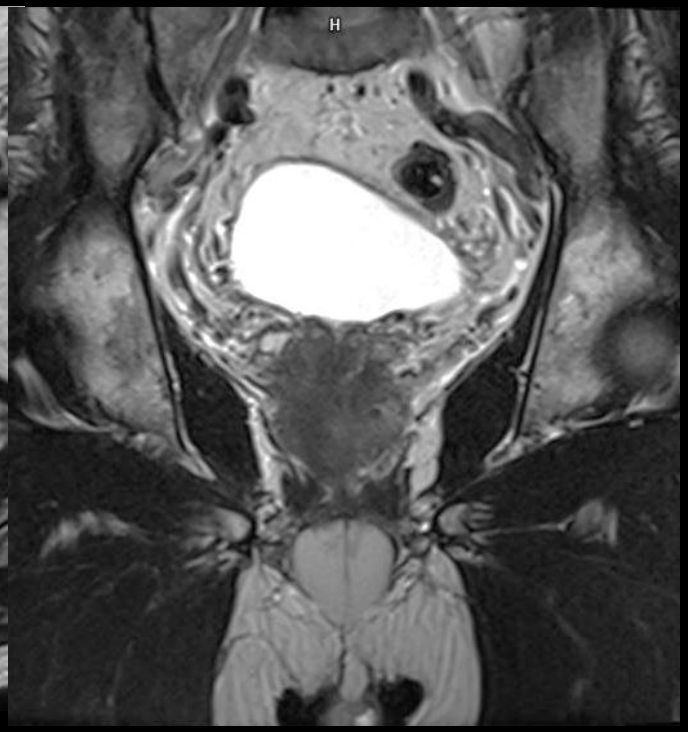


T2: Tumour High resolution TSE	**TR**	7000
	TE	105
	NEX	2
	FOV Matrix	163*200 216*512
	ST	3mm

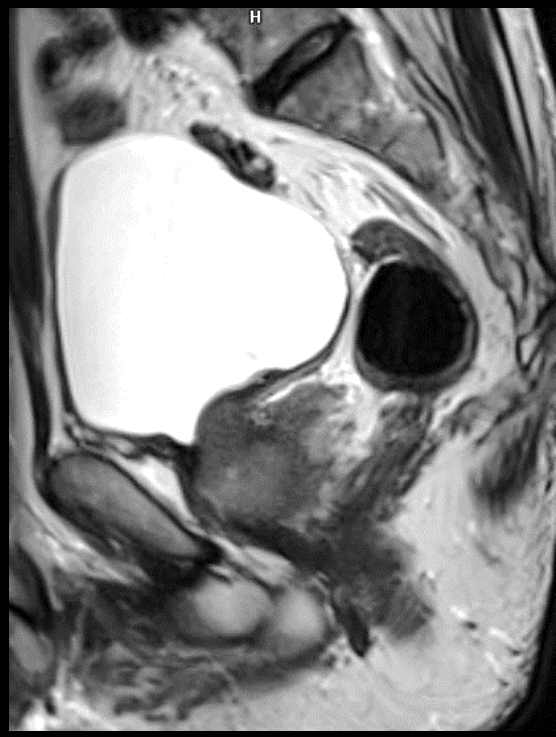
- Phased surface array coils centred for good SNR at prostate level
- Pelvic coverage: Sacral promontary to below symphysis pubis
- Endorectal coil: Not necessary



Axial



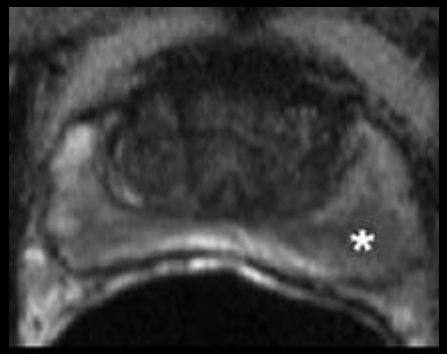
Cor

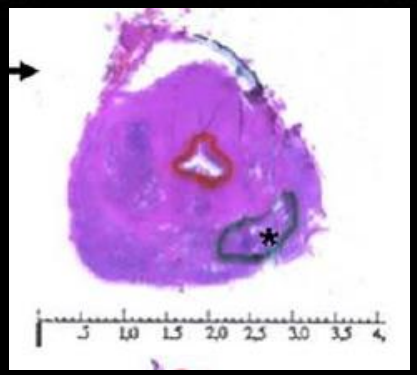


Sagittal

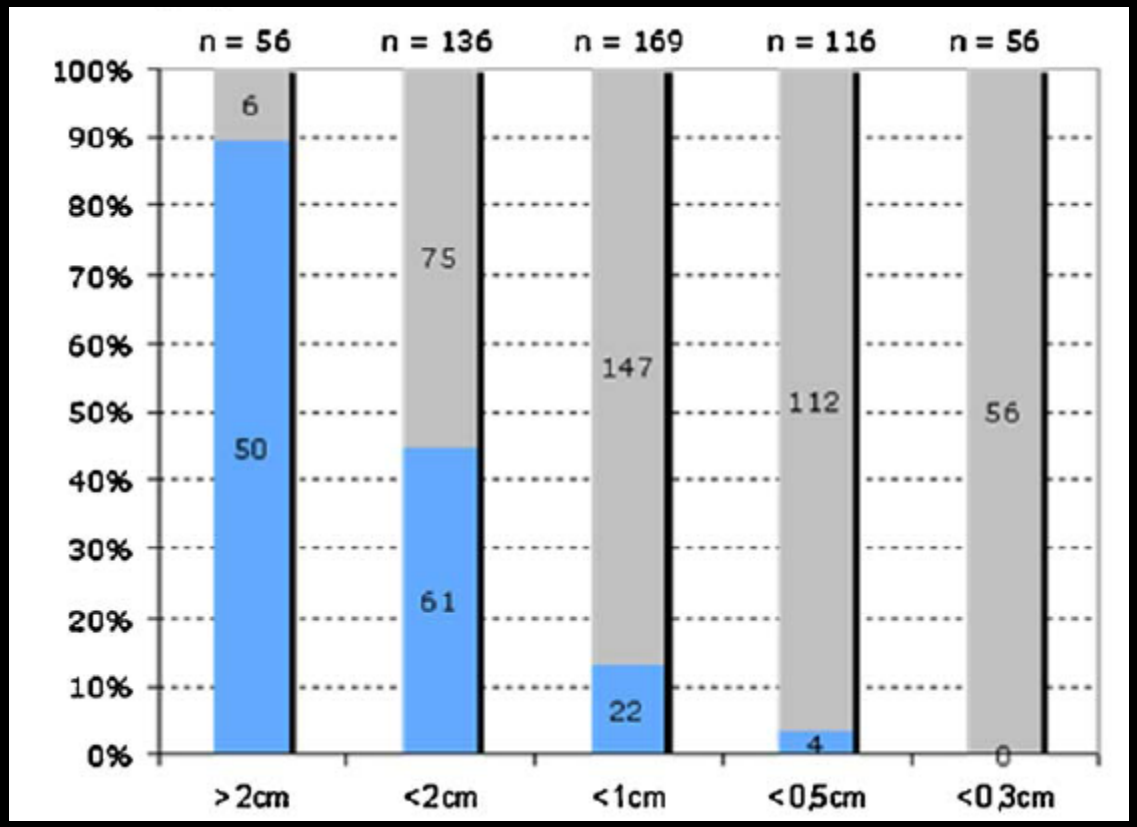
Multiplanar Imaging of the Prostate Gland

Tumour Detection: T2W MRI





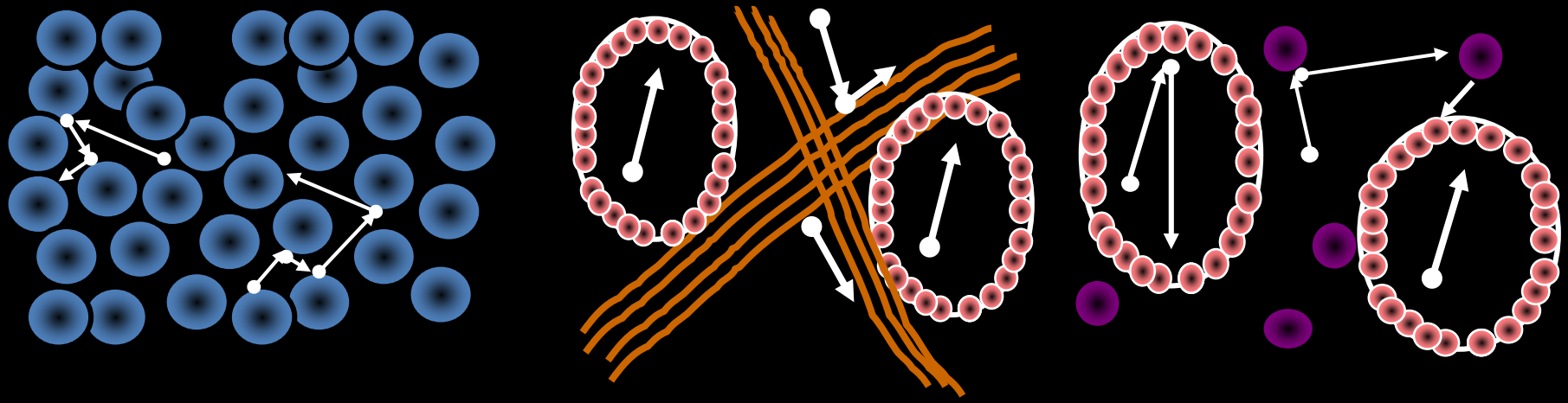
n=70,
Endorectal coil
Total tumour foci: 553



Detected by MRI (%)	89	45	13	3	0

Roethke MC et al. Eur J Radiol 2011; 79(2): 189-95

Diffusion Weighted MRI



Tightly packed cellular tumour

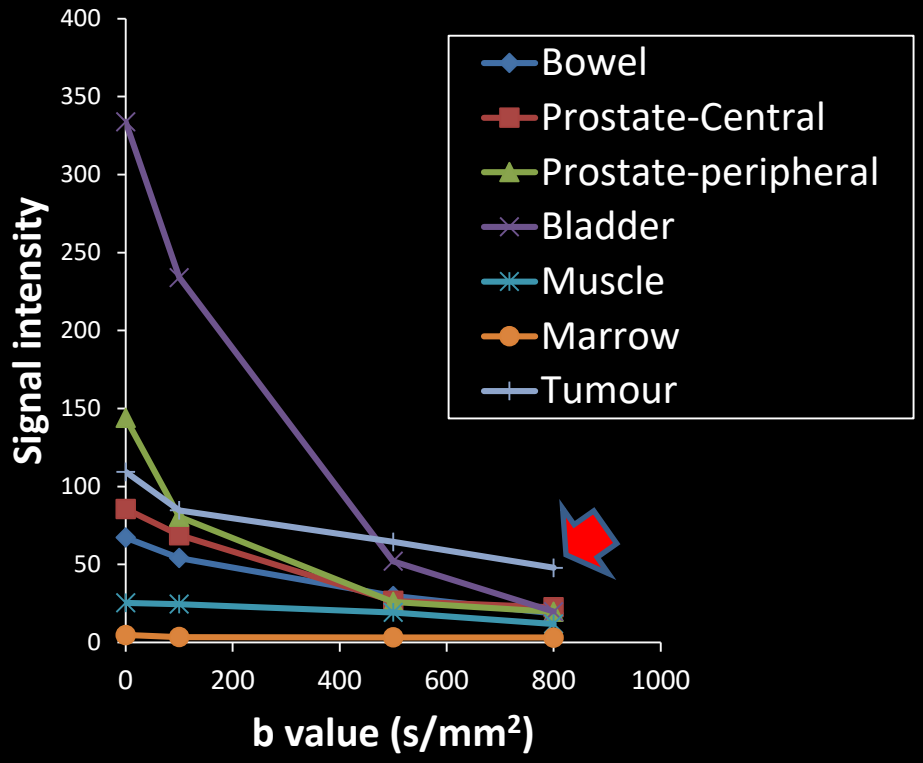
Fibroglandular BPH

Glandular tissue

Courtesy: AR Padhani

Increasing restriction of water diffusion

Diffusion Weighted MRI

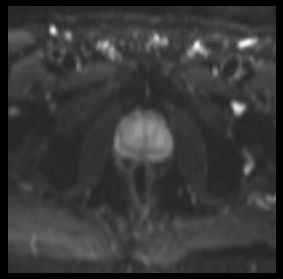


$$\frac{S}{S_0} = e^{-bD}$$

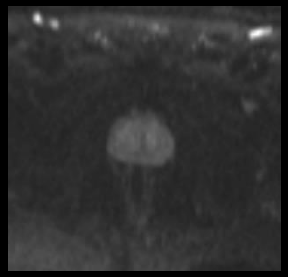
S = DW signal
S_0 = signal without DW
b=diffusion factor
D = diffusion coefficient

Normal prostate

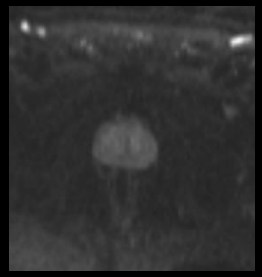
b0



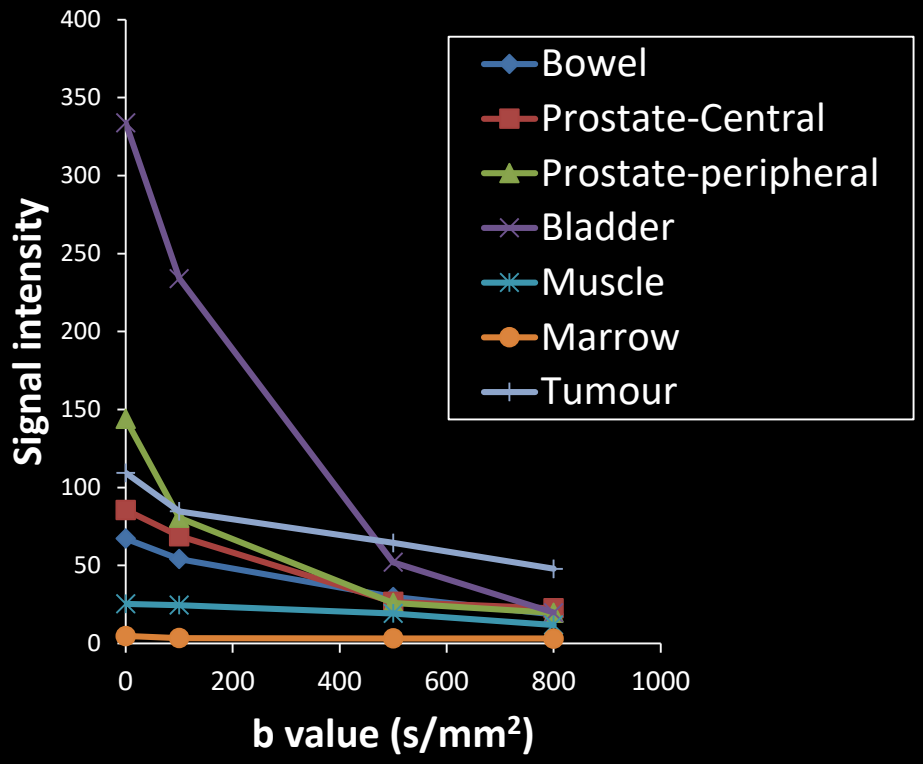
b100



b800



Diffusion Weighted MRI



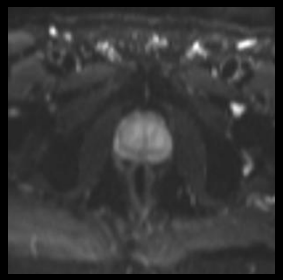
$$ADC = -\frac{1}{bi} x \ln\left(\frac{Si}{S0}\right)$$

Apparent Diffusion Coefficient

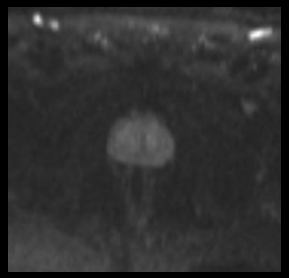
Gradient of $_{ln}$SI change (mm^2/s)

Normal prostate

b0



b100



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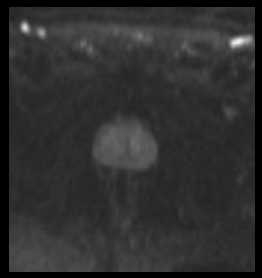
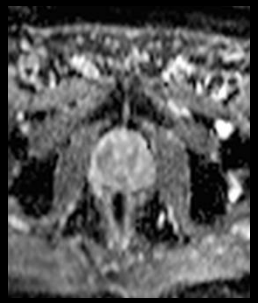
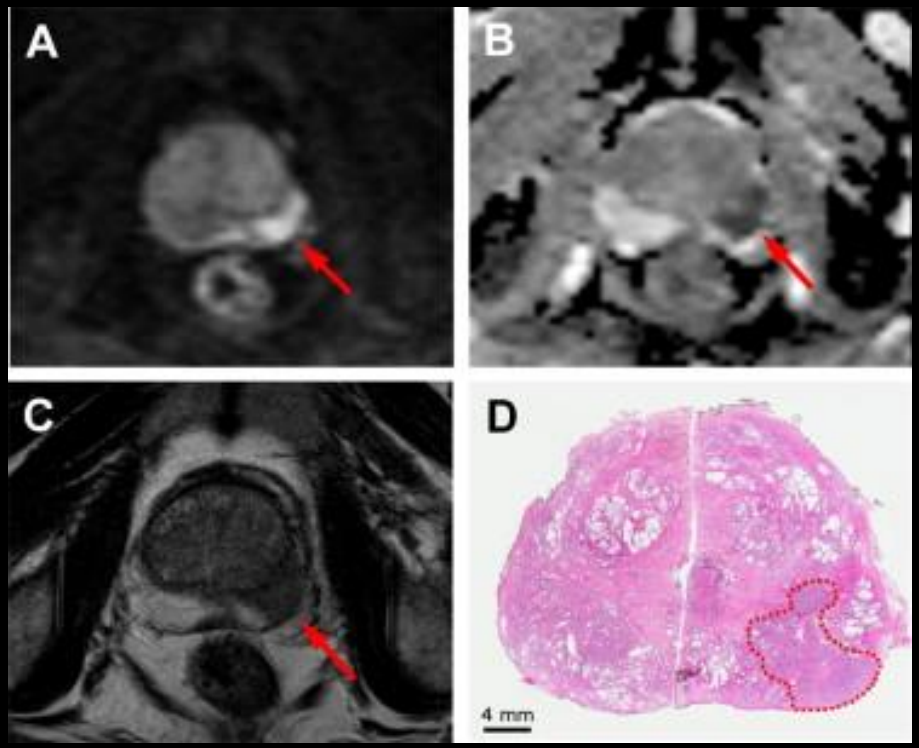


ADC



Diffusion Weighted MRI



Bains LJ et al. J Urol 2014; 192(3):737-42

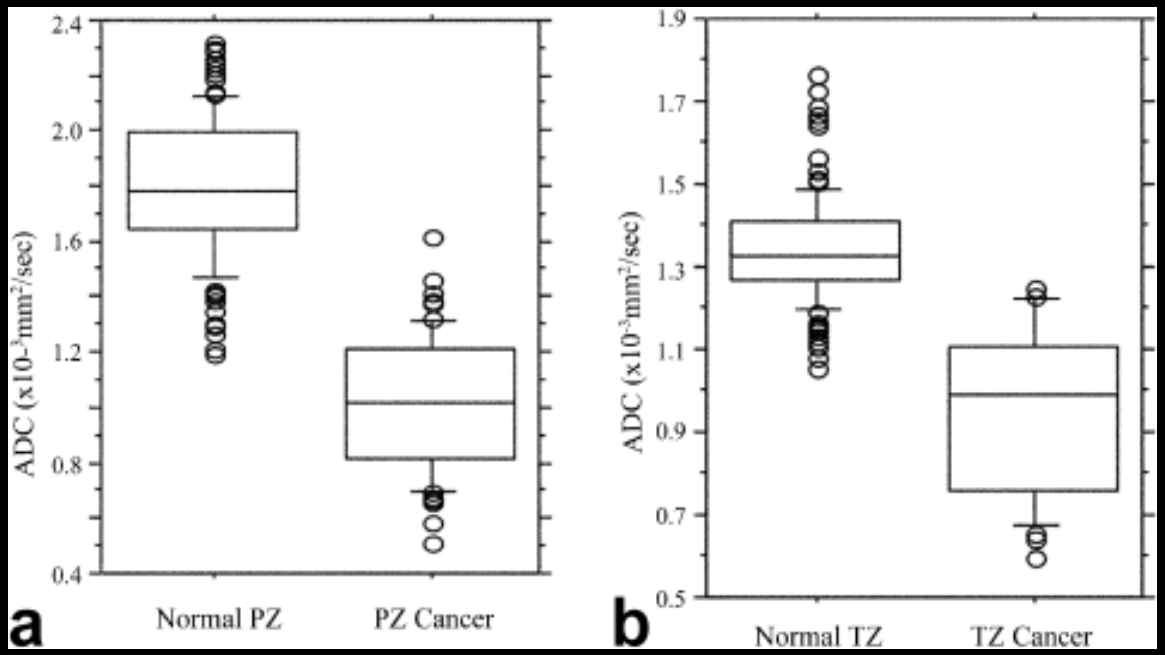
3T-MRI with b: 0, 500,1000 s/mm²

DWI	Sensitivity (%)	Specificity (%)
Reader 1	89	77
Reader 2	90	81
Reader 3	91	77

N=111: 93 with prostate cancer

Diffusion Weighted MRI

Lower ADC in cellular tumours:



- ADCs associated with different Gleason scores in the whole prostate

Caveat:
Overlapping ADCs

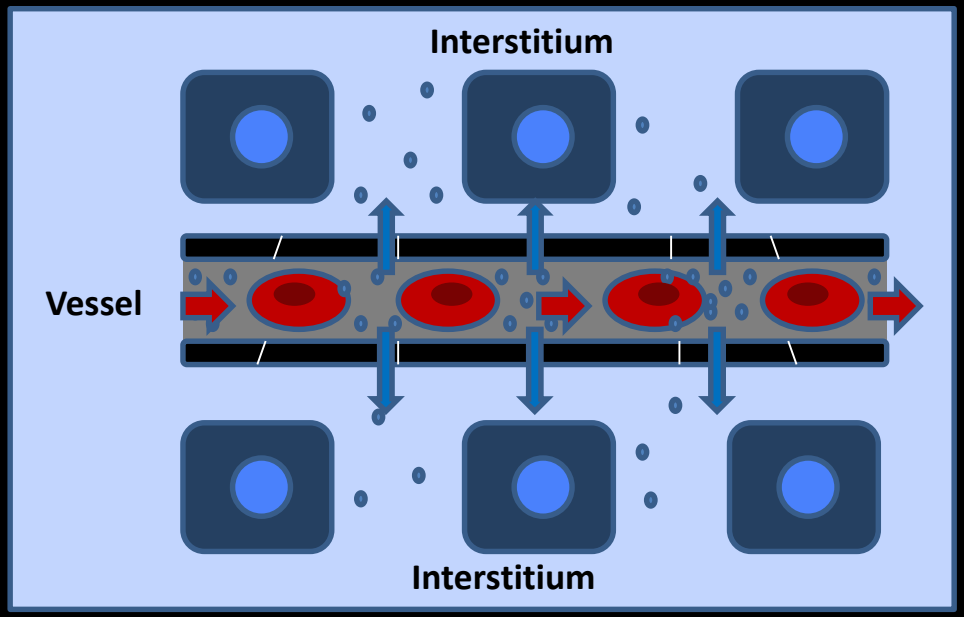
- Low-mod differentiated
- Benign Hyperplasia

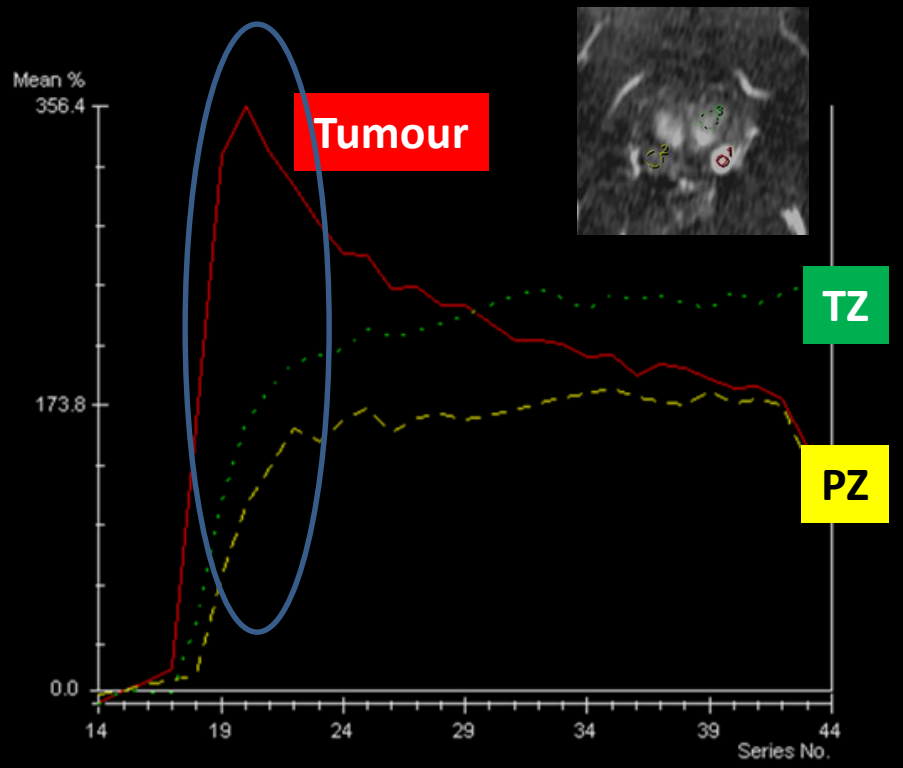
Tamada T et al. J Magn Reson Imaging 2008; 28(3): 720-6

Zelhof B et al. BJU Int 2009; 103: 883-8

Turkbey B et al. Radiology 2011;258:488-495

Dynamic Contrast Enhanced MRI

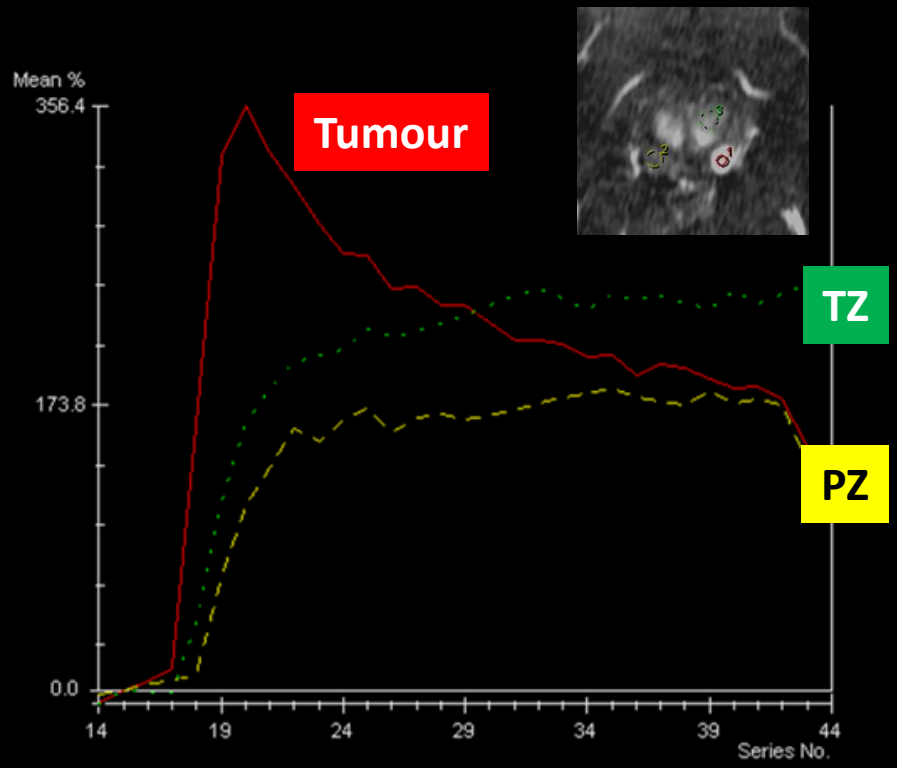




Contrast agent kinetics may differ between tumour & normal prostate

Early vascularisation within tumours

Dynamic Contrast Enhanced MRI

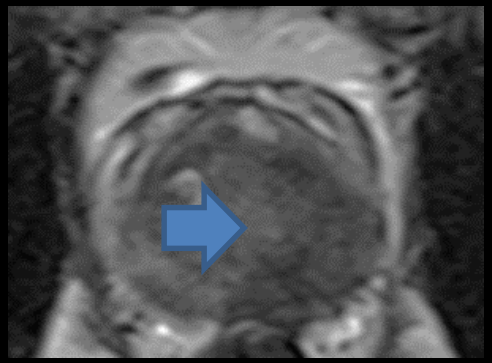


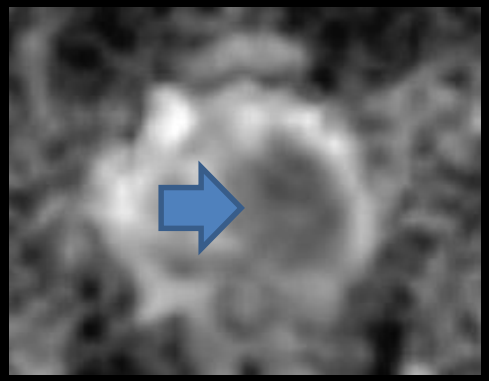
- Can detect clinically important cancer in 93% of cases*
- Role in TRUS biopsy-negative cancers with elevated PSA

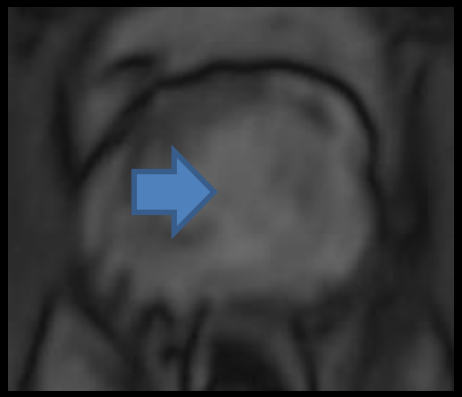
*Hara et al. Prostate 2005; 62: 140-7
Beyersdorff et al. Radiology 2002; 224: 701-6

Multi-parametric MRI: Typical Tumour Appearances

MRI	Appearances
Anatomical	Focal T2 low signal intensity lesion
DWI	Focal high signal on high b value sequence Focal low signal on ADC maps
DCE-MRI	Early enhancement & wash-out







PIRADS v2

Scoring:

- 1: Very low, clinically significant PCa highly unlikely
- 2: Low, clinically significant PCa is unlikely
- 3: Intermediate, equivocal presence of clinically significant PCa
- 4: High, clinically significant PCa likely
- 5: Very high, clinically significant Pca highly likely

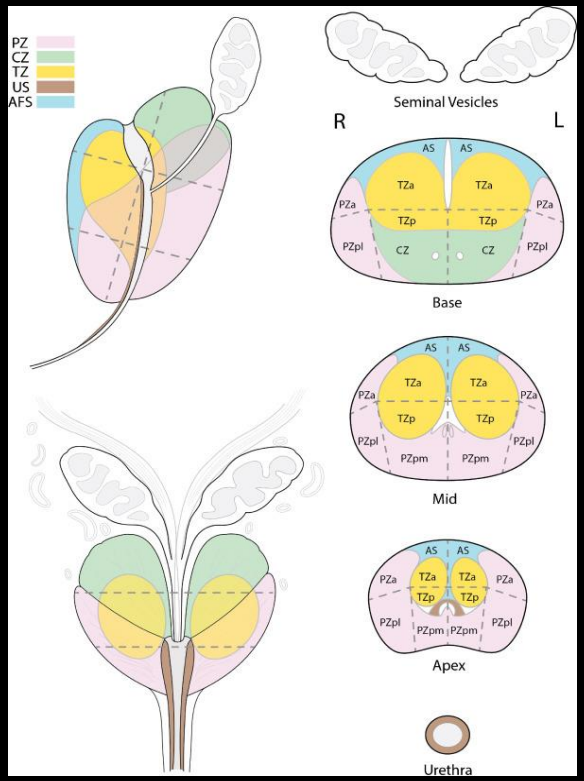
http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS

Barentsz J et al. Synopsis of the PI-RADS v2 Guidelines for Multiparametric Prostate Magnetic Resonance Imaging and Recommendations for Use. Eur Urol 2016; 69: 41-9.

PIRADS v2

- Overall scores from the T2W, DWI & DCE applied sequentially
- Certain sequences are dominant according to zonal anatomy
- PZ: **DWI** is primary determinant
  - E.g. if the DWI score is 4 & T2W score is 3, the PI-RADS assessment category should be 4
- TZ: **T2W** is the primary determinant
  - E.g. if T2W score is 4 & DWI score is 2, the PI-RADS assessment category should be 4

39 sector map



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http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/PIRADS

PIRADS v2

Peripheral Zone (PZ)

DWI	T2W	DCE	PI-RADS
1	Any*	Any	1
2	Any	Any	2
3	Any	–	3
		+	4
4	Any	Any	4
5	Any	Any	5

* "Any" indicates 1-5

Transition Zone (TZ)

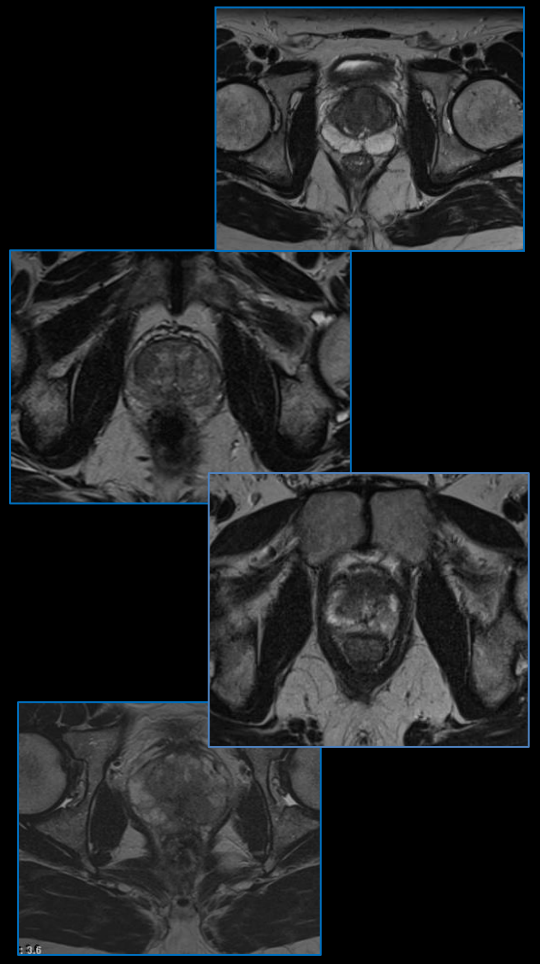
T2W	DWI	DCE	PI-RADS
1	Any*	Any	1
2	Any	Any	2
3	≤4	Any	3
	5	Any	4
4	Any	Any	4
5	Any	Any	5

* "Any" indicates 1-5

T2 Evaluation: PZ

Score	Peripheral Zone (PZ)
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

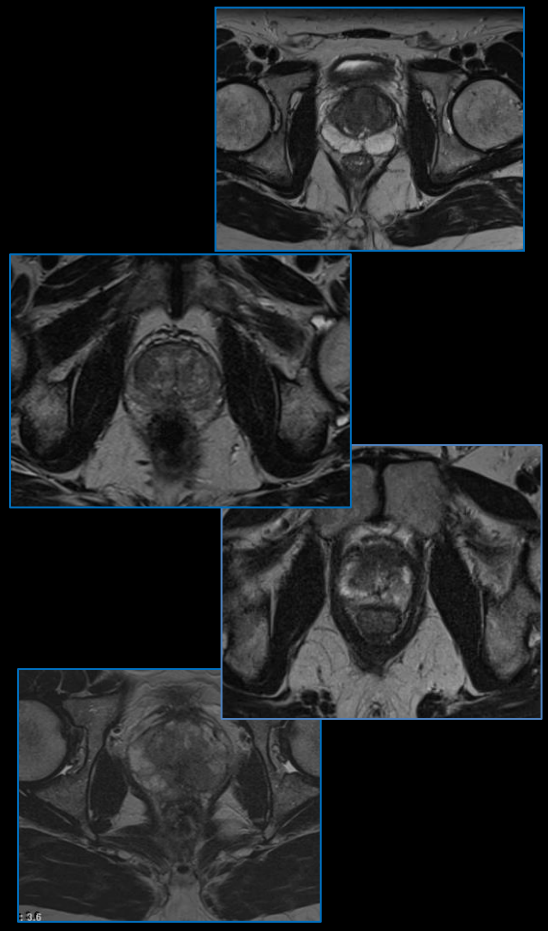
http://www.acr.org



T2 Evaluation: PZ

Score	Peripheral Zone (PZ)
1	Uniform hyperintense signal intensity (normal)
2	Linear or wedge-shaped hypointensity or diffuse mild hypointensity, usually indistinct margin
3	Heterogeneous signal intensity or non-circumscribed, rounded, moderate hypointensity Includes others that do not qualify as 2, 4, or 5
4	Circumscribed, homogenous moderate hypointense focus/mass confined to prostate and <1.5 cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior

http://www.acr.org



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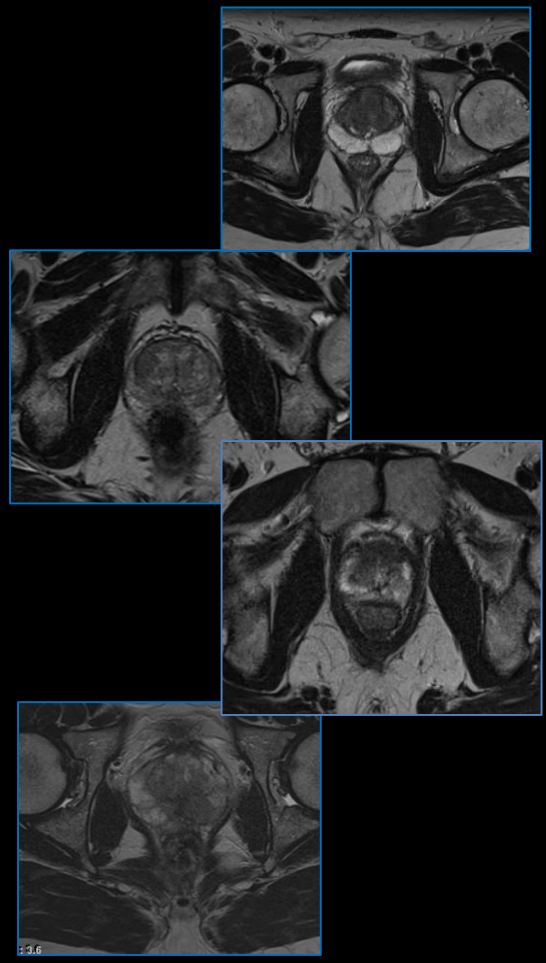

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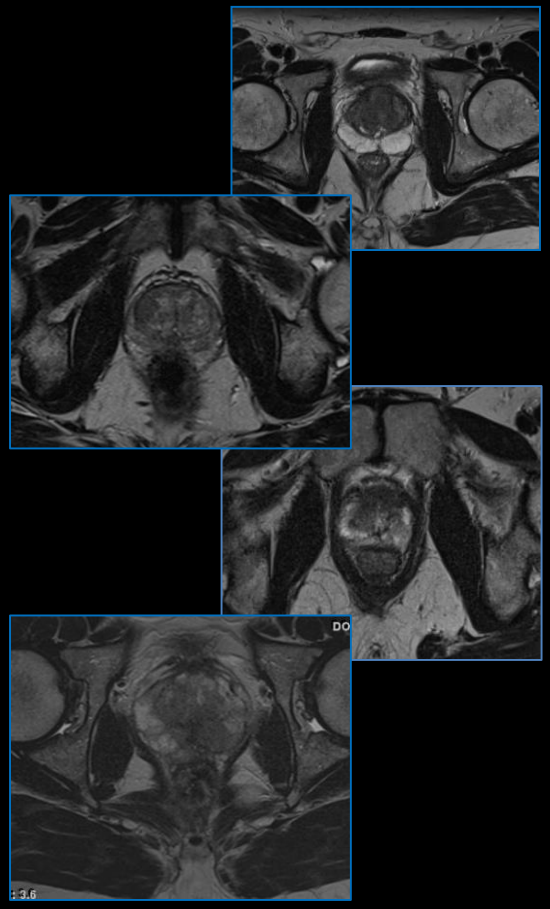
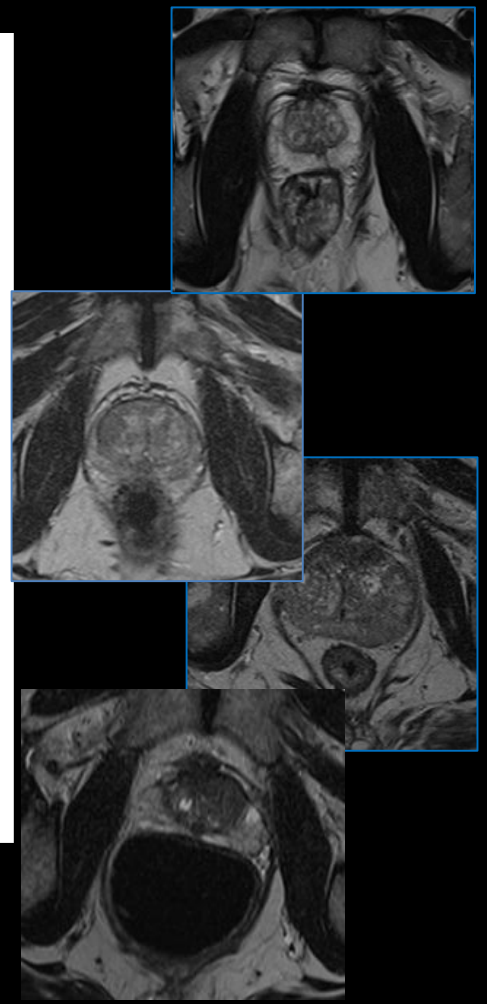


T2 Evaluation: TZ

Score	Transition Zone (TZ)
1	Homogeneous intermediate signal intensity (normal)
2	Circumscribed hypointense or heterogeneous encapsulated nodule(s) (BPH)
3	Heterogeneous signal intensity with obscured margins Includes others that do not qualify as 2, 4, or 5
4	Lenticular or non-circumscribed, homogeneous, moderately hypointense, and <1.5 cm in greatest dimension
5	Same as 4, but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior



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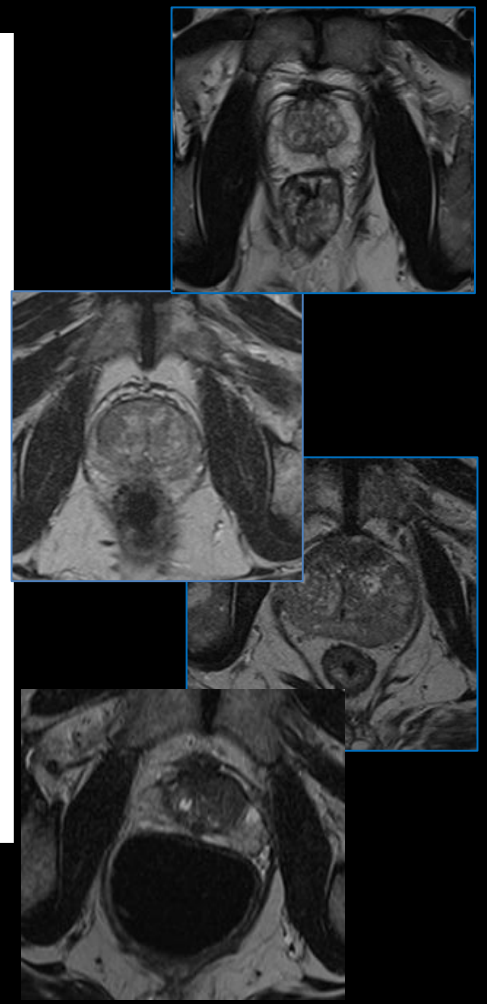

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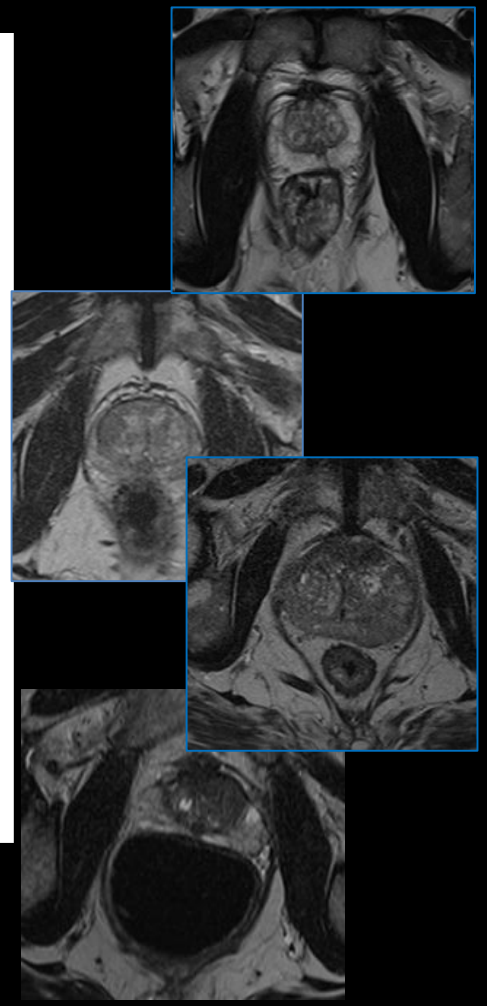

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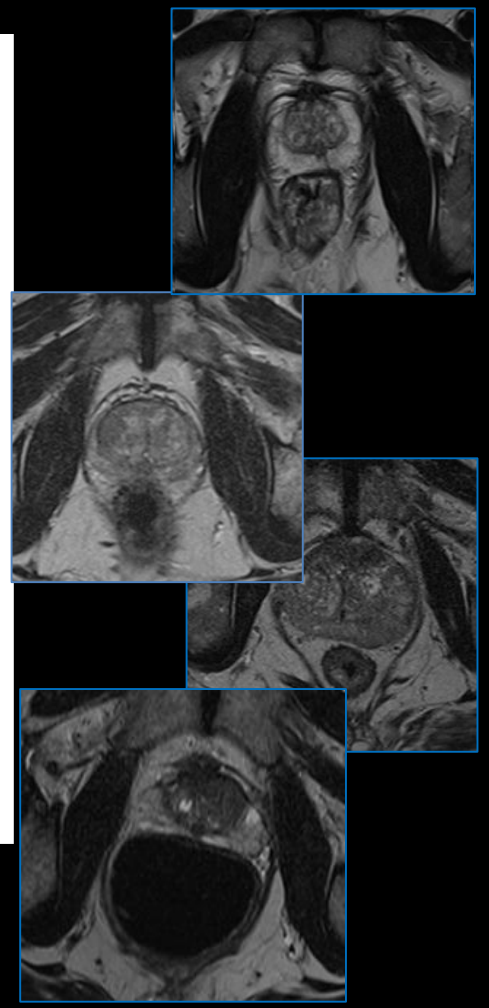
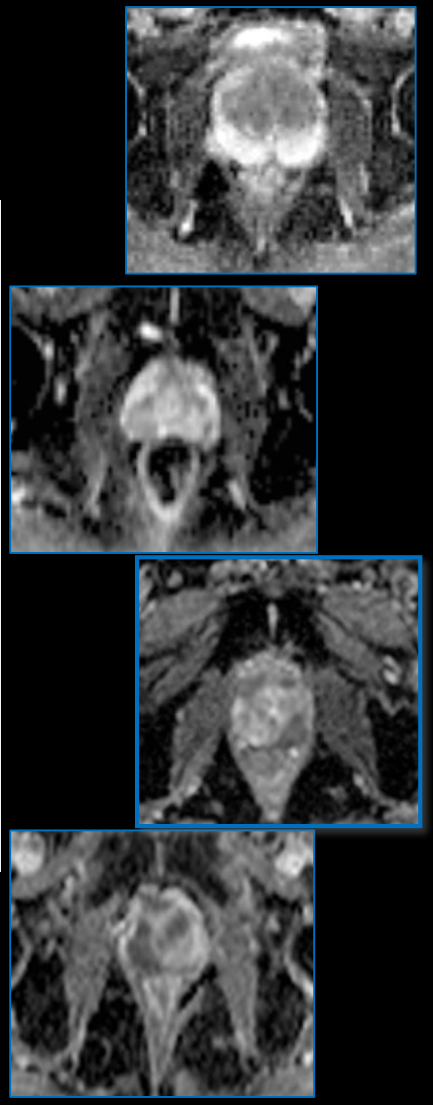


DWI Evaluation

Score	Peripheral Zone (PZ) or Transition Zone (TZ)
1	No abnormality (i.e., normal) on ADC and high b-value DWI
2	Indistinct hypointense on ADC
3	Focal mildly/moderately hypointense on ADC and isointense/mildly hyperintense on high b-value DWI.
4	Focal markedly hypointense on ADC and markedly hyperintense on high b-value DWI; <1.5cm in greatest dimension
5	Same as 4 but ≥1.5cm in greatest dimension or definite extraprostatic extension/invasive behavior



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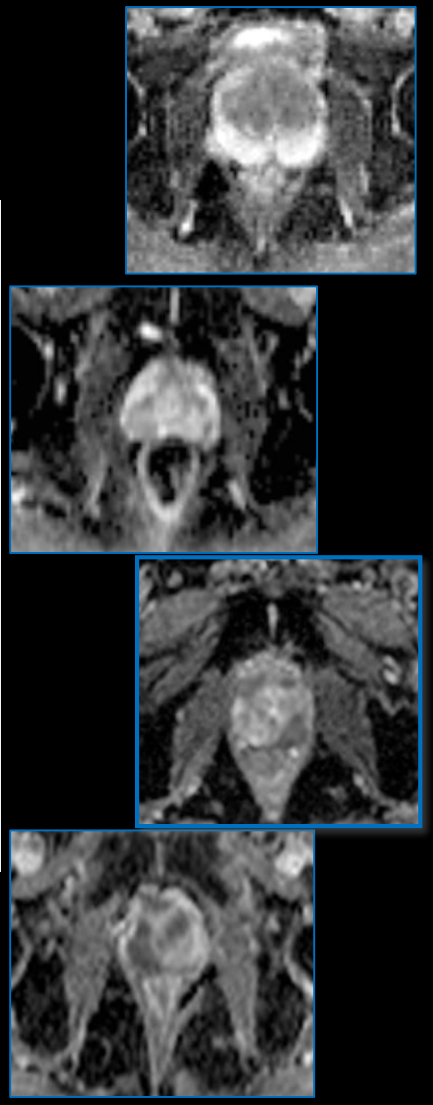

http://www.acr.org

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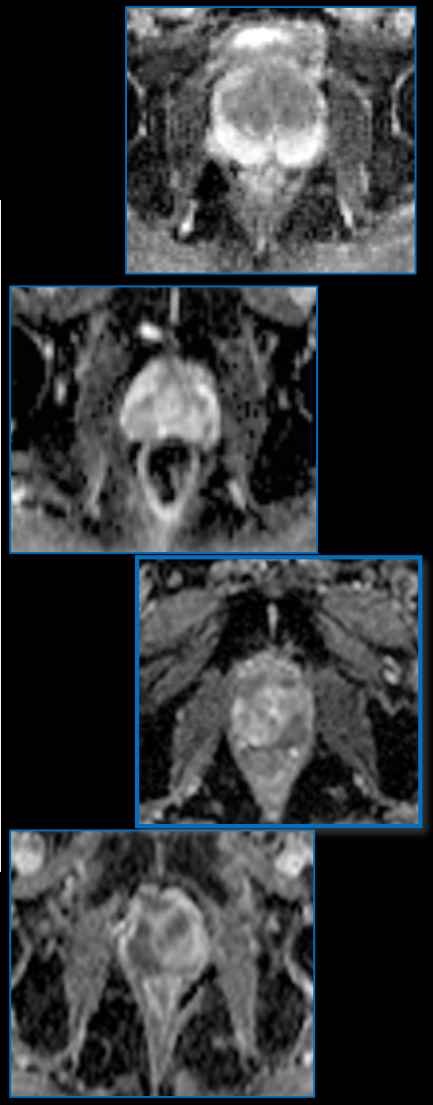

http://www.acr.org

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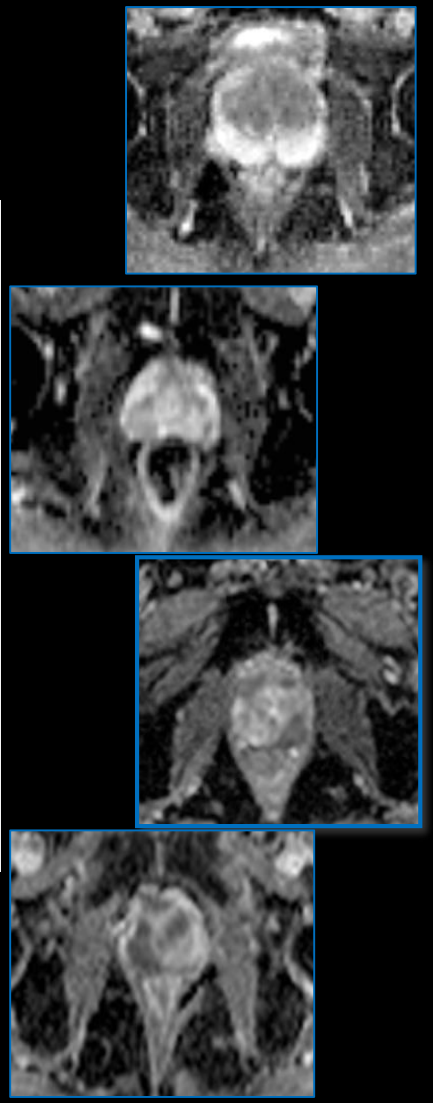
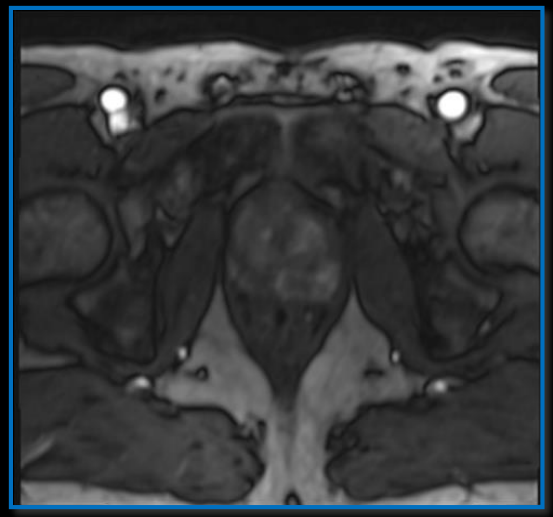


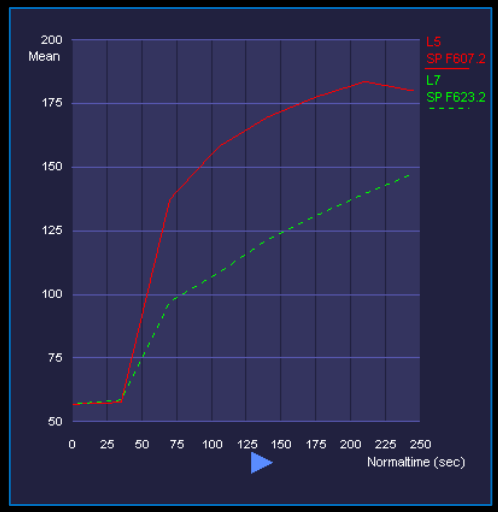
http://www.acr.org

DCE Evaluation

Score	Peripheral Zone (PZ) or Transition Zone (TZ)
(–)	no early enhancement, or diffuse enhancement not corresponding to a focal finding on T2W and/or DWI or focal enhancement corresponding to a lesion demonstrating features of BPH on T2WI
(+)	focal, and; earlier than or contemporaneously with enhancement of adjacent

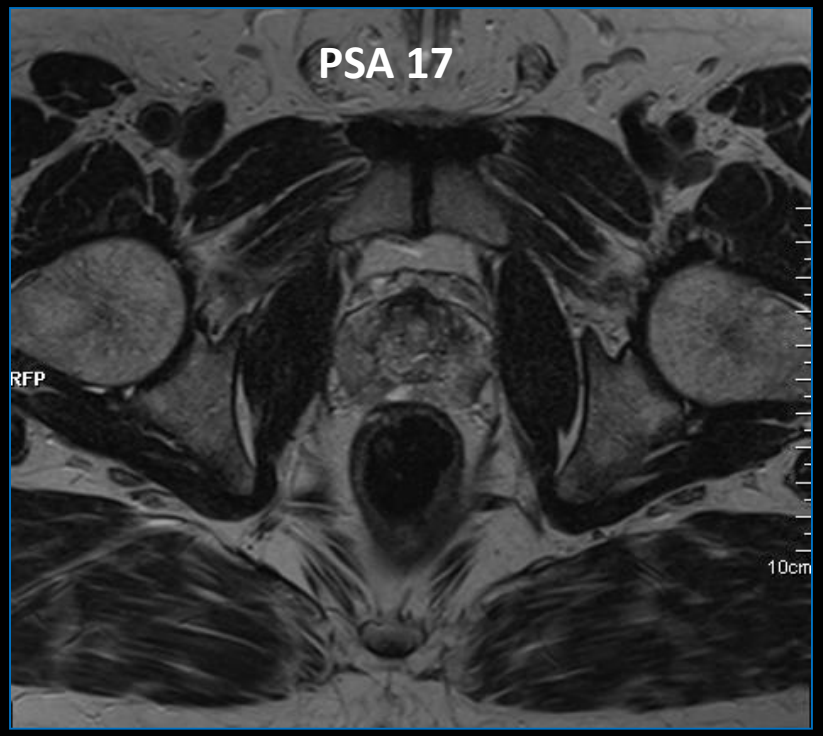
http://www.acr.org





False Positives

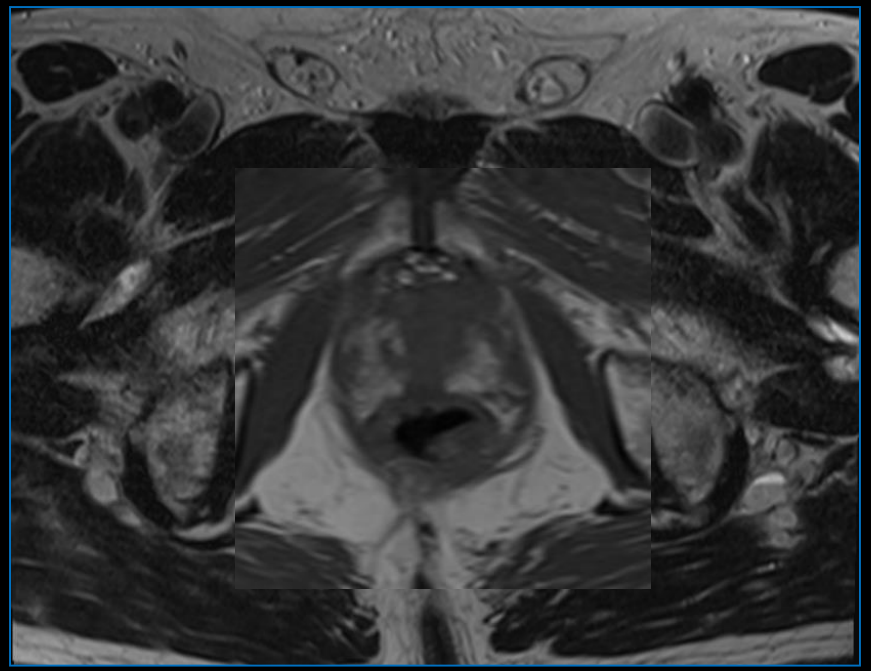
- False positives:
  - Prostatitis
  - Haemorrhage



Prostatitis

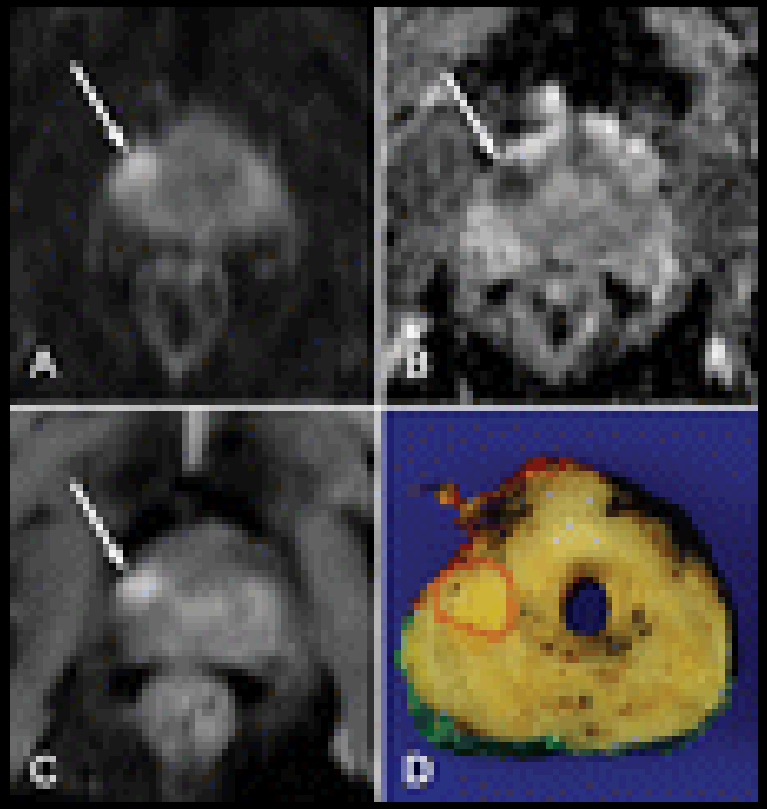
False Positives

- False positives:
  - Prostatitis
  - Haemorrhage
  - Treatment effects



Haemorrhage

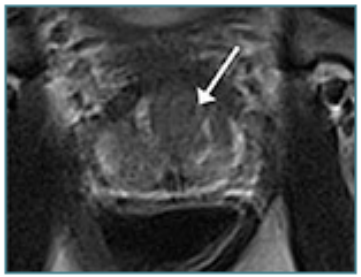
Improved Diagnosis



- PIRADS v2.0 predicts clinically significant cancer
- 425 patients with prostate cancer who had radical prostatectomy
- Defined by: (a) Gleason score of 7 or greater, (b) tumour volume of 0.5 cm3 or greater, or a (c) positive extracapsular extension or seminal vesicle invasion
- ROC AUC: 0.79-0.81

Park SY et al. Radiology 2016;280(1): 108-116

Interobserver Agreement: PIRADS v2.0



Interobserver Reproducibility of PI-RADS Version 2 Lexicon Was Moderate among Experienced Radiologists

Six experienced radiologists achieved moderate reproducibility for Prostate Imaging Reporting and Data System (PI-RADS) version 2 and neither required nor benefitted from a training session. In a study of six radiologists who assessed prostate MR imaging examinations by using the PI-RADS lexicon, Rosenkrantz et al found agreement tended to be better in the peripheral zone (PZ) than the transition zone (TZ), although it was weak for dynamic contrast-enhanced imaging in the PZ. Despite considerable variation in reproducibility for individual features within the PI-RADS version 2 lexicon, the system achieved moderate interreader reproducibility among experienced radiologists for PI-RADS score of 4 or greater in both the PZ and TZ; further studies are needed to evaluate reproducibility and the influence of training interventions among less experienced radiologists.

Inter-observer agreement

PI-RADS score of ≥4 :

κ = 0.593 in peripheral zone

κ = 0.509 in transition zone

Diffusion-weighted imaging

κ = 0.535–0.619

Dynamic contrast enhanced

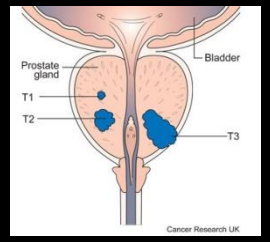
κ = 0.266–0.439

Definite T2-w extraprostatic extension

κ = 0.289

Rosenkrantz AB et al. Radiology 2016; 280(3): 793-804

Staging



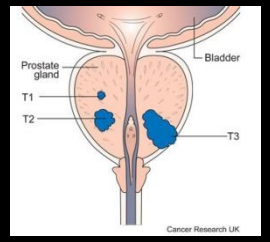
Not visible on MRI

- T1: Clinically inapparent
- Tumour neither palpable nor visible by imaging
  - T1a: incidental histologic finding in ≤5% of resected tissue
  - T1b: incidental histologic finding in >5% of resected tissue
  - T1c: identified by needle biopsy

Visible on MRI

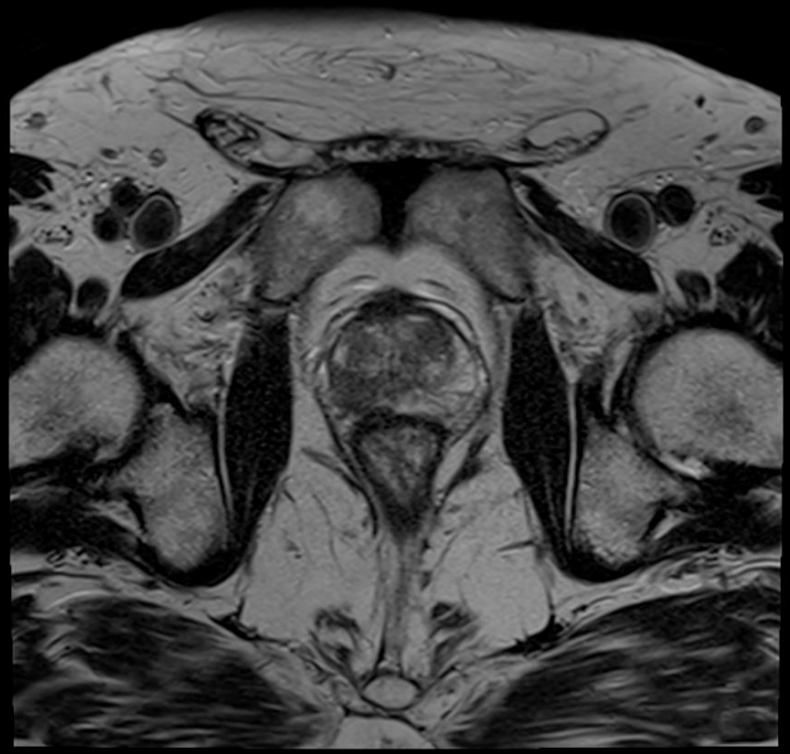
- T2: Confined to prostate
  - T2a: ≤ one half of one lobe
  - T2b : >one half of one lobe
  - T2c: involves both lobes

T Staging



Visible on MRI

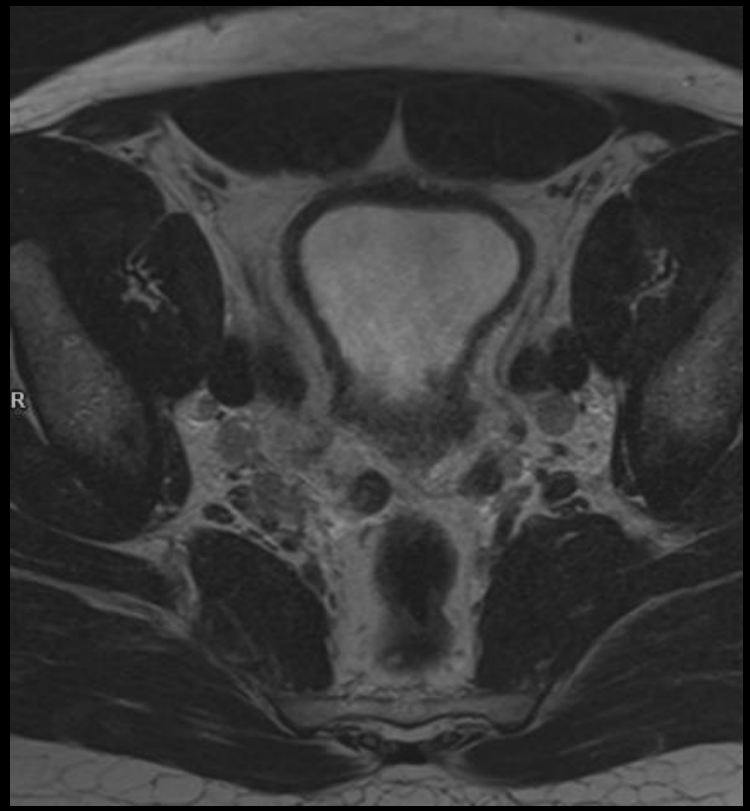
- T3: Extension through capsule
  - T3a: Extracapsular extensions
  - T3b: Invades seminal vesicles
- T4: Tumour is fixed or invades adjacent structures e.g. rectum, bladder, levator &/or pelvic wall



N Staging

N Staging

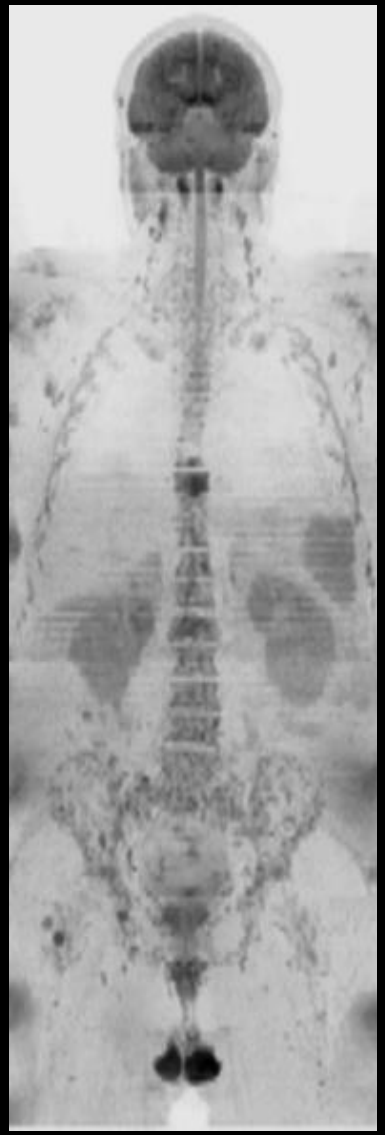
- Locoregional nodes:
  - N0: No nodes involved
  - N1: Locoregional nodes involved



N & M Staging

M Staging

- M0: No metastases
- M1a: Metastatic nodes
- M1b: Bones metastases
- M1c: Other distant metastases



WB-DWI

Limitations of MRI for Staging

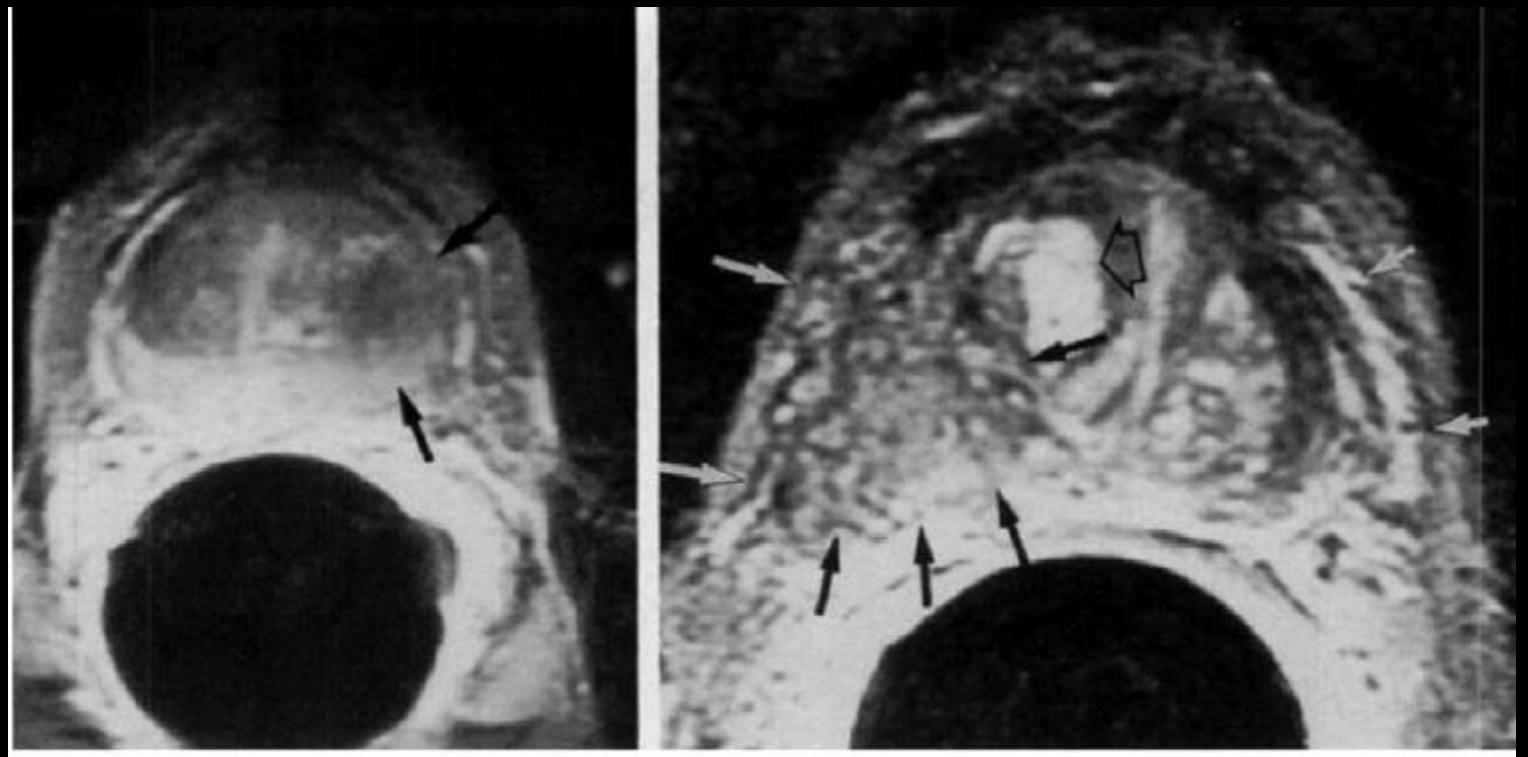
Nodal staging:

- Tumour may be present in normal sized nodes
- High incidence of enlarged reactive pelvic nodes
- High incidence of microscopic nodal spread to surgically non-sampled sites

Tumour staging:

- Varying ability to distinguish T2 (localised) from T3 (extracapsular) disease
- Sensitivity of T2-weighted MRI : 37-96% *
- DCE-MRI may improve tumour staging: Increased specificity for extracapsular extension+

*Kirkham A et al. Eur Urol 2006; 50 (6): 1163-74
+ Bloch B et al. Eur Radiol 2012; 22(10):2201-10



a. b.

Figure 4: MR images in two patients with prostatic carcinoma. **(a)** Low-intensity lesion in left peripheral zone is in region with positive biopsy findings (arrows). **(b)** Low-intensity lesion in right side of the prostate extends into the periprostatic fat (large solid arrows). High-signal-intensity glandular benign prostatic hypertrophy is seen in the central gland (open arrow) (images from reference 30).

Schnall MD et al. Prostate: MR imaging with an endorectal surface coil. Radiology 1989;172: 570-4

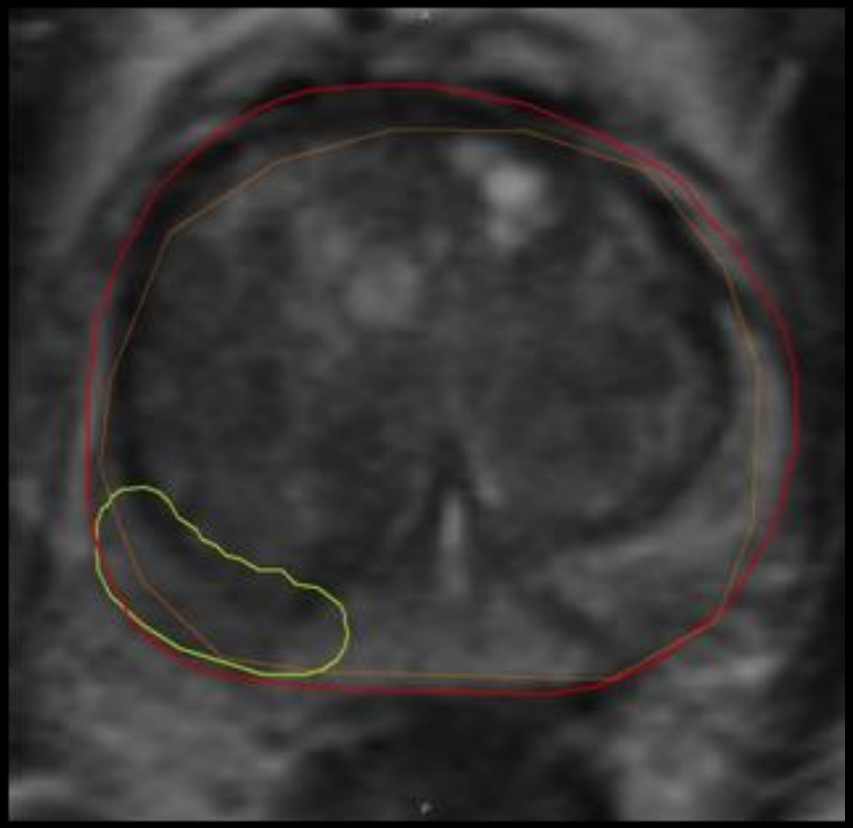
MR-Guided Biopsy & Treatment

Urol Clin North Am. 2014; 41(2): 315–326

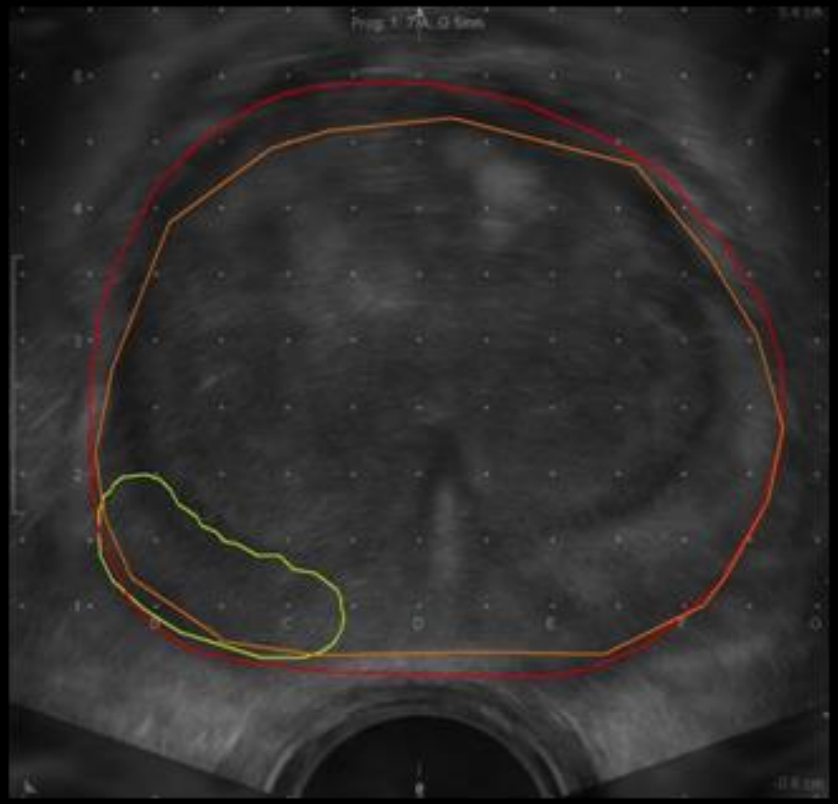
- MR guided biopsy possible of suspicious areas
- MR-US fusion allow biopsy to be performed in OP setting

Bayersdorff D et al. Radiology 2005; 234 (2): 576-81
Anastasiadis AG et al. Eur Urol; 50(4): 738-48
Engelhard K et al. Eur Radiol; 16(6): 1237-43

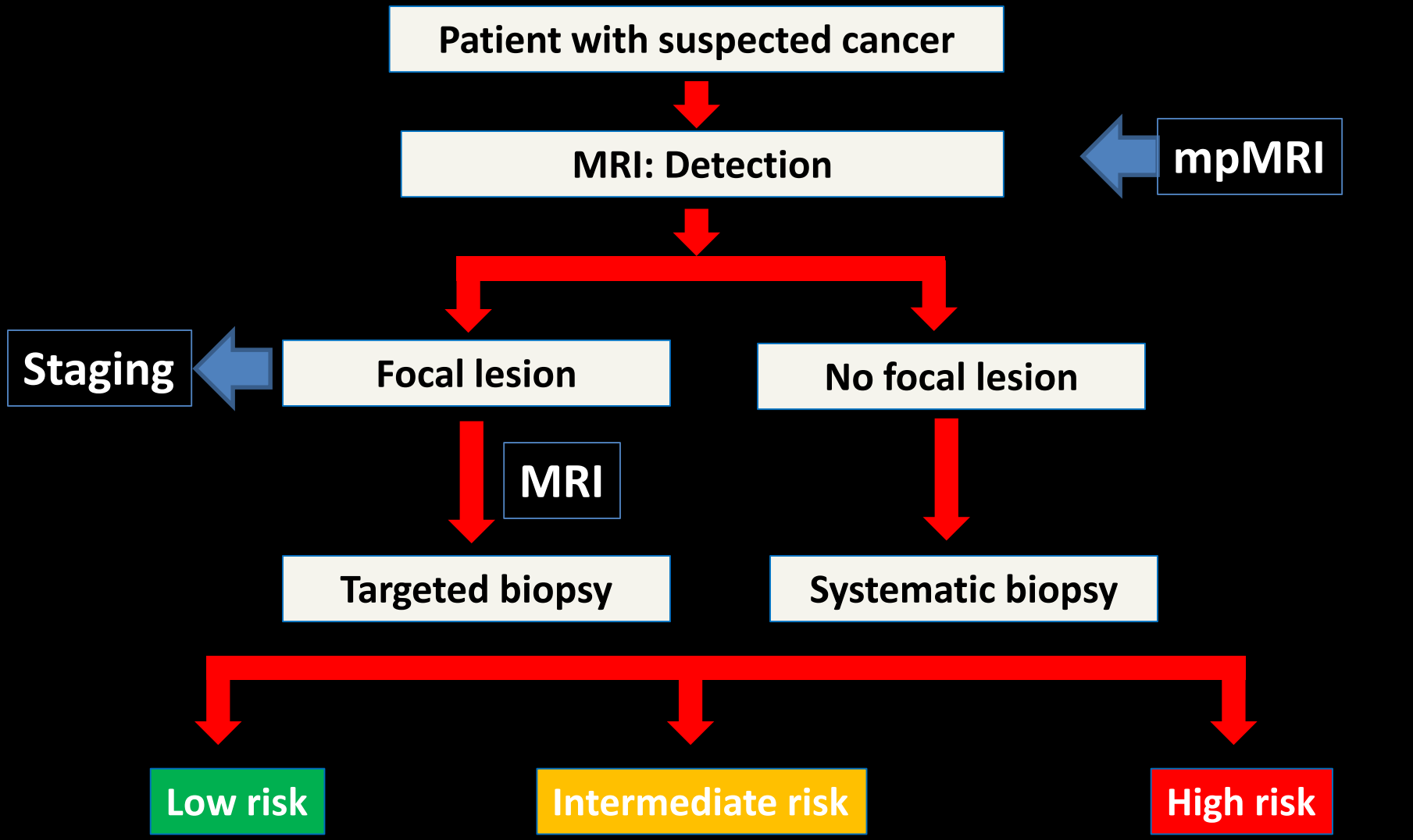
Tumour Delineation: Guided Biopsy



MRI: Tumour is delineated



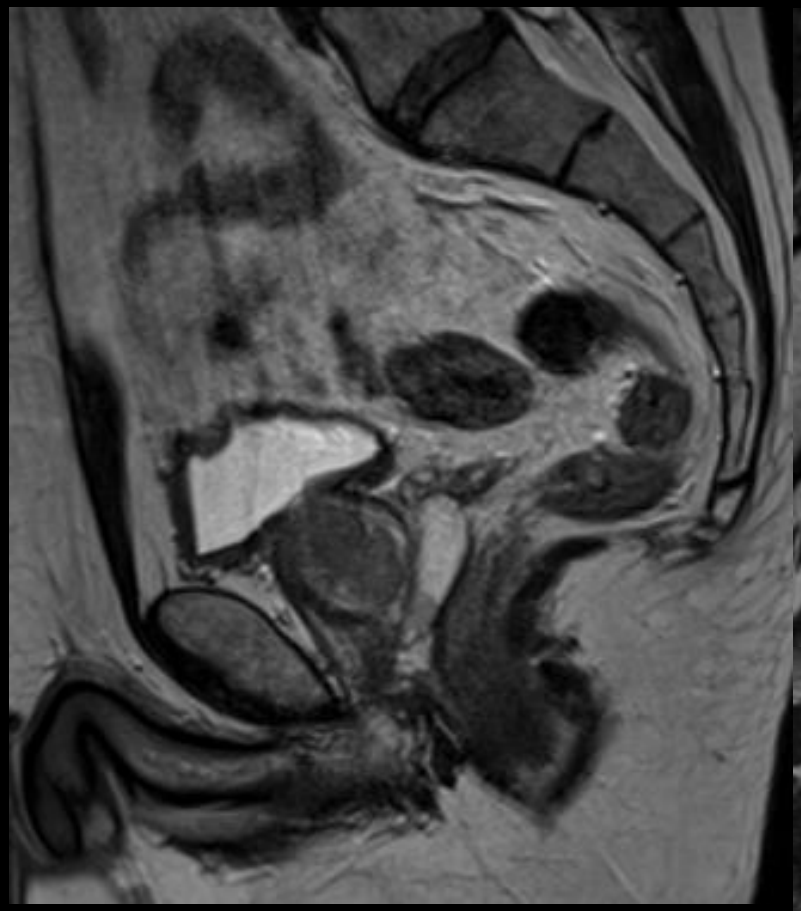
MRI- US fusion

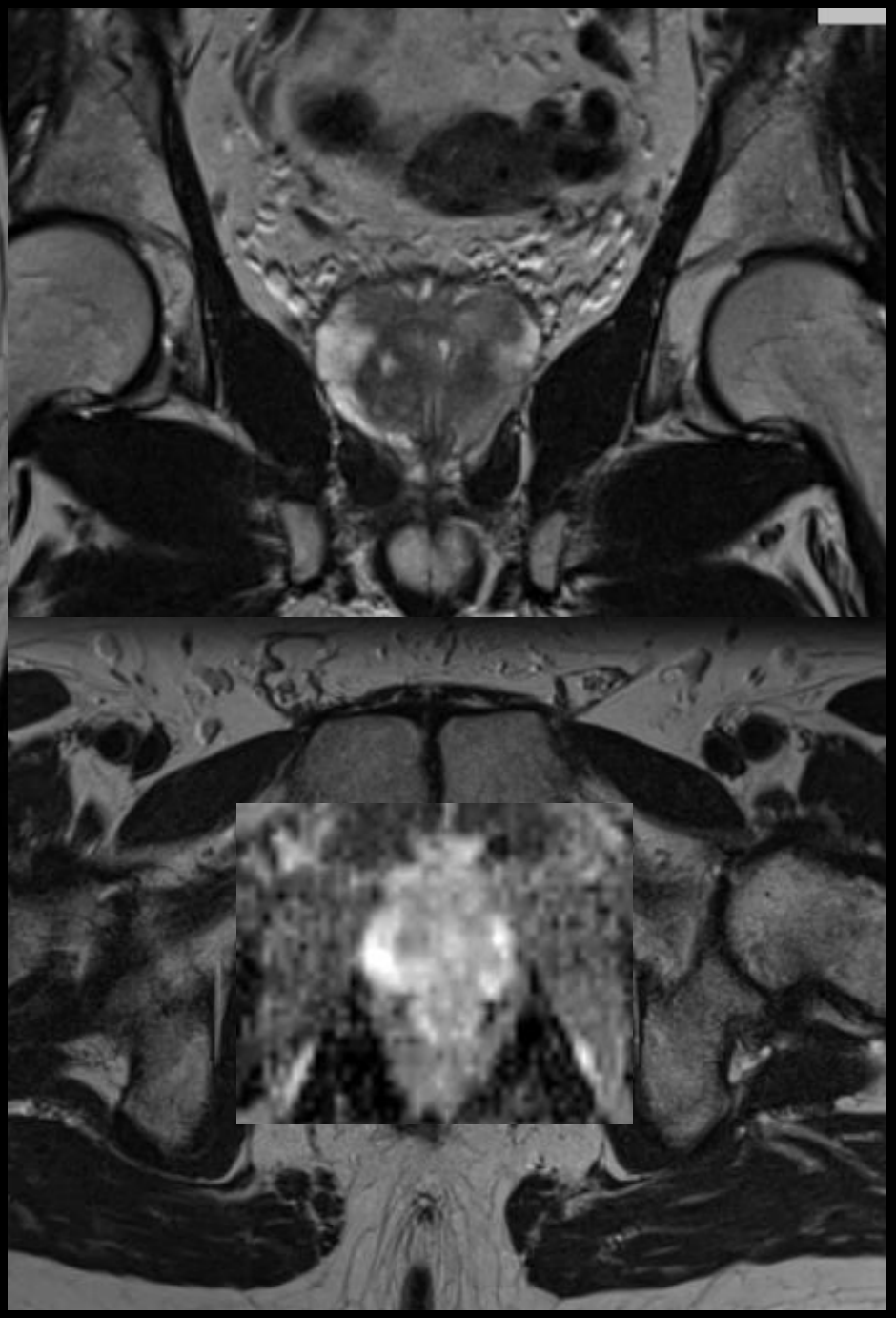


Stage	T1-2a
& PSA ng/mL	<10
& Gleason	≤6

Stage	T2b-c
or PSA ng/mL	10-20
or Gleason	7

Stage	≥T3a
or PSA ng/mL	>20
or Gleason	8-10





Is there a suspicious lesion?

Can you assign a PIRADS score?

What stage is this?

With respect to prostate cancer, which of the following is correct?

A. Its is a multifocal disease with multiple dominant lesions
B. All cancer foci are visible on MRI
C. A high risk cancer is a cT2c cancer, PSA >20ng/dl, Gleason 7+
D. A stage T3a cancer is invading the seminal vesicle
E. A PIRADS score of 4 & above is highly suspicious of cancer

With respect to prostate imaging, which of the following is correct?

A. Ultrasound is the initial modality of choice to diagnose prostate cancer
B. MRI should be performed at 3T
C. Multiparametric MRI (T2-, diffusion & multiphasic contrast enhanced) should be used to diagnose prostate cancer
D. Multiparametric MRI (T2-, diffusion, multiphasic contrast enhanced & spectroscopy) should be used to diagnose prostate cancer
E. Multiparametric MRI is essential for staging

PET/CT
for Prostate Cancer

Maria Picchio, Milan, Italy

Wouter V. Vogel, NKI-AVL, Amsterdam, the Netherlands

ESNM European School of Nuclear Medicine

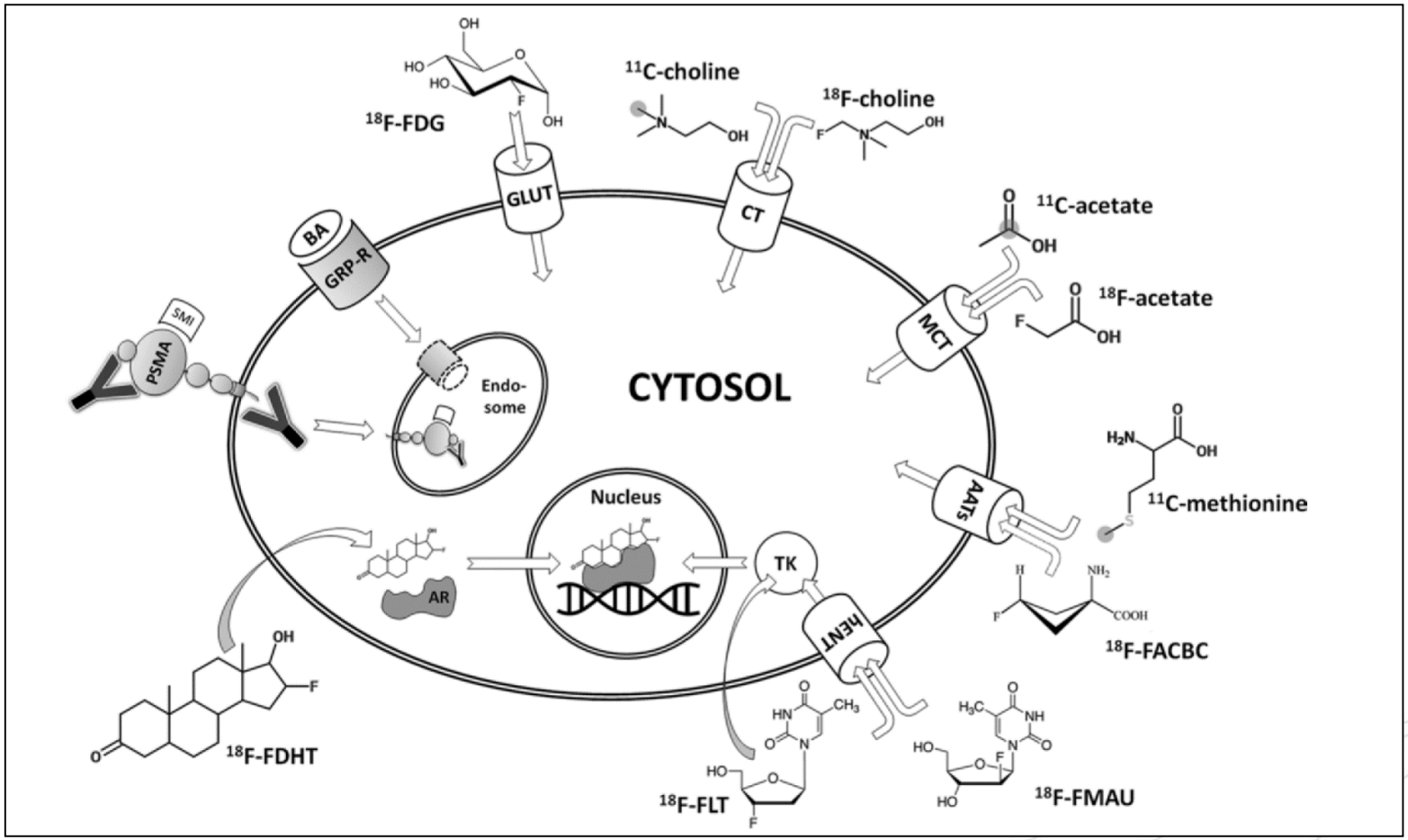
ESTRO School

Prostate Cancer

- **Prostate Cancer** (PCa) is currently the cancer with the highest prevalence in men (417,000 cases, 22.8% of all incidental cases) and the third most common cause of cancer deaths in men (9.5%) in Europe.

- **Imaging**
  - DIAGNOSIS - Detection and Characterization of Primary PCa lesions
  - STAGING – T/N/M
  - RESTAGING - Detection and Localization of relapse

PET Radiotracers in PCa: overview

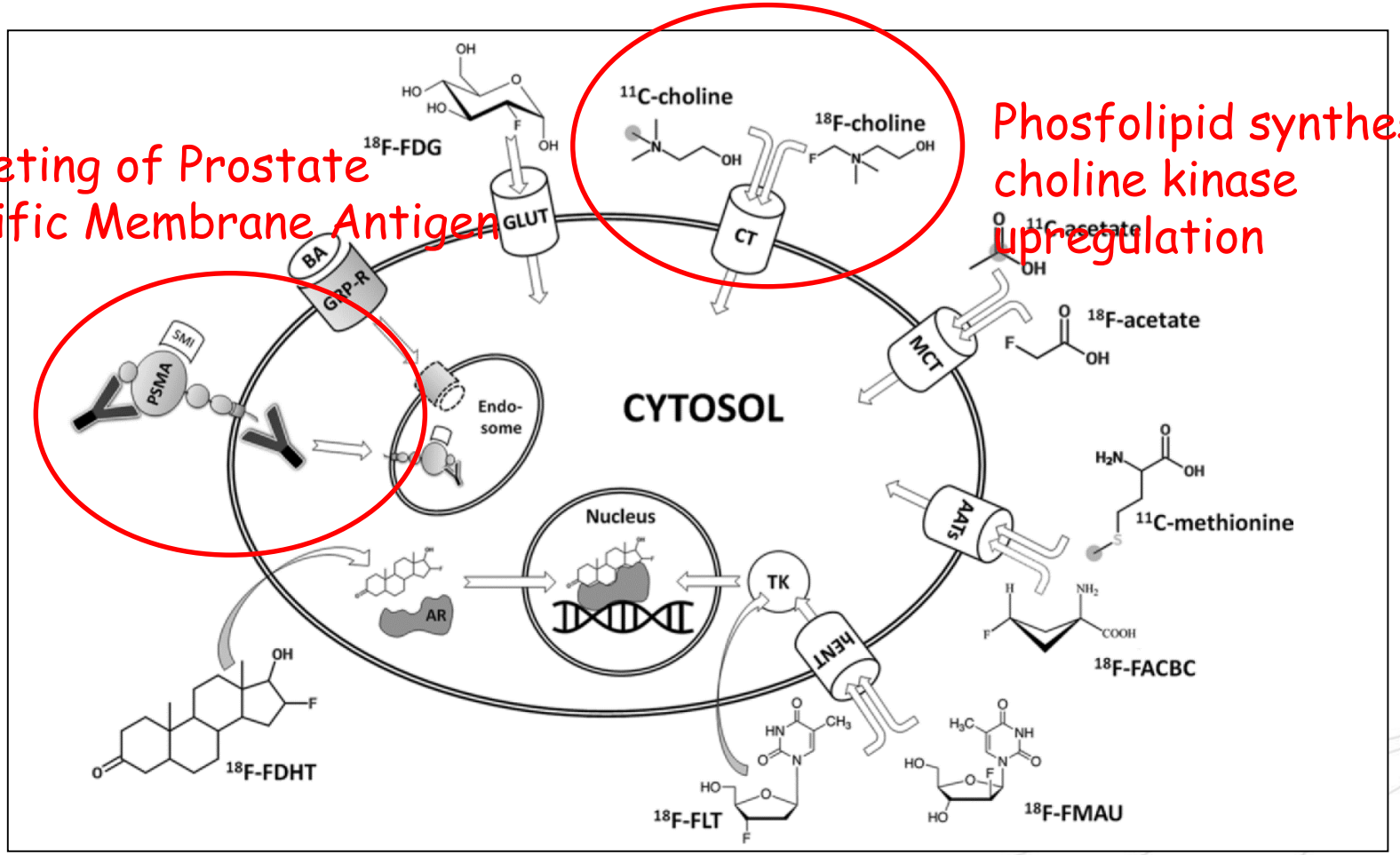


Wibmer et al. Radiographics, 2016

PET Radiotracers in PCa: overview

Targeting of Prostate Specific Membrane Antigen

Phosfolipid synthesis choline kinase upregulation



Wibmer et al. Radiographics, 2016

Choline PET/CT in Radiation Treatment Planning

- **Primary Treatment**: detection of intraprostatic lesions (Diagnosis) and patient selection for treatment (Staging)

- **Treatment of Relapse**: detection of recurrences (Restaging) and treatment monitoring

Choline PET/CT in Radiation Treatment Planning

- **Primary Treatment**: detection of intraprostatic lesions (Diagnosis) and patient selection for treatment (Staging)

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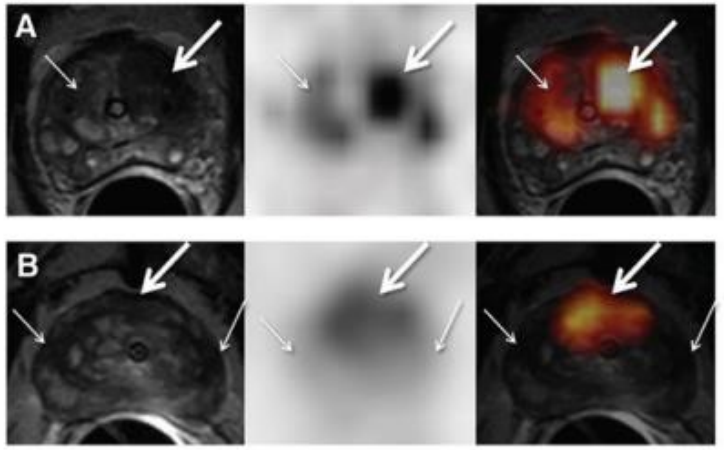
Choline PET – Primary Prostate Cancer

Study	n	Choline-PET–CT	
		Sensitivity (%)	Specificity (%)
Tumour			
Van den Bergh *et al.*[12]	49	77.4	44.9
Testa *et al.*[22]	50	55.0	86.0
Watanabe *et al.*[23]	43	73.0	59.0



	Primary Tumor
Sensitivity	54-100%
Specificity	43-86%

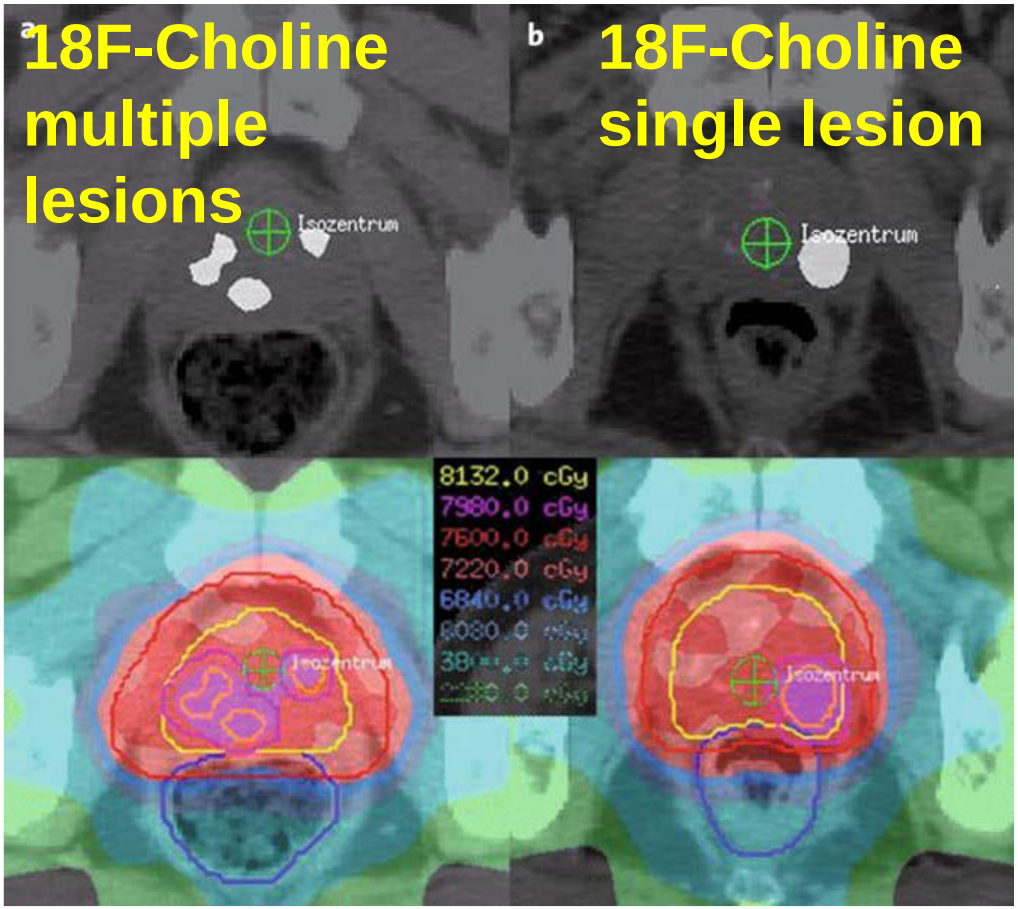
Mapelli and Picchio, Nat Rev Urol 2015

Hartenbach et al, CCR 2014

Brogsitter et al, Nucl Med Mol Imaging. 2013

Watanabe et al, JMRI 2010

Choline PET/CT for Pca Primary Treatment



66 prostate cancer pts

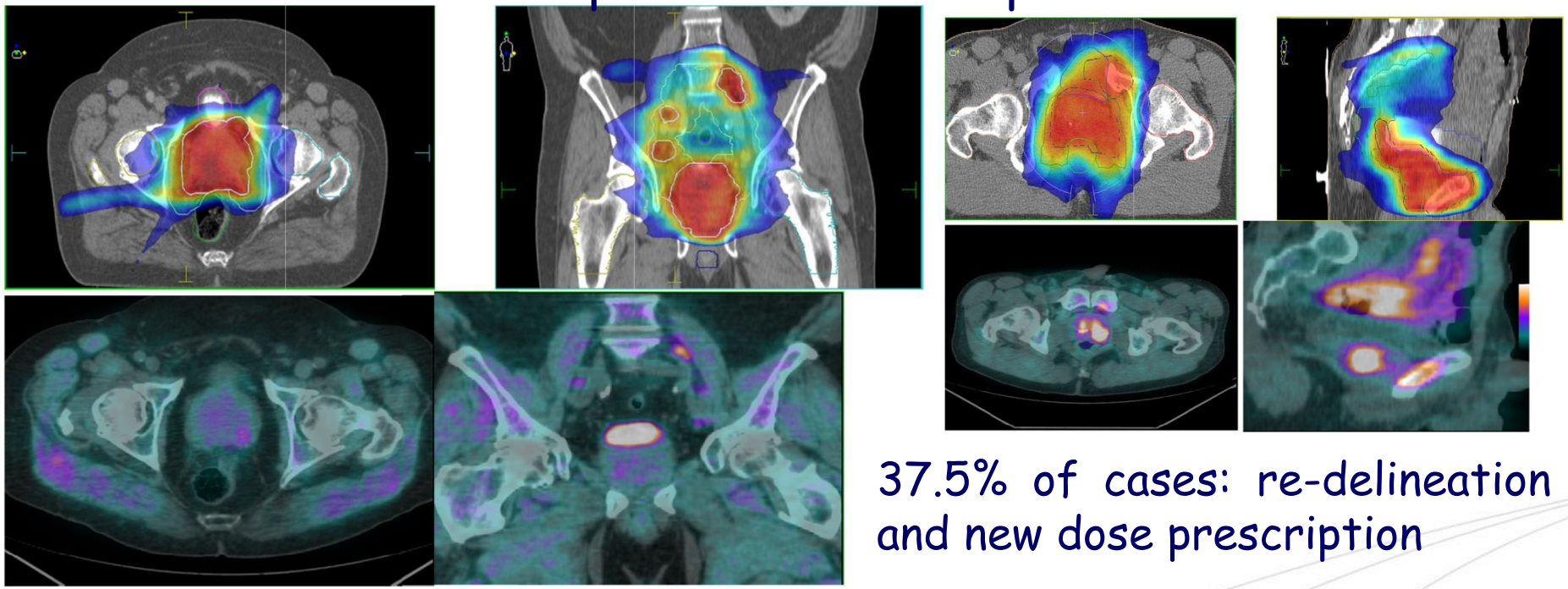
Treatment planning with Choline allows the definition of an integrated boost

GTV_{PET} and SUV are dependent on prognostic risk factors

Pinkawa et al. Strahlentherapie und Onkologie, 2011

Influence of ^{11}C-choline PET/CT on radiotherapy planning in prostate cancer

AIM: to analyse RT planning modification based on 11C-Choline PET/CT in 16 prostate cancer patients

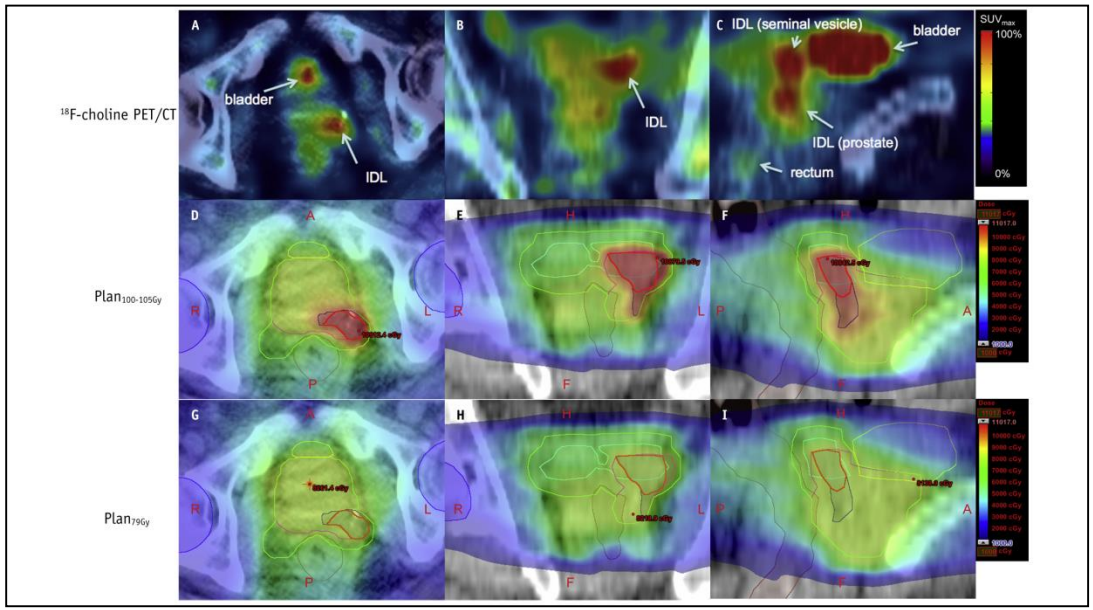


37.5% of cases: re-delineation and new dose prescription

Data show good preliminary clinical results in terms of biochemical control and toxicity. Lopez et al. Rep Pract Onc Radiot, 2015

Volumetric Modulated Arc Therapy Planning for Primary Prostate Cancer With Selective Intraprostatic Boost Determined by ^{18}F-Choline PET/CT

30 pts with localized Pca; 18F-choline PET/CT before treatment. Two VMAT plans for each pt: 79Gy vs 79Gy and 100-105Gy on intraprostatic dominant lesion (IDL)

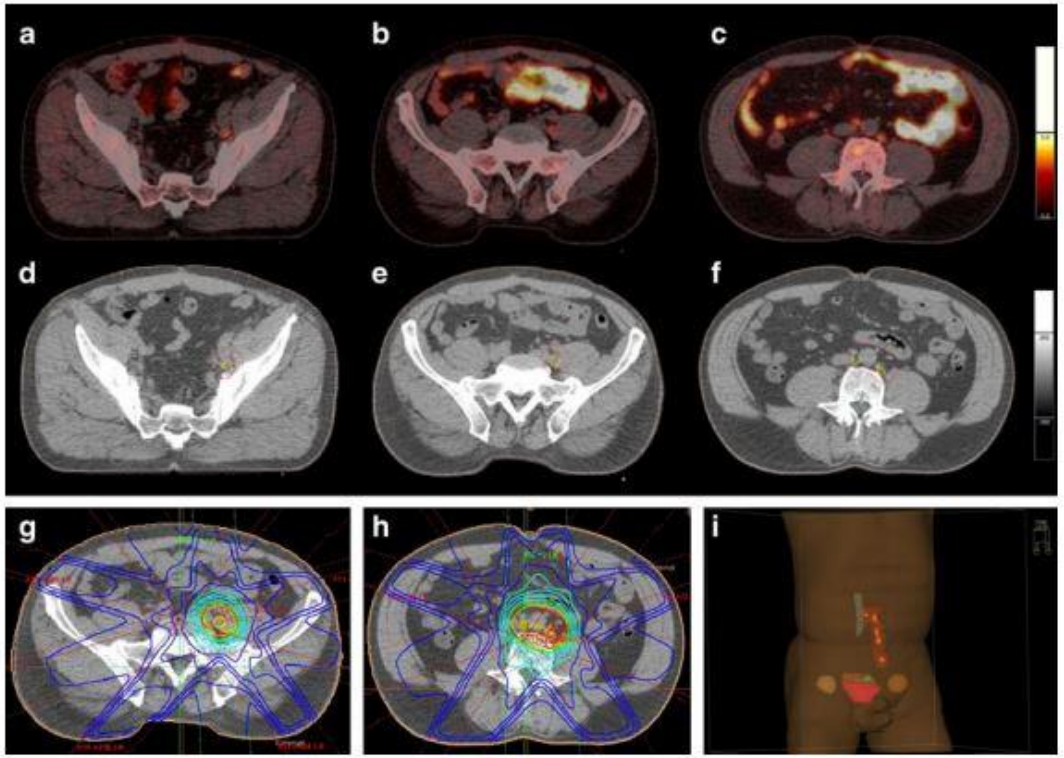


Kuang et al. Int J Rad Onc, 2015

Plan 100-105 Gy had significantly higher tumor control probability than plan 79 Gy across all prostate regions → increasing likelihood of tumor control in primary PCa

Choline PET/CT for Pca Primary Treatment

Choline PET/CT prior to RT might be useful in high-risk prostate cancer **to detect lymph node metastases** which might be included in the conventional irradiation field (instead of irradiation of single lymph nodes) influencing conventional PTV and surgery.



Eur J Nucl Med Mol Imaging (2013) 40 (Suppl 1):S28–S35
DOI 10.1007/s00259-013-2404-0

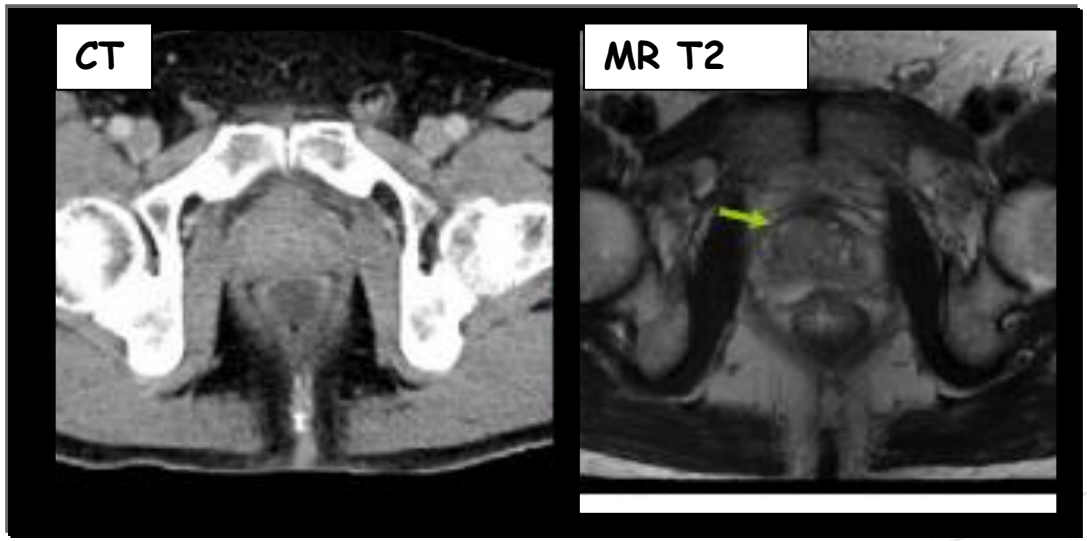
REVIEW ARTICLE

Role of choline PET/CT in guiding target volume delineation for irradiation of prostate cancer

S. M. Schwarzenböck · J. Kurth · Ch. Gocke · T. Kuhnt · G. Hildebrandt · B. J. Krause

MRI – Primary Prostate Cancer

- High spatial resolution - excellent soft tissue contrast
- Distinguish changes in the prostatic parenchyma
- Assess small structures in the small pelvis



Souvatzoglou M. et al. EJNMMI, 2013

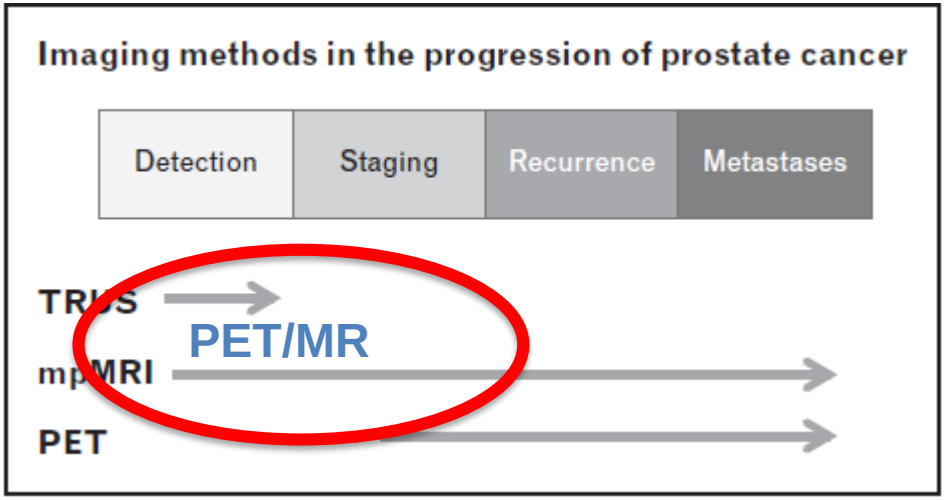
Diagnosis and Staging

Future directions

PET/CT

?

PET/MR

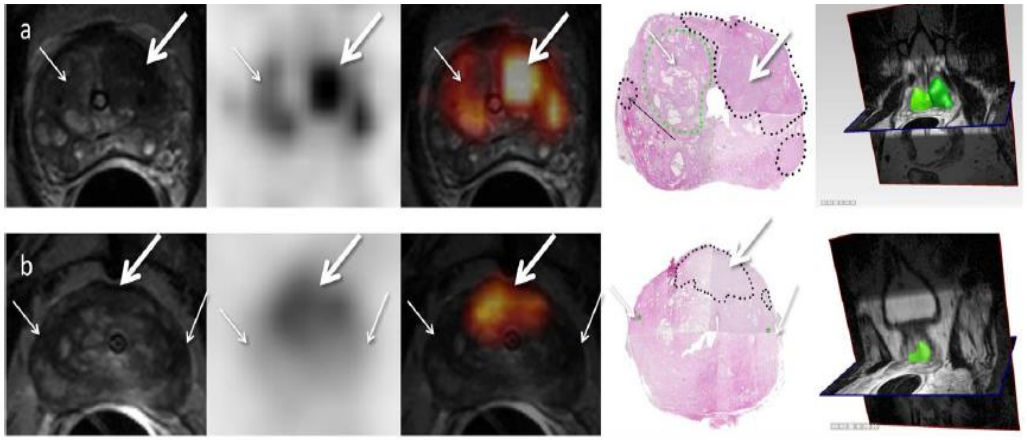


Bouchelouche et al. Curr Opin Oncol, 2015

PET/MRI – Primary Prostate Cancer

N=98 Lesions >5 mm

Modality	Sens (%)	Spec (%)	PPV (%)	NPV (%)	Acc (%)
MR (T2)	67	35	59	44	54
PET (18F-Chol)	85	45	68	69	68
PET/MR	**84**	**80**	**85**	**78**	**82**



Hartenbach et al. Clin Cancer Res., 2014

PET/MRI – Primary Prostate Cancer

Gleason >6 vs <6	Sens	Spec	PPV	NPV	Acc
Biopsy	56	71	60	68	67
PET/MR	**63**	**90**	**83**	**76**	**81**

- **Enhance the success rate of needle biopsies**
- **Potential role in pt selection for active surveillance and watchful waiting**

Hartenbach et al. Clin Cancer Res., 2014

Choline PET – Primary Prostate Cancer

Choline PET

- Not recommended for primary staging
- Not recommended for RT dose painting
- Any attempts should be limited to controlled trials
- Possible role of PET/MRI

Choline PET - N in newly diagnosed PCa

Intermediate and high risk	Sensitivity	Specificity	NPV	PPV	Accuracy
Patient-based analyses	19-60%	95-97%	59-87%	63-90%	75-80%
Region-based analyses	9-41%	99.7%	91-97%	50-94%	NA

Change therapeutical approach in almost 15-20% of pts

Heck et al, Eur J Nucl Med Mol Imaging 2014
Schiavina et al, Eur Urol 2008
Van Der Bergh et al, Urol Oncol 2015

Influence of ^{11}C-choline PET/CT on radiotherapy planning in prostate cancer

Table 3 – Planning modification after ^{11}C-choline PET/CT.[a]

Patient	PET findings	CTV prior to PET	CTV after PET	Dose prescribed prior to PET	Dose prescribed after PET
1	Positive bone metastases	Prostate plus seminal vesicles	Pelvic lymph nodes, seminal vesicles, prostate, pubic bone	66 Gy[b]	70 Gy[c]
2	Negative bone metastases	Pelvic lymph nodes, seminal vesicles, prostate, vertebral bone	Prostate plus proximal seminal vesicles	No RT or 70 Gy[c]	66 Gy[b]
3	Positive lymph nodes	Prostate plus proximal seminal vesicles	Retroperitoneal and pelvis lymph nodes, seminal vesicles, prostate	66 Gy[b]	70 Gy[c] (64.4 Gy, 2.3 Gy to retroperi-toneal positive lymph nodes)
4	Positive lymph nodes	Prostate plus proximal seminal vesicles	Pelvic lymph nodes, seminal vesicles, prostate	66 Gy[b]	70 Gy[c]
5	Positive tumour bed and lymph nodes	Tumour bed	Pelvic lymph nodes, tumour bed	60 Gy[b]	70 Gy[c]
6	Positive tumour bed and lymph nodes	Tumour bed	Pelvic lymph nodes, tumour bed	60 Gy	70 Gy[c]

[a] PET/CT: positron emission tomography/computed tomography.
[b] 3 Gy/fraction.
[c] 2.5 Gy/fraction.

Lopez et al. Rep Pract Onc Radiot, 2015

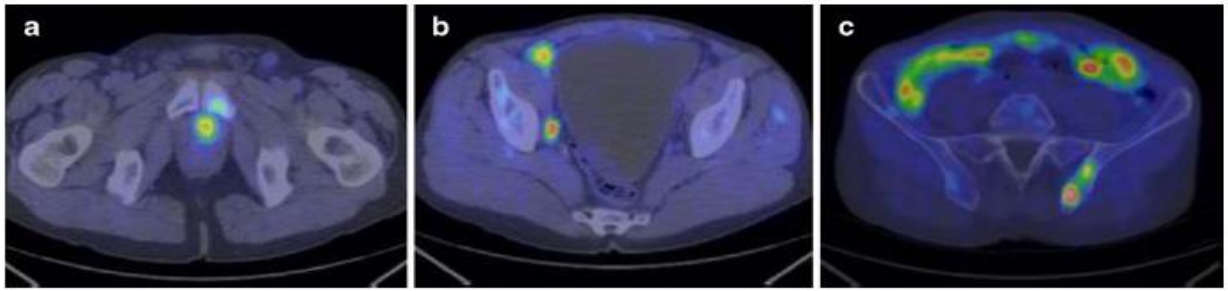
Choline PET/CT in Radiation Treatment Planning

- Primary Treatment: detection of intraprostatic lesions (Diagnosis) and patient selection for treatment (Staging)

- **Treatment of Relapse**: detection of recurrences (Restaging) and treatment monitoring

Choline PET – Recurrent disease

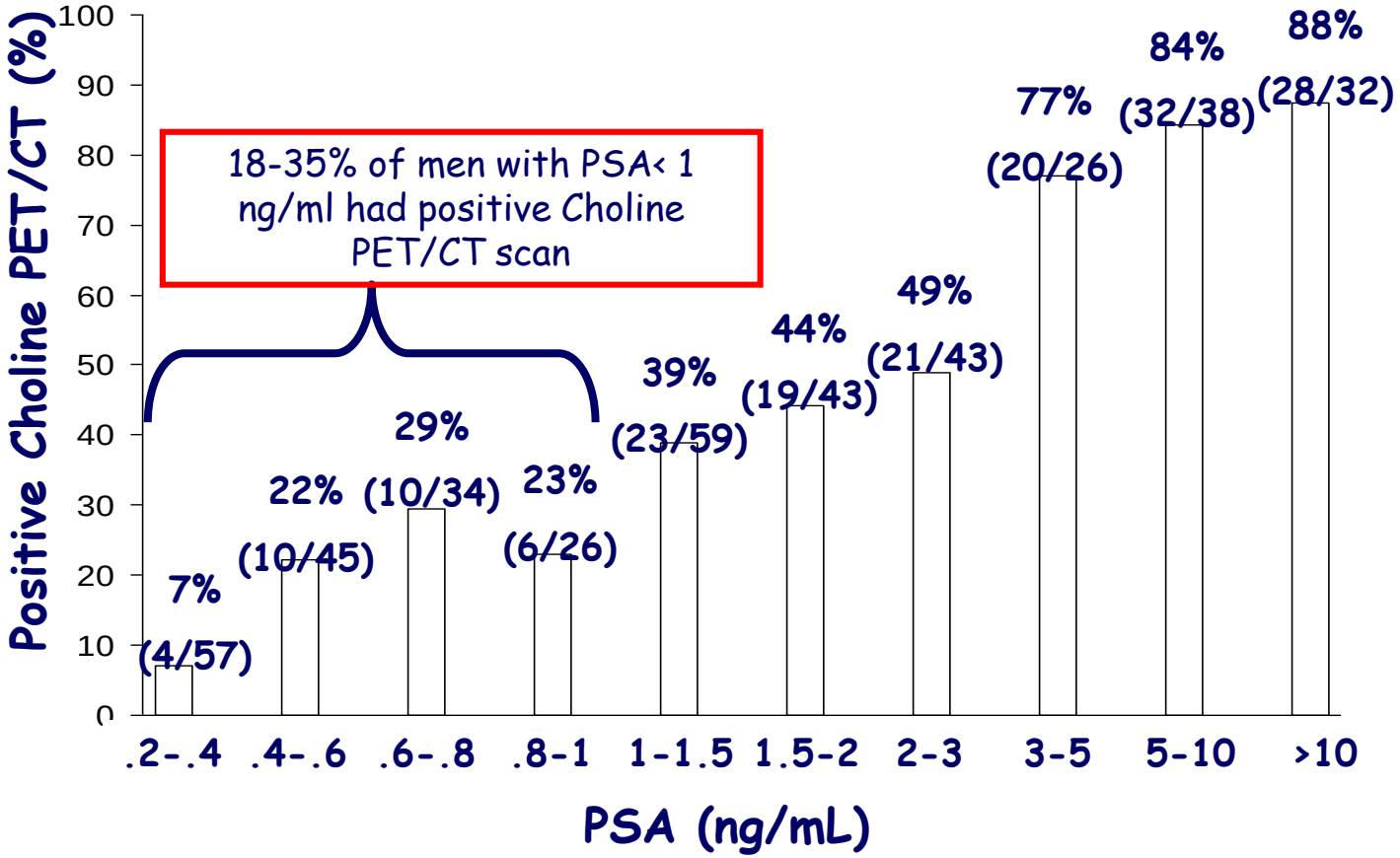
	Patient-based analyses 12 studies, 1055 pts
Sensitivity	85% (95% CI, 89-89%)
Specificity	88% (95% CI, 73-95%)



Umbehr et al, Eur Urol, 2013

Giovacchini et al, EJNMMI, 2010

Choline PET – PSA Dependency



Giovacchini et al. Eur J Nucl Med Mol Imaging, 2010

Picchio et al. Eur Urol, 2011

Choline PET – PSA Dependency

IS IT POSSIBLE TO SOLVE THIS ISSUE?

The best predictors of positive imaging at low PSA level (<1/1.5 ng/ml) are PSA kinetics (PSA doubling time)

	Imaging approach	Patient population	Detection rates
Castellucci et al	11C-choline PET/CT	PSA<1.5 ng/ml	Overall: 28% PSA DT <7 months: 58%
Giovacchini et al	11C-choline PET/CT	PSA<1.5 ng/ml (n=75)	Overall 21% PSADT<6 months: 50%

Castellucci et al, Eur J Nucl Med Mol Imaging, 2011

Giovacchini et al, J Urol, 2013

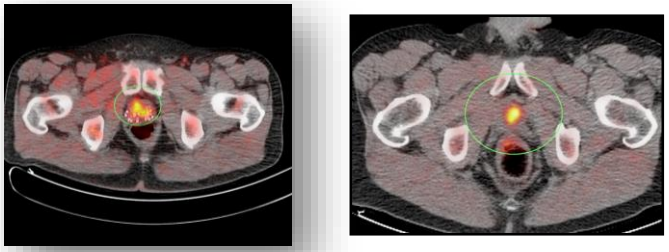
Castellucci and Picchio, Eur J Nucl Med Mol Imaging, 2013

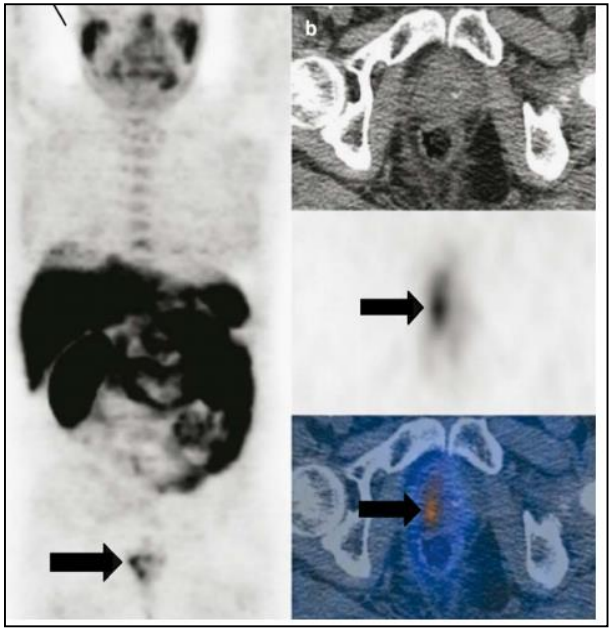
Evangelista L. Clin Nuc Med., 2013

Choline PET – Local Recurrence

	Prostatic Fossa Relapse
	Pooled Value (95% CI)
Sensitivity	75.4% (66.9–82.6)
Specificity	82.0% (68.6–91.4)
Positive likelihood ratio	2.35 (1.03–5.39)
Negative likelihood ratio	0.44 (0.26–0.74)
Diagnostic odds ratio	5.86 (1.81–18.94)

Evangelista et al. Clin Nuc Med, 2013





Husarik et al. EJNMMI, 2008

Main limitations:
- microscopic diseases (beyond spatial resolution)
- inflammatory uptake in the prostatic site

Choline PET/CT in Radiation Treatment of local recurrence

60 pts with biochemical progression after radical prostatectomy. Median PSA before RT: 0.9 ng/mL

High-dose salvage radiation therapy delivered up to total dose of 80Gy to choline PET/CT-positive area.

Mean follow-up: 31.2 months, 76.6% pts free of recurrence.

3-year biochemical progression-free survival rate: 72.5%.

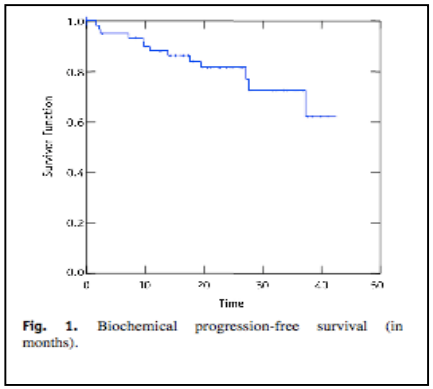


Fig. 1. Biochemical progression-free survival (in months).

18F-choline PET/CT-driven high-dose salvage radiation therapy seems to be feasible and well tolerated, with a low rate of toxicity.

D'angelillo et al. Int J Rad Onc, 2014

Choline PET – N Recurrence

Table 1 Comparison of PET/CT reliability based on the results from different authors

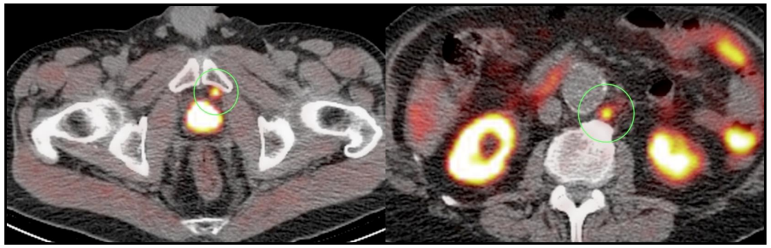
	Sensitivity	Specificity	PPV	NPV
(Farsad et al. 2005)	66.0%	81.0%	87.0%	55.0%
(Castellucci et al. 2011)	93.0%	74.0%	60.0%	96.0%
(Schiavina et al. 2008)	41.4%	99.8%	94.4%	97.2%
(Budiharto et al. 2011)	9.4%	99.7%	75.0%	91.0%
(Kjölhede et al. 2013)	33.0%	92.0%	76.0%	65.0%

Osmonov et al. Springerplus, 2014

Choline PET – N Recurrence

11C-Choline PET/CT After RP – lesion based analysis

	Lymph node metastases
Sensitivity	40-64%
Specificity	90-96%
PPV	75-86%
NPV	72-83%
Accuracy	72-82%
MEDIAN PSA: 1.9-6 ng/ml	



Scattoni et al, Eur Urol, 2007

Scattoni et al, Eur Urol, 2007

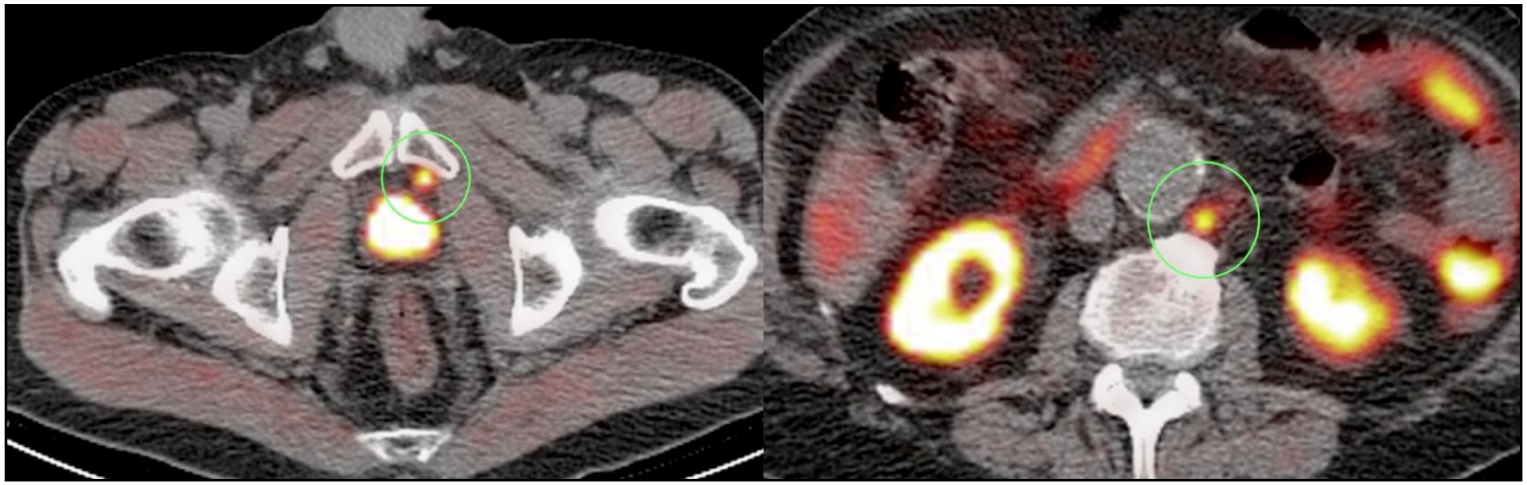
Hovels et al, Clin Radiol, 2008

Picchio et al, Eur J Nucl Med Mol Imaging, 2012

Evangelista et al, Clin Nucl Med, 2013

Tilki et al, Eur Urol, 2013

Regional recurrence in lymph nodes



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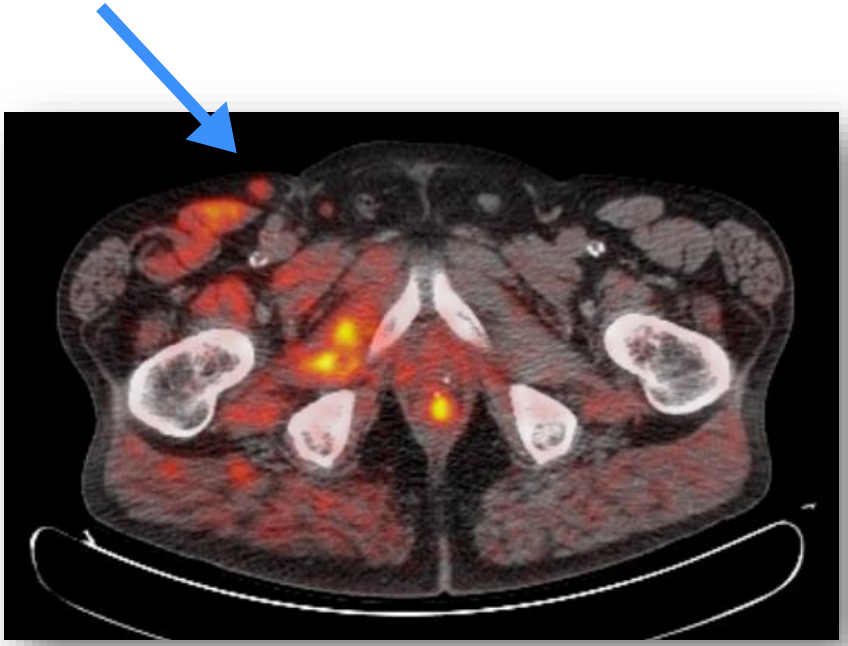
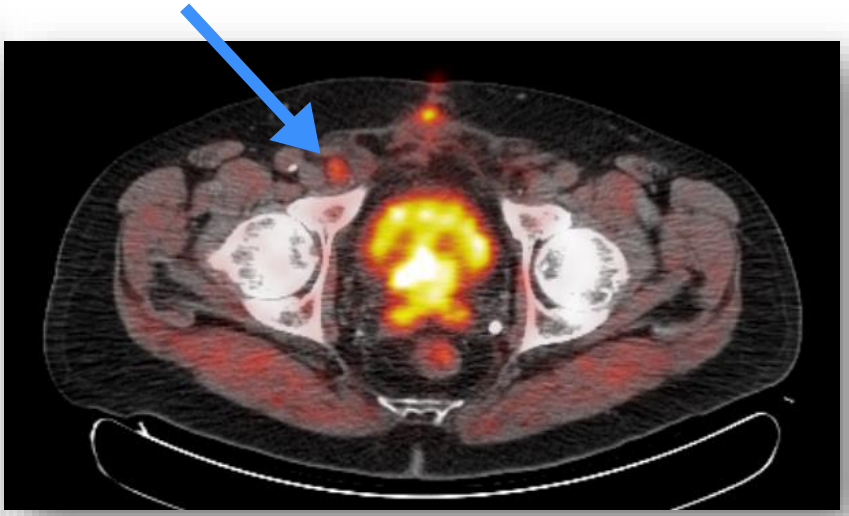
Reactive lymph nodes





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FP

Choline PET: Utility of Imaging after Primary treatment

EAU guidelines: imaging studies such as 11C-choline PET/CT should only be performed if therapeutic consequences such as salvage LND/RT or RP are considered

Choline PET/CT: MDT

Study	No. of patients	Site of metastasis: node/bone/visceral	Median PSA at time of metastasis	Staging method	Type of MDT	Median follow-up, mo	Median PFS
Casamassima et al. [23]	25	25/0/0	5.65	Choline PET/CT	SBRT	29	24 mo
Muacevic et al. [24]	40	0/40/0	5.4	Choline PET/CT	SBRT	14*	NR
Würschmidt et al. [25]	15	15/0/0	1.79	Choline PET/CT	NRT	28	Median not reached: 3-yr PFS: 75%
Ahmed et al. [26]	17	1/15/1	2.1	Choline PET/CT ($n = 9$), MRI ($n = 6$), CT ($n = 1$), and biopsy ($n = 1$)	SBRT	6	12 mo
Jereczek-Fossa et al. [27]	19	18/1/0	1.77 (pelvic nodes); 10.7 (M1)	Choline PET/CT	SBRT	17	Median not reache 30-mo PFS: 63.5%
Schick et al. [28]	50	33/15/2	6.7	Choline PET/CT and bone scintigraphy	SBRT ($n = 14$) NRT ($n = 36$)	31	Median not reache 3-yr PFS: 58.6%
Decaestecker et al. [29]	50	27/22/1	3.8	Choline ($n = 18$) or FDG ($n = 32$) PET/CT	SBRT	25	19 mo
Picchio et al. [30]	83	83/0/0	2.6	Choline PET/CT	HRT	22	NR
Rinnab et al. [31]	15	15/0/0	1.98	Choline PET/CT	LND	13.7*	NR
Schilling et al. [32]	10	10/0/0	8.75	Choline PET/CT	LND	11*	NR
Winter et al. [33]	6	6/0/0	2.04	Choline PET/CT	LND	24 mo	NR
Busch et al. [37]	6	6/0/0	37.6*	Choline ($n = 3$), MRI ($n = 1$), CT ($n = 2$)	LND	NR	15.5 mo
Jilg et al. [34]	47	47/0/0	11.1*	Choline PET/CT	LND	35.5	27 mo**
Martini et al. [35]	8	8/0/0	1.62	Choline PET/CT	LND	NR	NR
Suardi et al. [36]	59	59/0/0	2.0	Choline PET/CT	LND	76.6	60 mo**

Ost et al. Eur Urol., 2014

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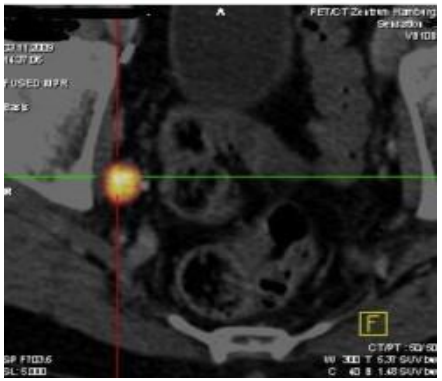
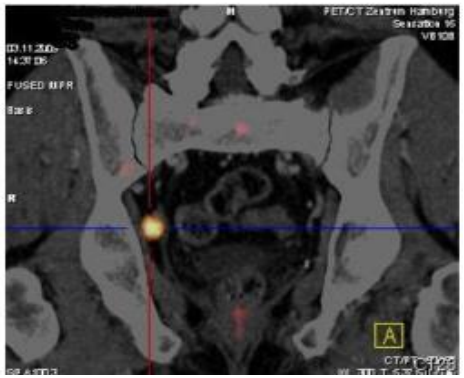
Metastases directed therapy (MDT: Surgery/RT)

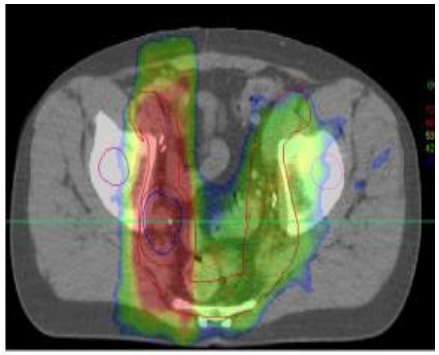
- Reduce toxicity of systemic therapies
- Randomized trails are necessary
- PFS 1-3 yrs in half of pts after treatment

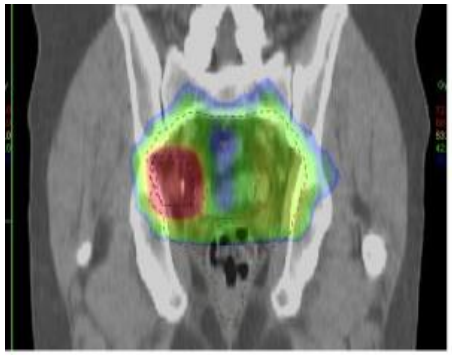
Ost et al. Eur Urol., 2014

PET/CT as guide for MDT









Wurschmidt et al. Radiation Oncology, 2011

19 Pts with recurrent PC

(median PSA: 1.9 ng/ml, range 0.42 - 65)

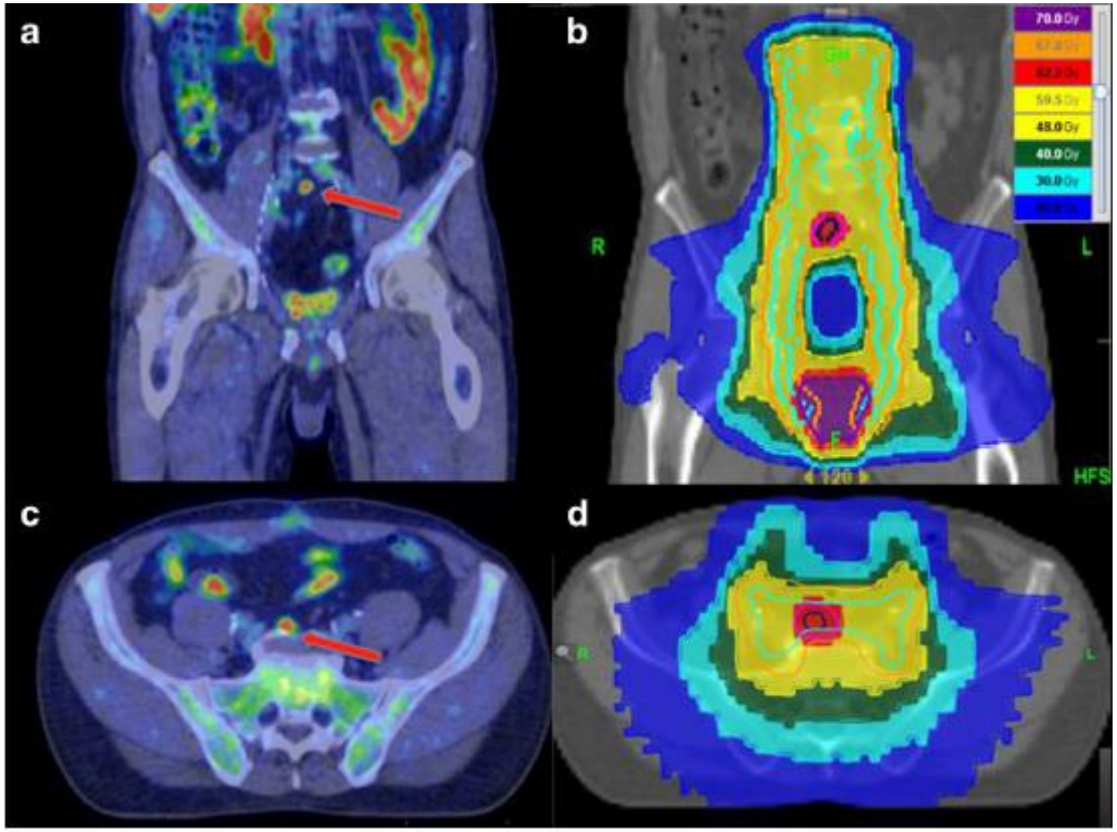
Chol+ at Right Obturatoria LN (SUVmax: 6.0)

IMRT (45 Gy) on pelvic LN

Boost dose (66.6 Gy) on positive LN

- **18F-Choline PET/CT planning could be helpful in dose escalation to lymph nodal sites of prostate cancer**

PET/CT as guide for MDT



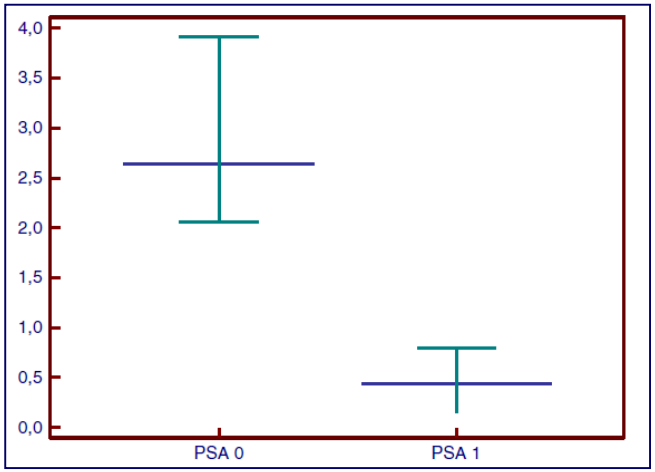
11C-Choline PET/CT is a valuable tool for planning and monitoring HTT in LN relapse after primary treatment.

Well tolerated and associated with a high early biochemical response rate

Picchio et al. EJNMMI, 2014

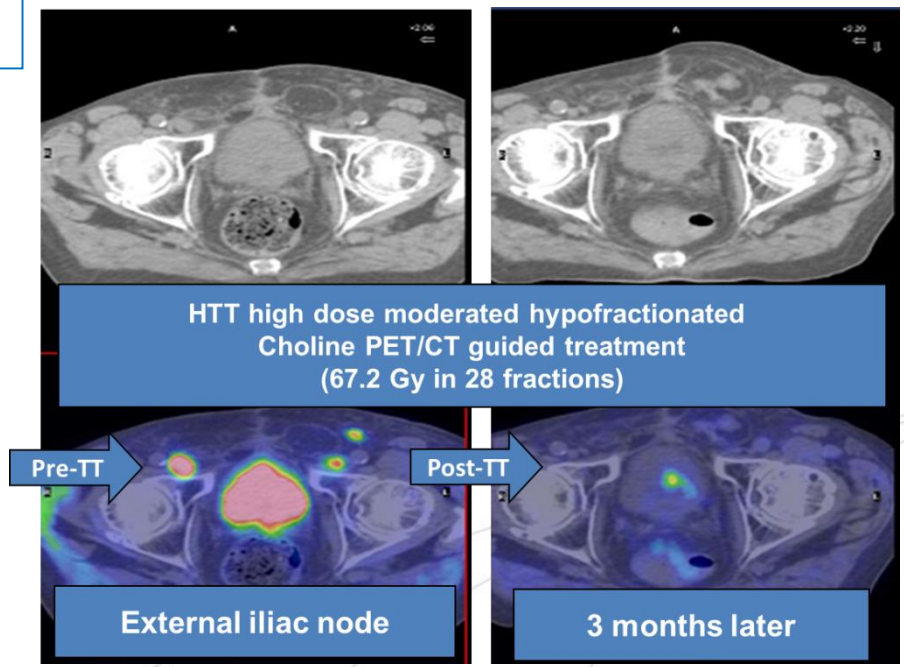
PET/CT to monitor Treatment

Table 3 Biochemical response results (PSA_1 vs. PSA_0)	
Biochemical response	No. (%) of 94 treatments
Complete response	66 (70.2)
Partial response	12 (12.8)
Stable disease	1 (1.0)
Progression of disease	15 (16.0)



PSA_0 and PSA_1 ($p<0.0001$)

83 prostatectomized Pca pts
PSA: 7.6 ng/ml
HTT with SIB of Choline positive LNs



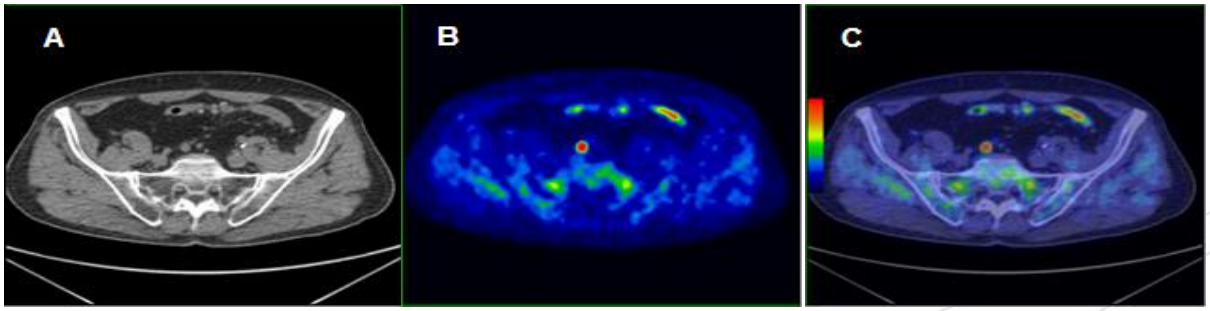
Picchio et al. EJNMMI, 2014

Radiation Treatment of Lymph Node Recurrence from Prostate Cancer: Is ^{11}C-Choline PET/CT Predictive of Survival Outcomes?

Elena Incerti[1], Andrei Fodor[2], Paola Mapelli[1], Claudio Fiorino[3], Pierpaolo Alongi[1], Margarita Kirienko[4], Giampiero Giovacchini[5], Elena Busnardo[1], Luigi Gianolli[1], Nadia Di Muzio[2], and Maria Picchio[1]

Choline-PET/CT-guided HTT - 68 PCa pts with biochemical recurrence after primary treatment (median PSA: 2.42 ng/ml)

MTV60>0.64 and extra-pelvic disease are independently correlated with cRFS (MTV60> 0.64: HR= 4.1, *p*: 0.010 and extra-pelvic disease: HR= 7.3, *p*: 0.0005)

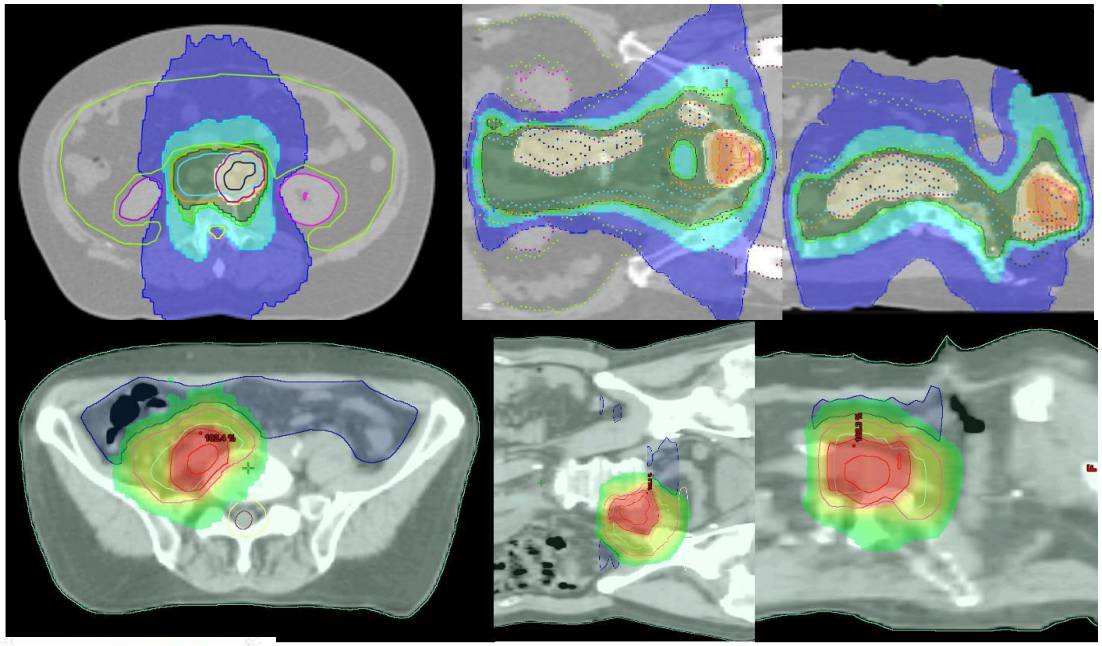


JNM, 2015 – Alavi-Mandell Award 2016

Choline PET/CT for RT of Recurrence PCa

81 recurrence patients after surgery±RT.

The 3 year overall, local-relapse-free and clinical-relapse-free survival were 80.0%, 89.8% and 61.8%, respectively.



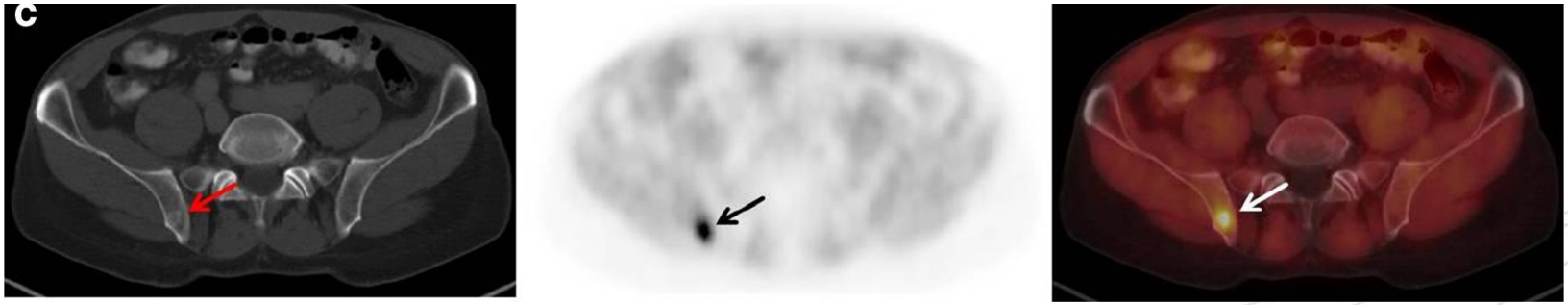
Toxicity	Small bowel	Rectal	Genito-urinary
G1	31.7% (25/79)	22.8% (18/79)	6.4% (5/79)
G2	2.5% (2/79)	3.8% (3/79)	3.8% (3/79)
G3	0	0	2.5% (2/79)

11C-Ch-PET/CT-guided HTT is safe and effective in the treatment of LN relapses of previously treated prostate cancer patients.

Fodor et al, BJU International, 2016

Choline PET – Bone Recurrence

	Sensitivity	Specificity
Fuccio et al. Ann Nucl med 2010	86%	100%
Picchio et al. EJNMMI 2012	89%	98%
Langsteger et al. QJNMMI 2011	90%	96%



Ceci et al, Eur J Nucl Med Mol Imaging, 2014

SBRT to oligometastatic bone metastasis

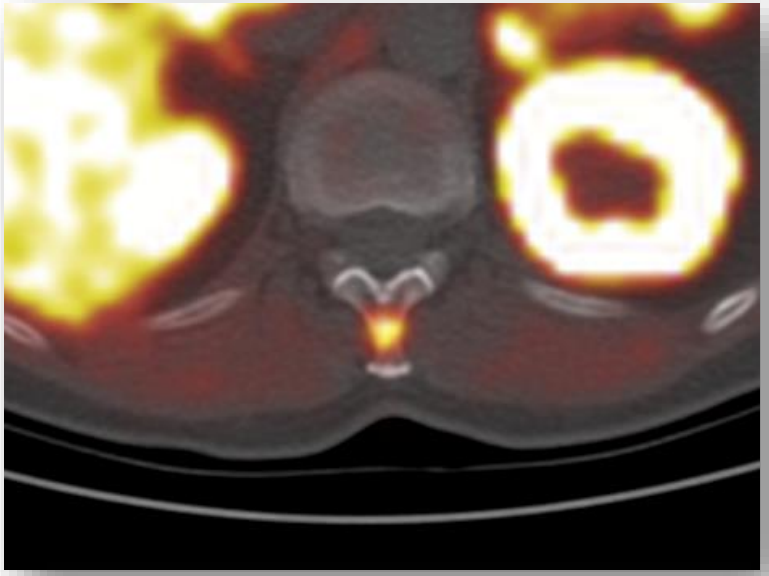
Methods

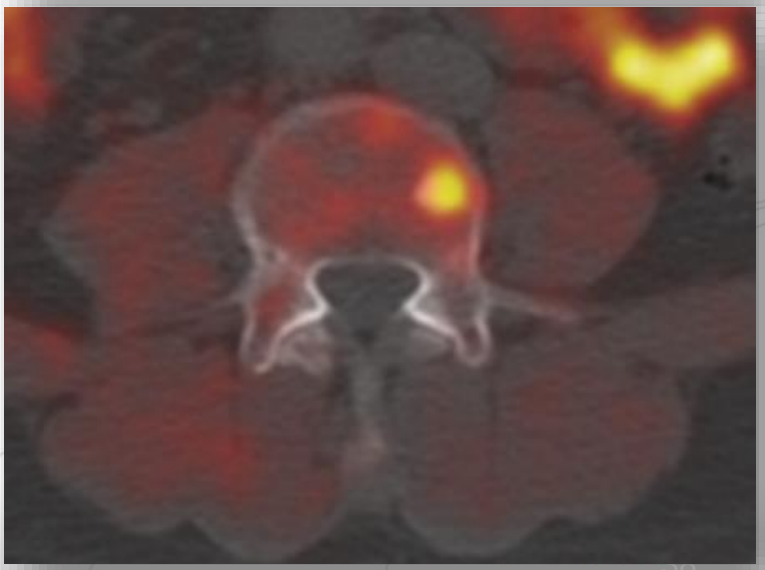
- 40 patients, 64 lesions
- SBRT 1x20Gy to PET lesion
- Follow-up 14 months

Results

- Local control 95%
- PSA reduction average 50%

Muacevic A et al., Urol Oncol., 2011





[^{11}C]Choline PET/CT Impacts Treatment Decision Making in Patients With Prostate Cancer Referred for Radiotherapy

Barbara Alicja Jereczek-Fossa,[1,6] Marcello Rodari,[4] Maria Bonora,[1,6] Paola Fanti,[1,6] Cristiana Fodor,[1] Giovanna Pepe,[4] Egesta Lopci,[4] Dario Zerini,[1] Barbara Vischioni,[3] Guido Baroni,[3,5] Deliu Victor Matei,[2] Ottavio De Cobelli,[2,6] Arturo Chiti,[4] Roberto Orecchia[1,3,6]

74 Pca pts referred for first radiotherapy (primary or recurrent tumor)

Cho-PET/CT changed the treatment approach in 27% of cases compared with standard treatment that would have been adopted without cho-PET/CT.

Cho-PET/CT is valuable in defining the extent of disease and supporting therapeutic decisions in the management of prostate cancer.

Clinical Genitourinary Cancer, Vol. 12, No. 3, 155-9 © 2014

Prostate cancer
Choline PET- Radiation therapy
Conclusions

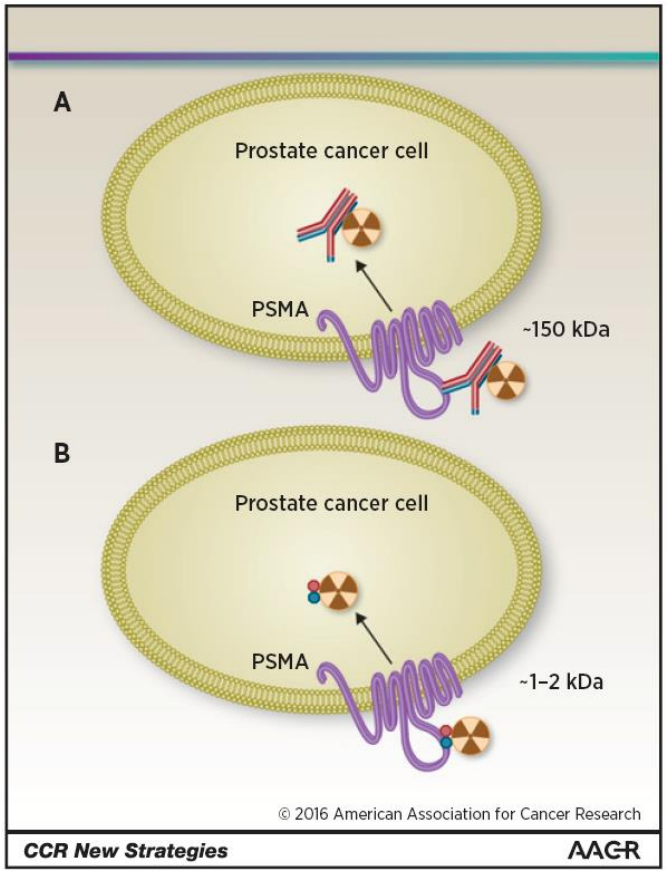
Primary Treatment:

- Limited role→ possible improvement with PET/MRI

Treatment of Relapse:

- Accurate for N and M → Role in guiding and monitoring MDT
- Predictive role

Prostate-Specific Membrane Antigen (PSMA)



- PSMA, also known as **Glutamate carboxypeptidase II**, is a type II transmembrane glycoprotein (Upon ligand binding PSMA is internalized with bound molecules)
- PSMA is expressed in a number of tissues including prostate, kidney, and both the central and peripheral nervous systems.
- PSMA is an established cancer marker. In particular, it is upregulated in prostate cancer and has proven to be an effective diagnostic and prognostic indicator of cancer.
- Ideal for developing targeted radiopharmaceuticals (fast blood clearance and low background activity)

Prostate-specific membrane antigen (PSMA)

- 68Ga-labelled PET tracer Glu-NH-CO-NH-Lys-(Ahx)-[[68Ga]Ga(HBED-CC)] ([68Ga]Ga-**PSMA-HBED-CC**) is the isoform most diffuse for PET/CT Imaging

- PSMA PET/CT presents a detection rate higher than Choline PET/CT for Pca and its M+

- PSMA is **not related to PSA**, but it is a biomarker of the in vivo expression of Glutamate carboxypeptidase II

- PSMA is **NOT a Pca specific Biomarker**

PSMA PET/CT guidelines

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-017-3670-z

GUIDELINES

^{68}Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0

Wolfgang P. Fendler[1,2] · Matthias Eiber[1,3] · Mohsen Beheshti[4] · Jamshed Bomanji[5] · Francesco Ceci[6] · Steven Cho[7] · Frederik Giesel[8] · Uwe Haberkorn[8] · Thomas A. Hope[9] · Klaus Kopka[10] · Bernd J. Krause[11] · Felix M. Mottaghy[12,13] · Heiko Schöder[14] · John Sunderland[15] · Simon Wan[5] · Hans-Jürgen Wester[16] · Stefano Fanti[6] · Ken Herrmann[1,17]

68Ga PSMA-HBED-CC
Normal biodistribution

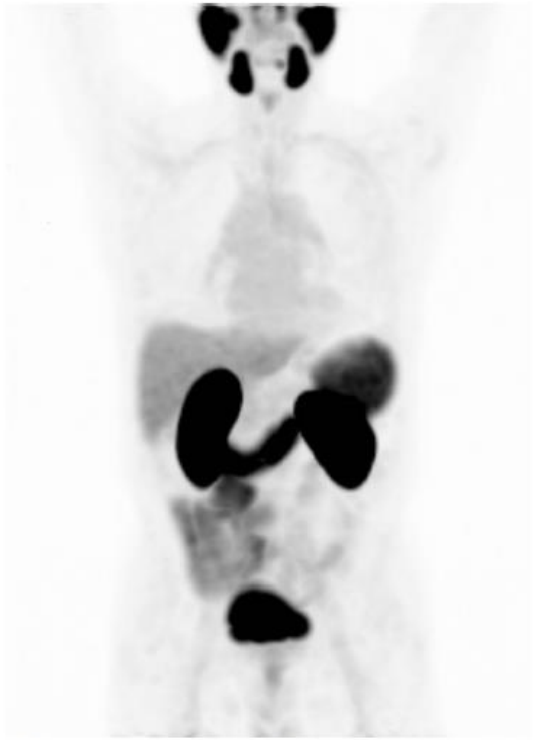


Fig. 2 Normal body distribution of ^{68}Ga-PSMA-11. Maximum intensity projection of a 78-year-old male patient after injection of 217 MBq ^{68}Ga-PSMA-11

- Parotis and salivary glands
- Spleen
- Liver
- Kidneys
- Duodenum
- Bladder

Fendler et al. EJNMMI 2017

PSMA PET/CT - Indications

- Localisation of tumor tissue in recurrent Pca

- Primary staging in high-risk disease before surgical procedures or planning external beam radiation

Fendler et al. EJNMMI 2017

PSMA PET/CT - Indications

- **Localisation of tumor tissue in recurrent Pca**

- Primary staging in high-risk disease before surgical procedures or planning external beam radiation

Fendler et al. EJNMMI 2017

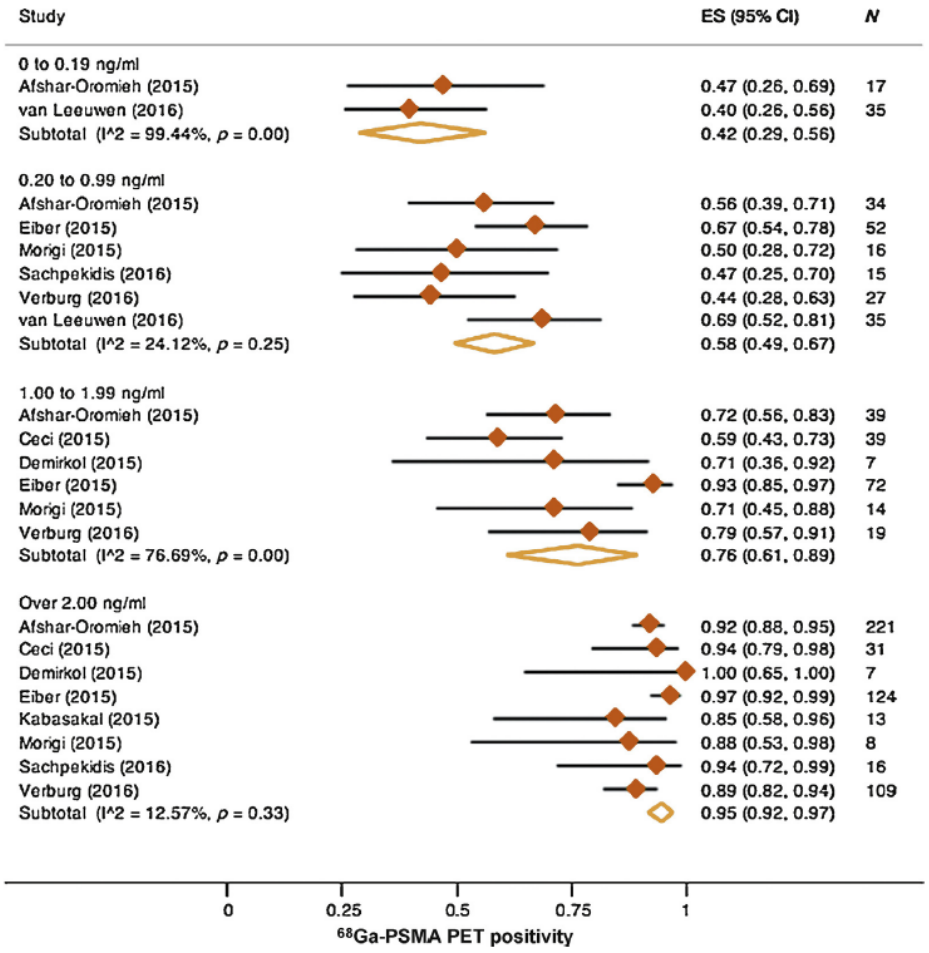
PSMA PET/CT - Indications

Localization of tumour tissue in recurrent prostate cancer

Most studies, mainly retrospective data, are available on the use of ^{68}Ga-PSMA PET/CT for localization of prostate cancer in the setting of biochemical recurrence [8, 9, 15–21]. Here, the use is especially recommended in patients with low PSA values between 0.2 and 10 ng/mL to identify the site of recurrence and to potentially guide salvage therapy. Higher sensitivities are noted in patients with shorter PSA doubling times and those with higher initial Gleason scores [21].

Fendler et al. EJNMMI 2017

PSMA – ReStaging Prostate Cancer

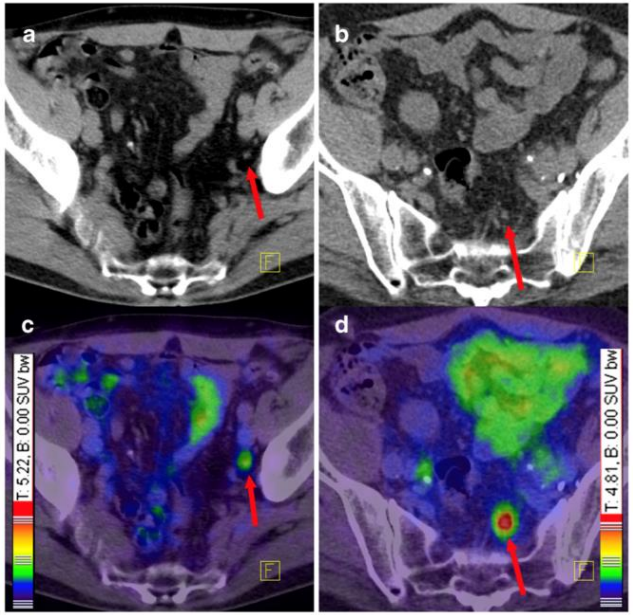


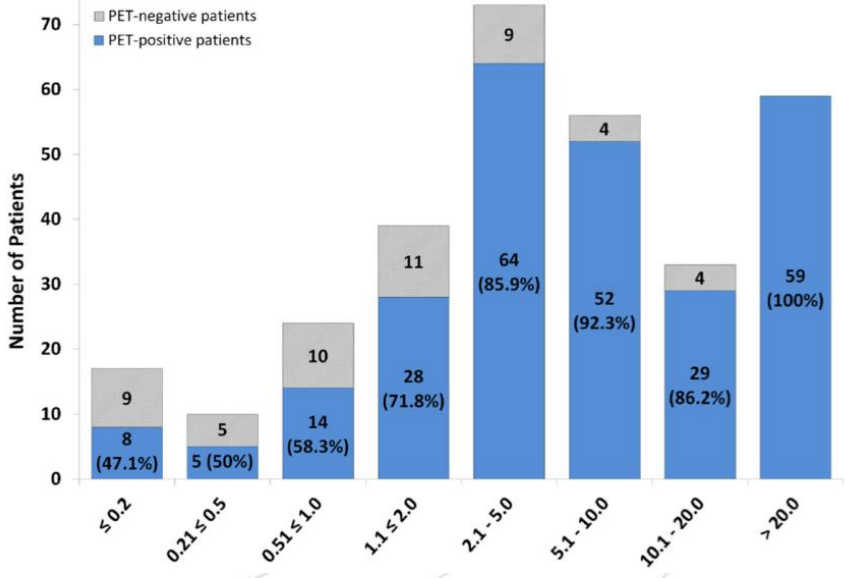
12 studies
736 pts in BCR
DR: 76%

Perera et al. Eur Urol 2016

The diagnostic value of PET/CT imaging with the ^{68}Ga-labelled PSMA ligand HBED-CC in the diagnosis of recurrent prostate cancer

- ✓ Retrospective analysis in **319 patients** who underwent 68Ga-PSMA-ligand PET/CT from 2011 to 2014 for recurrent PCa (90% of the cases after treatment with curative intent)
- ✓ In 82.8% of the patients at least one lesion indicative of PCa was detected





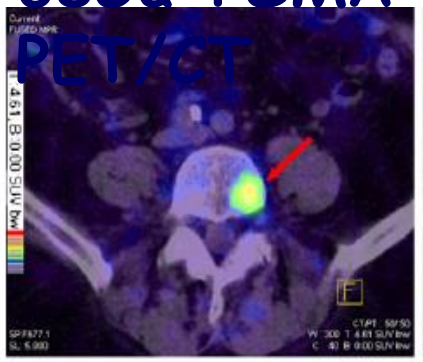
ESNM European School of Nuclear Medicine

ESTRO School

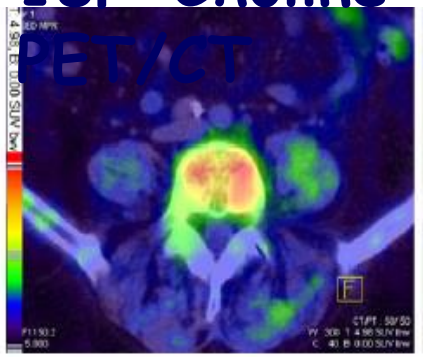
Afshar-Oromieh et al. Eur J Nucl Mol Imaging, 2015

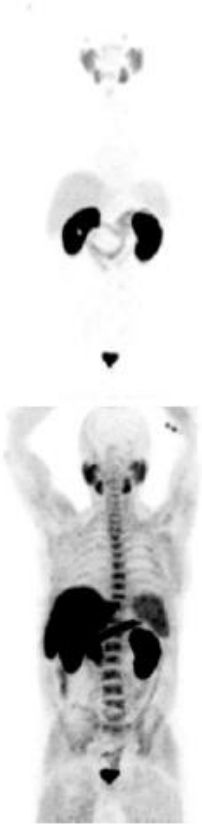
Comparison of PET imaging with a ^{68}Ga-labelled PSMA ligand and ^{18}F-choline-based PET/CT for the diagnosis of recurrent prostate cancer

68Ga-PSMA PET/CT



18F-Choline PET/CT

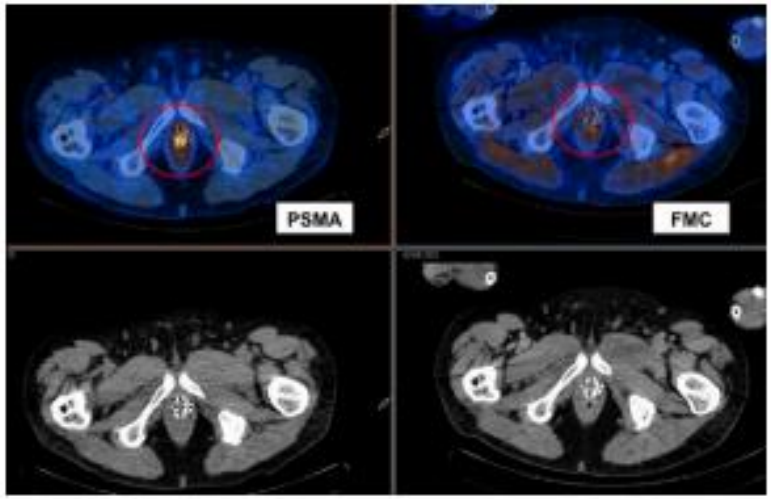




- 37 patients with biochemical relapse of Pca were retrospectively analysed
- 18F-fluoromethylcholine and 68Ga-PSMA PET/CT within a time window of 30 days
- 68Ga-PSMA PET/CT **improved contrast when compared to choline-based PET/CT**

Afshar-Oromieh et al. Eur J Nucl Mol Imaging, 2014

Prospective Comparison of ^{18}F-Fluoromethylcholine Versus ^{68}Ga-PSMA PET/CT in Prostate Cancer Patients Who Have Rising PSA After Curative Treatment and Are Being Considered for Targeted Therapy



38 pts with biochemically recurrent PCa

PSMA detected more lesions

than FCH (59 and 29)

Morigi et al. JNM, 2015

	PSMA PET/CT DR	Choline PET/CT DR
PSA ≤ 0.5 ng/ml	50%	12.5%
PSA 0.5-2.0 ng/ml	69%	31%
PSA > 2.0 ng/ml	86%	57%

PSMA PET/CT - Indications

- Localisation of tumor tissue in recurrent Pca

- **Primary staging in high-risk disease before surgical procedures or planning external beam radiation**

Fendler et al. EJNMMI 2017

Primary staging in high-risk disease before surgical procedures or planning external beam radiation

In patients with high-risk disease (Gleason score >7, PSA >20 ng/mL, clinical stage T2c – 3a) the likelihood of lymph node and bone metastases is increased. Several studies demonstrate the superiority of ^{68}Ga-PSMA PET/CT as compared to CT, magnetic resonance imaging (MRI) or bone scan for detection of metastases for initial staging at primary diagnosis [22–25]. The detection of radiologically occult lymph node metastases can significantly influence patient management, although the impact on overall survival of improved sensitivity by ^{68}Ga-PSMA PET/CT remains unanswered. A contrast-enhanced ^{68}Ga-PSMA PET/CT can replace abdomino-pelvic CT for the detection of lymph node metastases. In addition, preliminary data show that ^{68}Ga-PSMA PET/CT is also more accurate for detection of bone metastases [25]. Nevertheless, for local tumour delineation (if requested by the urological surgeon), pelvic MRI cannot be replaced. It is still under investigation and discussion whether additional functional imaging with bone0seeking agents (e.g. bone scintigraphy, ^{18}F-NaF PET/CT) has relevant additional value after performance of ^{68}Ga-PSMA PET/CT, e.g. in patients with PSMA-negative tumours or densely sclerotic bone lesions.

Fendler et al. EJNMMI 2017

ESTRO School

PSMA – Primary Prostate Cancer

	AUC (95% CI)	Youden-selected threshold	Sensitivity, %, at threshold (95% CI)	Specificity, %, at threshold (95% CI)
mpMRI	0.73[*,†] (0.66–0.80)	4[§]	43 (33–53)	98 (94–100)
		3	58 (49–66)	82 (69–90)
PET	0.83[*,#] (0.78–0.87)	4	64 (56–72)	94 (86–98)
PET/MRI	0.88[#,†] (0.84–0.92)	4	76 (68–82)	97 (90–99)

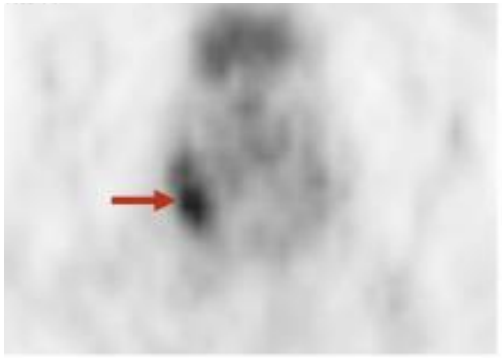
AUC = area under the curve; CI, confidence interval; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PET = positron emission tomography.

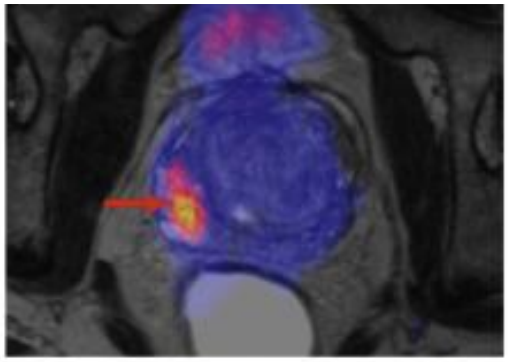
[*] mpMRI versus PET, $p = 0.003$.

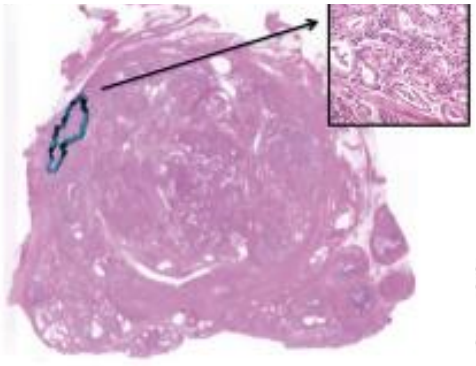
[†] mpMRI versus PET/MRI, $p < 0.001$.

[§] The threshold of 4 for mpMRI is presented to show data with the same threshold for all imaging methods; the threshold of 3 is the calculated optimal cut-off as described in the Material and methods section.

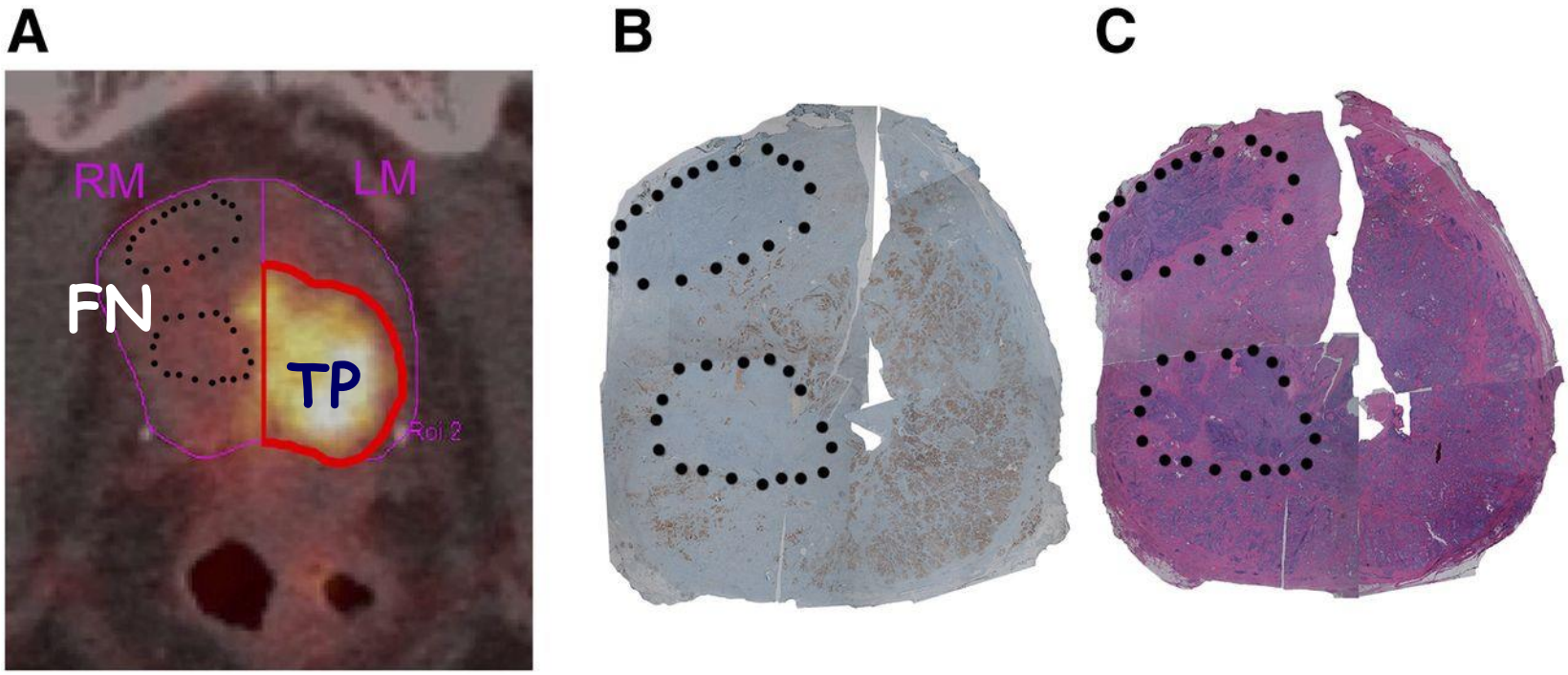
[#] PET versus PET/MRI, $p = 0.002$.







Eiber et al. Eur Urol 2016



False-negative PET finding for acinar adenocarcinoma with partial neuroendocrine differentiation. 68Ga-PSMA PET/CT image (A), PSMA-stained slice (B), and hematoxylin-stained slice (C) for left mid (LM) and right mid (RM) segments are shown. Wolfgang P. Fendler et al. J Nucl Med 2016;57:1720-1725

PSMA – Primary Prostate Cancer

Accuracy of ^{68}Ga-PSMA PET for Detection of Tumor Tissue per Segment

PET result	HP+ (n = 100)	HP− (n = 26)	Accuracy
PET+ (n = 69)	67	2	Positive predictive value, 97%
PET− (n = 57)	33	24	Negative predictive value, 42%
	Sensitivity, 67%	Specificity, 92%	Accuracy, 72%

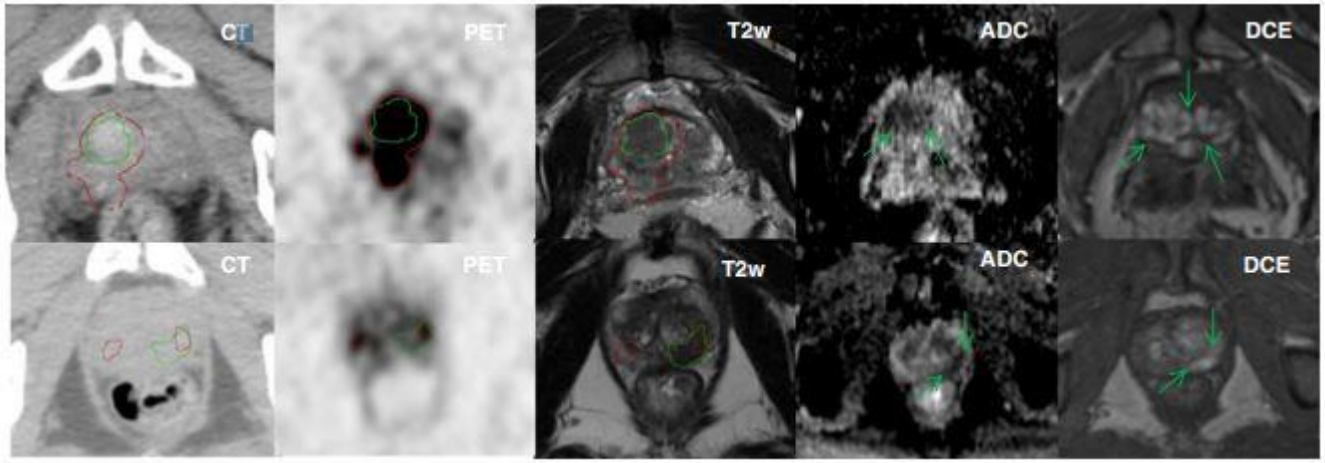
HP = histopathology.
Six segments from 21 patients were analyzed.

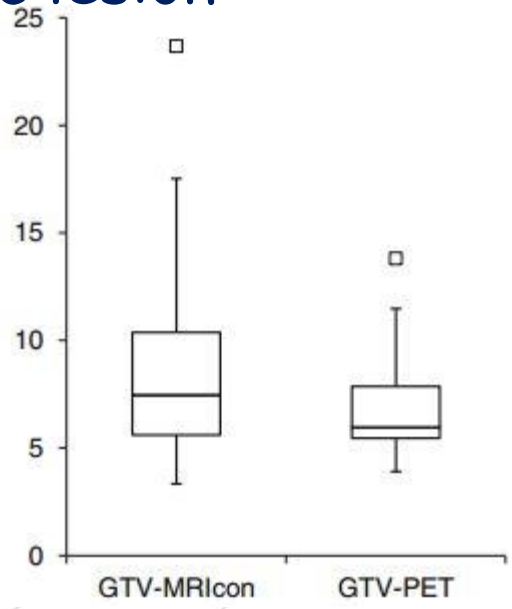
Fendler et al. EJNMMI 2017

PSMA PET and MR – RT primary PCa

22 patients with primary Pca - 68Ga-PSMA PET/CT and mpMRI

GTV-PET was significantly larger than GTV-MRI. 68Ga-PSMA PET/CT may have a role in radiation treatment planning for focal radiation to the dominant intraprostatic lesion





Zamboglou et al. Eur J Nucl Mol Imaging, 2016

PSMA – Staging Prostate Cancer

Table 6 – Guidelines for staging of prostate cancer

Risk group	LE	GR
Any risk group staging		
Do not use CT and TRUS for local staging	2a	A
Low-risk localised PCa		
Do not use additional imaging for staging purposes	2a	A
Intermediate-risk PCa		
Use prostate mpMRI for local staging	2b	A
Perform metastatic screening including at least cross-sectional abdominopelvic imaging and a bone-scan	2a	A

CT = computed tomography; GR = grade of recommendation; LE = level of evidence; mpMRI = multiparametric magnetic resonance imaging; MRI = magnetic resonance imaging; PCa = prostate cancer; TRUS = transrectal ultrasound.

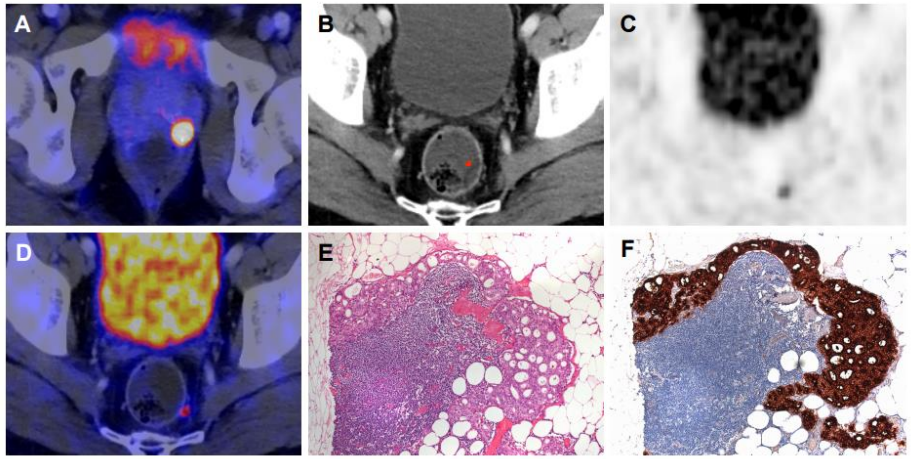
Therefore, choline PET/CT has no place for up-front staging in nodal metastasis. Currently, prostate-specific membrane antigen-PET CT (PSMA PET/CT) remains investigational.

Magnetic resonance imaging sensitivity is low for lymph node metastases and similar [245, 246] or inferior [247] to that of choline PET/CT.

Mottet et al Eur Urol 2017

PSMA PET – Pre-operative LN staging

	Number of patients	Sensitivity	Specificity
Budaus et al	*30 (ePLND)*	*33%*	*100%*
Maurer et al	*130 (ePLND)*	*66%*	*99%*



Budaus L, Eur Urol, 2016
Maurer et al, J Urol, 2016

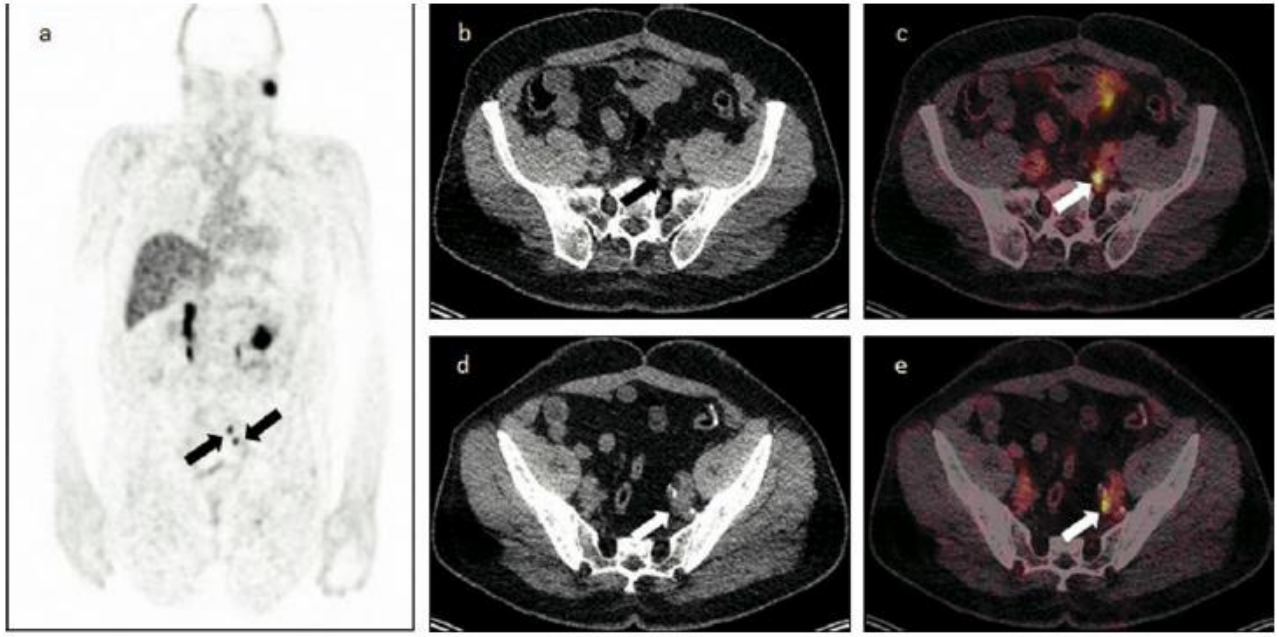
PSMA PET/CT – Emerging Indications

- Staging before and during PSMA-directed radiotherapy (mainly in metastatic castration-resistant prostate cancer)
- Targeted biopsy after previous negative biopsy in patients with high suspicion of prostate cancer
- Monitoring of systemic treatment in metastatic prostate cancer

ANTICANCER RESEARCH *37*: 1273-1280 (2017)
doi:10.21873/anticanres.11444

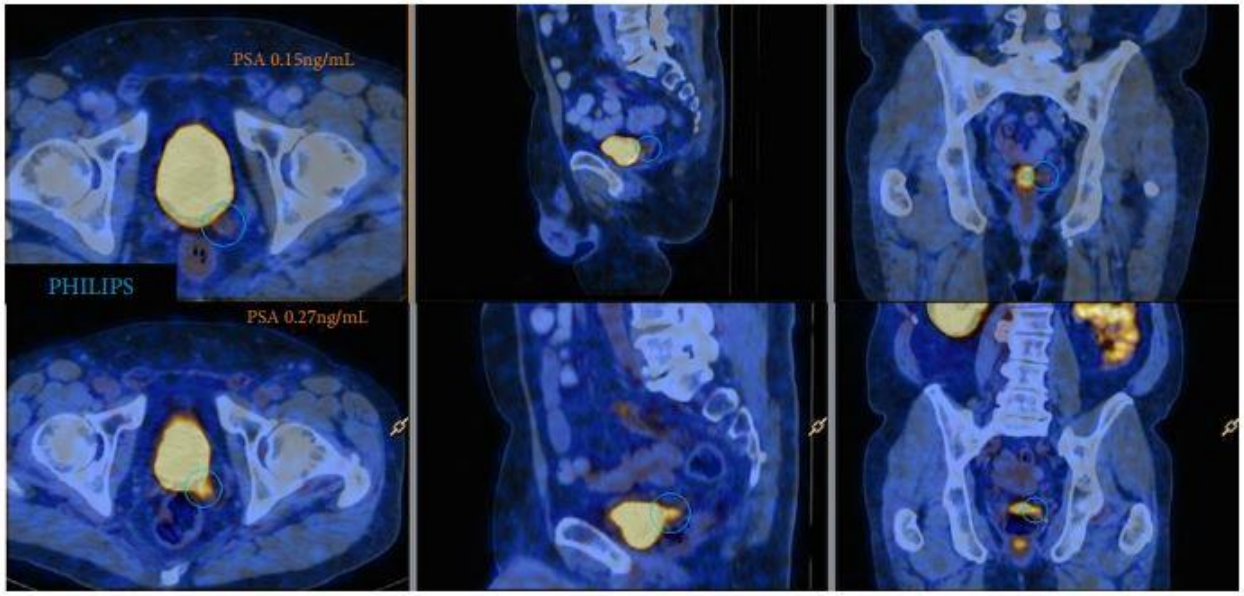
^{68}Ga-PSMA Ligand PET/CT-based Radiotherapy for Lymph Node Relapse of Prostate Cancer After Primary Therapy Delays Initiation of Systemic Therapy

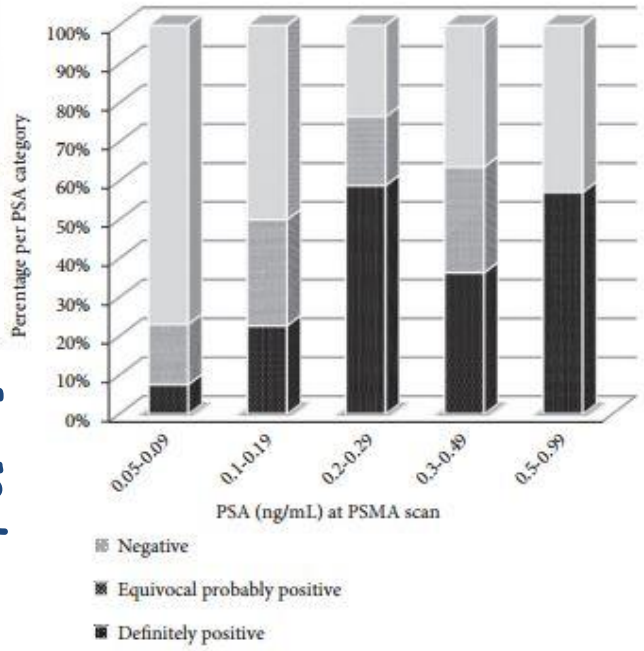
CHRISTOPH HENKENBERENS[1], CHRISTOPH A. VON KLOT[2], TOBIAS L. ROSS[3], FRANK M. BENGEL[3], HANS-JÜRGEN WESTER[4], KATJA HÜPER[5], HANS CHRISTIANSEN[1] and THORSTEN DERLIN[3]



PSMA PET– RT recurrent PCa

300 patients with with biochemical recurrence underwent 68Ga-PSMA-PET/CT, PSA level ≥0.05 and <1.0 ng/mL





68Ga-PSMA appears to be useful for re-staging PCa pts with rising PSA levels who are being considered for salvage RT even at PSA levels <0.5 ng/mL

van Leeuwen et al. BJU international, 2016

PSMA PET– RT PCa

54 Pca referred to PSMA-PET imaging

Table 2 Effect of PSMA PET on disease status outcomes and radiation oncologist decision-making

PSMA vs Conventional scans	PSMA-/CS-	17 (31.5 %)
	PSMA+/CS-	25 (46.3 %)
	PSMA-/CS+	7 (13.0 %)
	PSMA+/CS+	5 (9.3 %)
Change in RT management	No	29 (53.7 %)
	Yes	25 (46.3 %)
Change in ADT management	No	36 (66.7 %)
	Yes	18 (33.3 %)
Any change in management	No	25 (46.3 %)
	Yes	29 (53.7 %)

CS = conventional scans (CT, bone scan, MRI)
- = Negative
+ = Equivocal
RT = radiotherapy
ADT = androgen deprivation therapy

Table 3 Treatment plan before and after PSMA PET

Treatment plan	Pre-PET (%)	Post-PET (%)
Observe	50.0	18.5
Radical radiotherapy (to prostate or prostate bed)	31.5	27.8
Radical radiotherapy including nodes	1.9	0
Palliative radiotherapy to oligometastases	9.3	37.0
Systemic therapy alone	7.4	16.7

PSMA PET changed RT management in 46% of cases with an overall change in decision-making in 54% of pts.

Shakespeare TP. Radiat Oncol., 2015

Prostate Cancer
PSMA PET-Conclusions

- Promising role for staging and re-staging of PCa patients even with low PSA level
- Potential role to guide RT (primary and recurrent disease)
- Potential role for decision-making of radiation oncologists
- PET/MRI as new promising imaging tool

FDG PET/CT for response evaluation in radiation oncology

Wouter Vogel
NKI-AVL, Amsterdam

May 2016, Lisbon
Course on Molecular Imaging and Radiation Oncology

Contents

- Baseline **response prediction**
- On treatment **response monitoring**
- After treatment **response evaluation**

Response prediction

(before treatment)

Relevance

Treatment selection and optimization

- Curative intent treatment?
- Chemoradiotherapy?
- Dose escalation?
- Hyperfractionation?
- Hypoxia modulation?

Available parameters

- Anatomical tumor size / volume
- SUV-max / SUV-peak
- PET-derived volumes (visual, threshold, adaptive,…)
  - Volume
  - SUV-mean
  - Total metabolic volume

Retrospective analyses – Head-neck

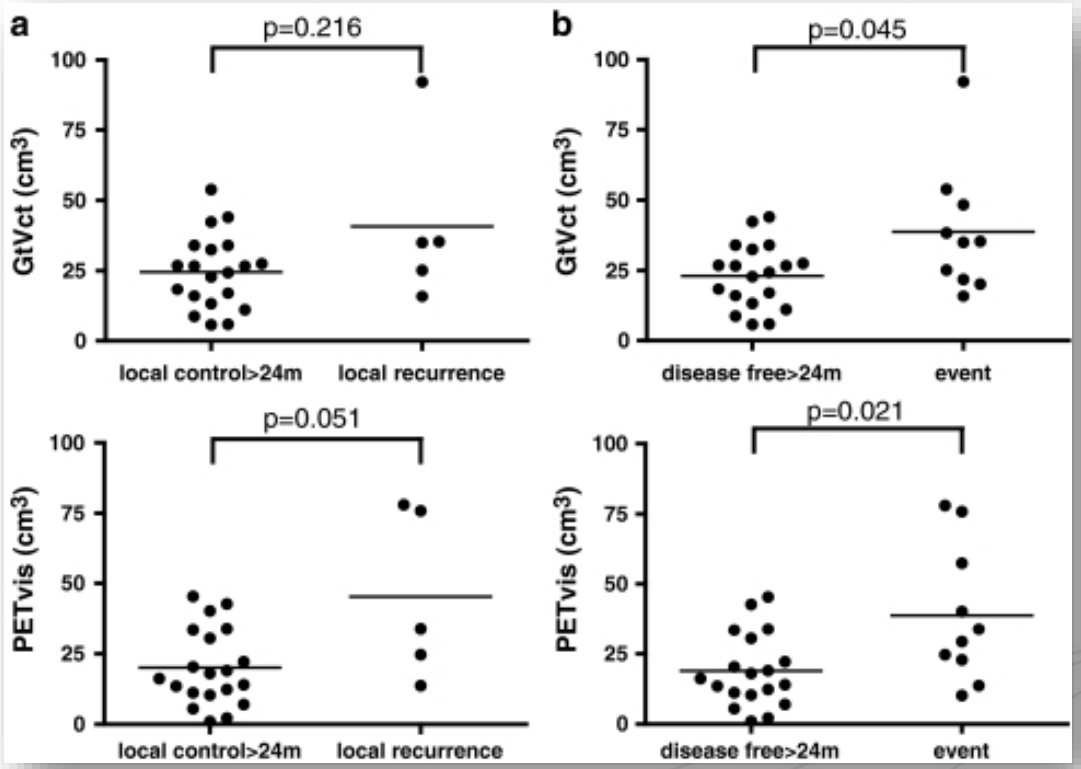
- Meta-analysis, 15 studies, 88 patients

Reference	No. of patients	Tumour site	Variable	Prediction	Treatment results
21	41	Nasopharynx (n = 41)	SUV_{MAX} primary tumour and/or metastatic lymph node	DFS worse when SUV_{MAX} >8.0	3 years DFS 74.3%
22	60[a]	Oral cavity/oropharynx (n = 44) Hypopharynx/Larynx (n = 16)	SUV_{MAX} primary tumour and/or metastatic lymph node	DFS and OS worse when SUV_{MAX} ≥9.0	If SUV_{MAX} ≥9.0 then 2 years DFS 37%; if <9.0 then 2 years DFS 76%
30	45	Nasopharynx (n = 16) Oropharynx (n = 20) Hypopharynx (n = 3) Others (n = 6)	SUV_{MAX} primary tumour	DFS not correlated with SUV_{MAX}	If SUV_{MAX} ≥5.5 then 2 years DFS 48%; if <5.5 then 2 years DFS 76%
19	47	Nasopharynx (n = 6) Oral cavity/oropharynx (n = 30) Hypopharynx/larynx (n = 10) Maxilla (n = 1)	SUV_{MAX} primary tumour	DFS and OS worse when SUV_{MAX} >9.0	LC 78% ('during follow-up time')
25	54[b]	Oral cavity/oropharynx (n = 34) Hypopharynx/larynx (n = 20)	SUV_{MAX} primary tumour	LC and DFS worse when SUV_{MAX} ≥9.0	If SUV_{MAX} ≥9.0 then 2 years LC 73%; <9.0 then 2 years LC 96%; ≥9.0 then 2 years DFS 69%; <9.0 then 2 years DFS 93%
1	120[c]	Oral cavity/oropharynx (n = 78) Hypopharynx/larynx	SUV_{MAX} primary tumour or metastatic lymph node	LC and DFS worse when SUV_{MAX} >4.8	4 years LC 75%; 4 years DFS 59%

Prospective study – Head-neck

Tumor volume and FDG uptake both have some value

- 77 patients
- Oral cavity
- Hypopharynx



Eur J Nucl Med Mol Imaging. 2011 Aug;38(8):1449-58. doi: 10.1007/s00259-011-1789-x. Epub 2011 Apr 2.
Can FDG PET predict radiation treatment outcome in head and neck cancer? Results of a prospective study.
Schinagl DA1, Span PN, Oyen WJ, Kaanders JH.

Prospective study – Head-neck

- SUV-max and SUV-mean had no predictive value
- No parameters with value in hypopharynx / larynx

Oral cavity / oropharynx:

Outcome	GTV_{CT}	PET_{VIS}	$PET_{40\%}$	$PET_{50\%}$	PET_{SBR}	$iSUV_{VIS}$	$iSUV_{40\%}$	$iSUV_{50\%}$	$iSUV_{SBR}$
LC	>0.1	0.031	>0.1	>0.1	>0.1	0.021	0.025	0.039	0.033
RRFS	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1
DMFS	0.003	0.046	0.080	0.064	>0.1	0.055	0.023	0.023	0.024
DFS	0.024	0.016	>0.1	>0.1	>0.1	0.033	0.041	0.054	0.051
OS	0.018	0.023	>0.1	>0.1	>0.1	0.026	0.038	0.052	0.040

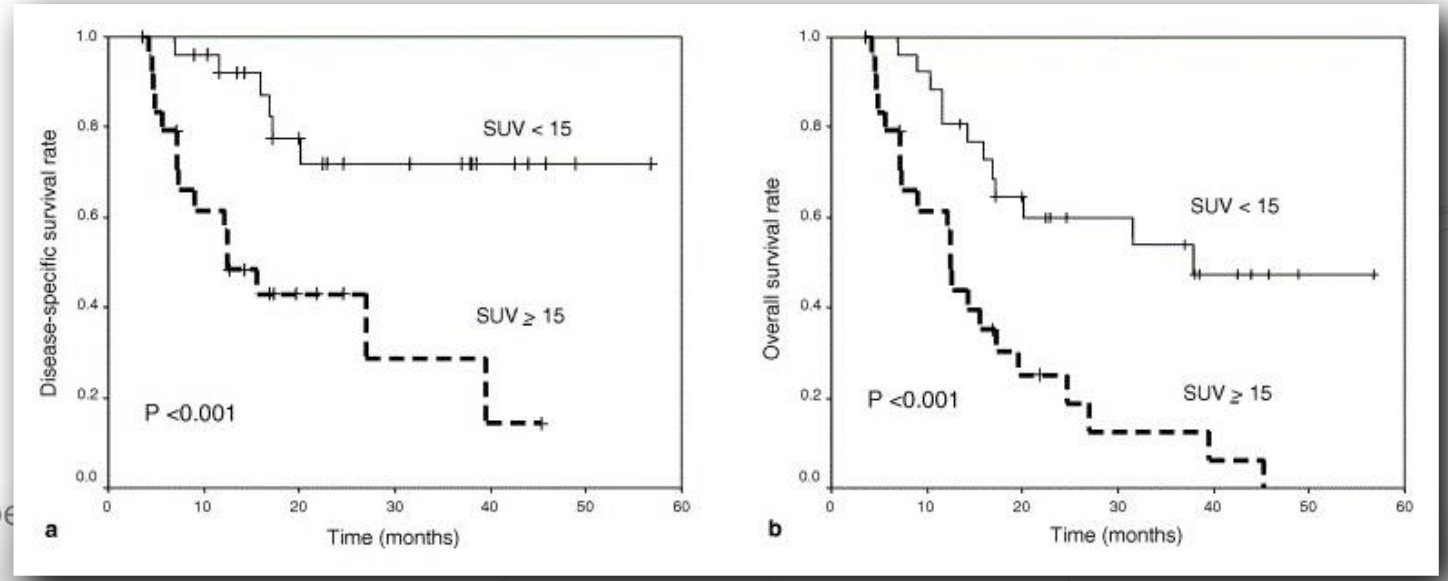
"There is no role yet for pretreatment FDG PET as a predictor of outcome in head and neck cancer in daily routine"

Lung cancer

Standardised FDG uptake: a prognostic factor for inoperable non-small cell lung cancer.
Borst et al., Eur J Cancer. 2005 Jul;41(11):1533-41

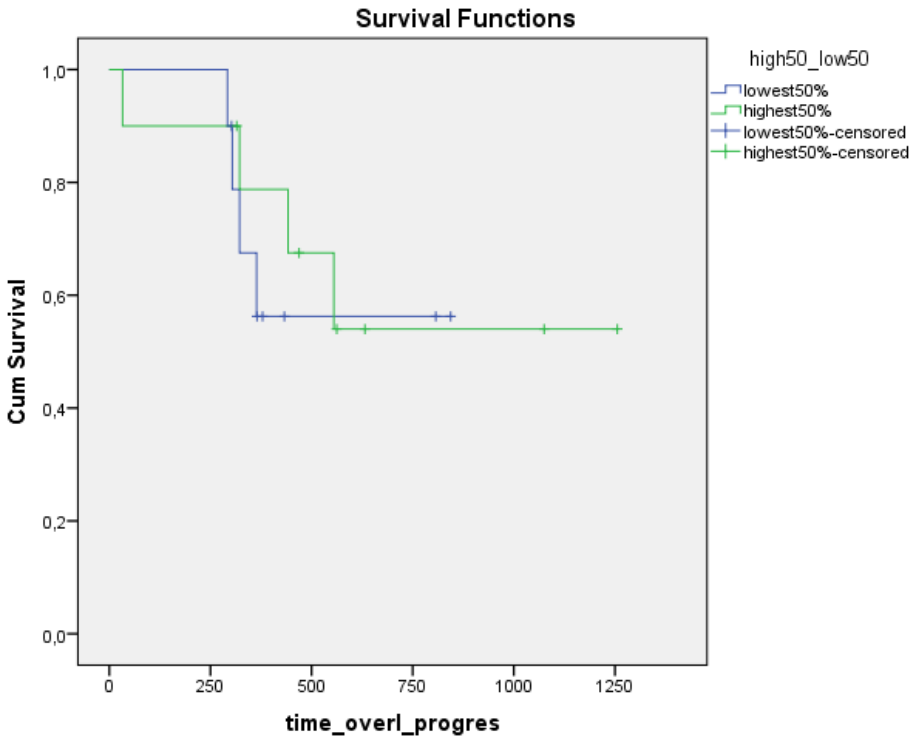
Prognostic factors for survival

- SUV(max) (P = 0.01)
- Stage (P = 0.04)
- Performance status (P = 0.008)



Lung cancer

- NKI experience



Conclusions

- There is a lot of biological data and potential
- But we do not have validated decision criteria yet

Response monitoring

(on treatment)

Biological concept

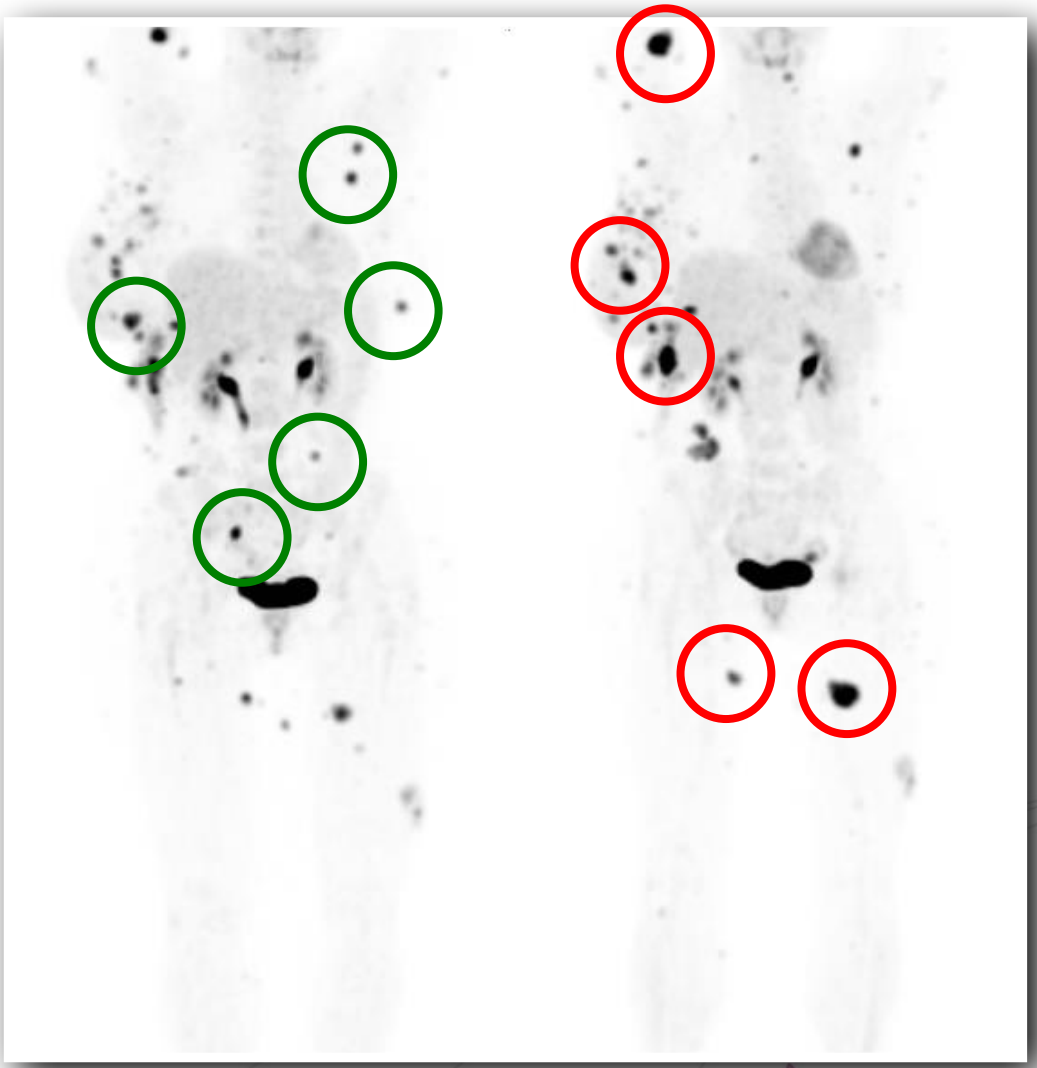
- Start of treatment
- Damage to tumor cells **Days**
- Loss of cellular functions **PET**
- Cell death (apoptosis)
- Leakage of signal molecules
- Activation of immune system
- Increase of mass and perfusion **Weeks**
- Tissue fragments and fagocytosis **dwiMR**
- Formation of scar tissue
- Reduction in perfusion **ceMR**
- Shrinkage of tumor mass **Months** **CT**
- End result

Inhomogeneous response

- M+ melanoma
- 2 weeks DTIC

Benefits

- All involved organs
- All lesions
- Quantitative
- Sensitive to all kinds of response
- Very early signal



Guidelines: RECIST 1.1

New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1).

Eisenhauer et al. Eur J Cancer. 2009 Jan;45(2):228-47.

- Assessment of the change in tumour burden is an important feature of the clinical evaluation of cancer therapy, both tumour shrinkage and disease progression.

- **It may be appropriate to move from anatomic assessment of tumour burden to (include) functional assessment with PET or MRI.**

Good example: Breast

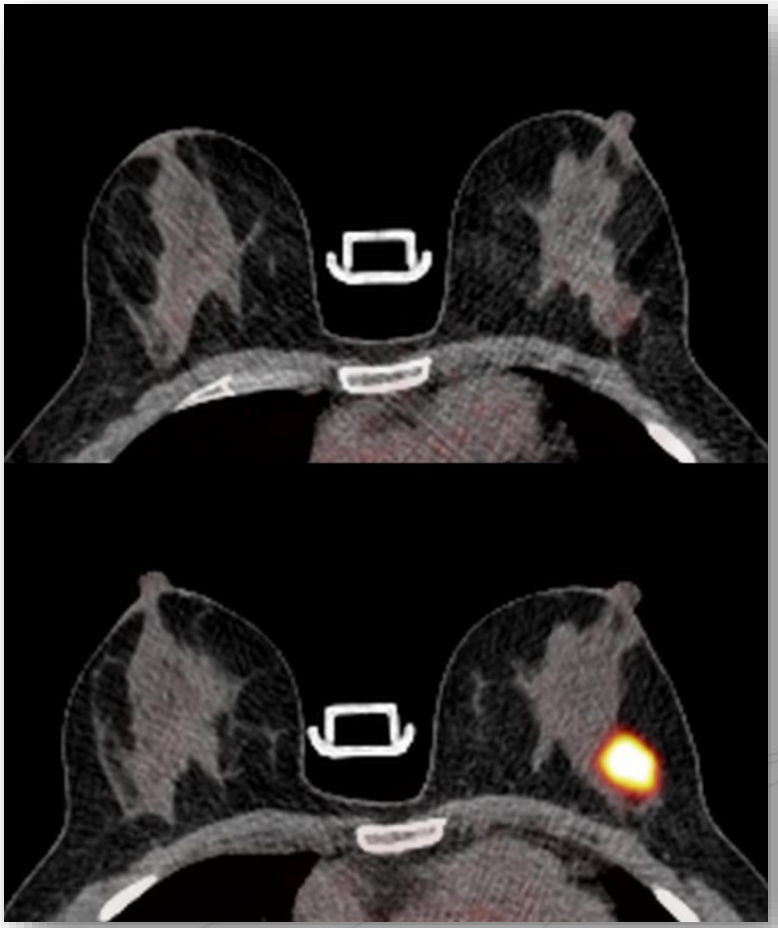
Clinical question

- Switch neo-adjuvant chemotherapy to achieve pCR ?

Preliminary results

- Specificity for pCR 95 %
- PPV for pCR 86 %

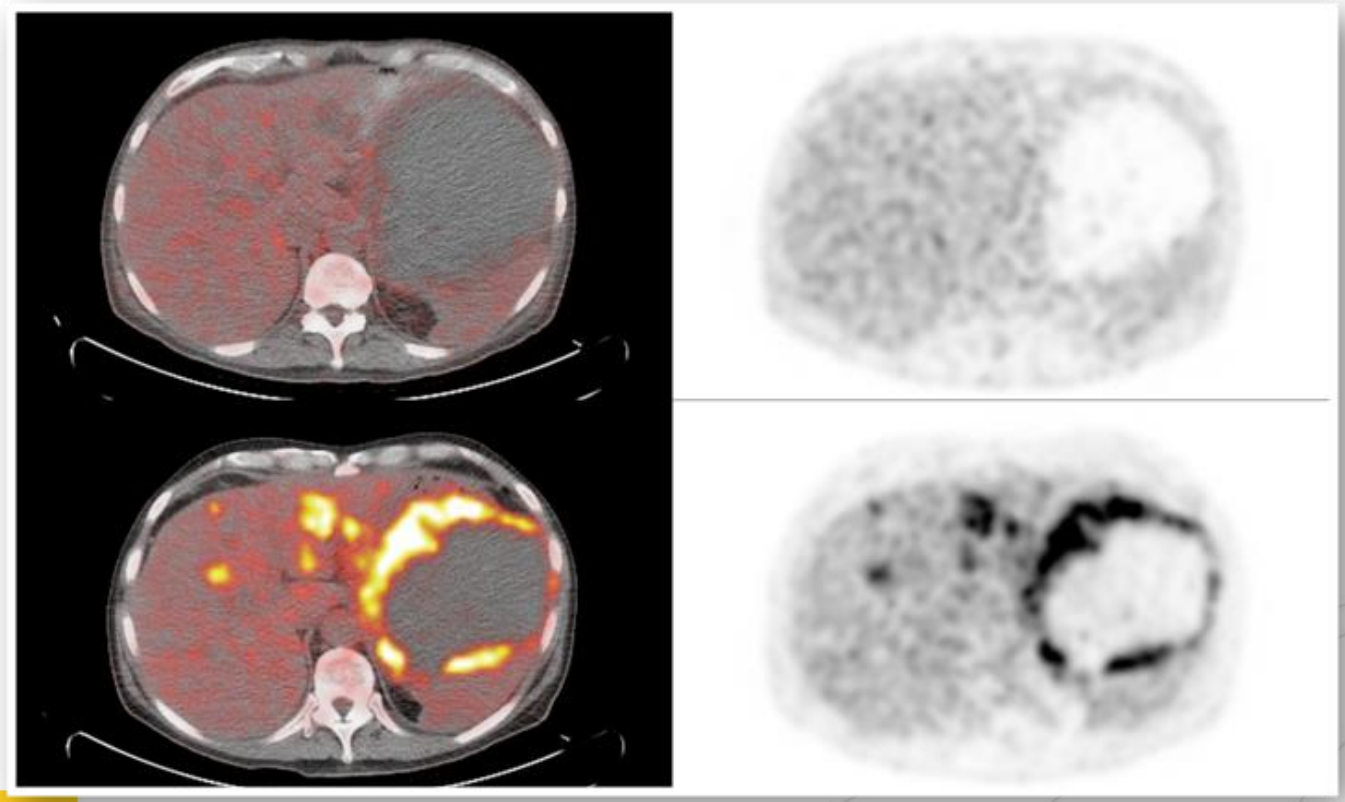
Just as good as MRI, can be used as alternative (but not in HER2+)



Good example: GIST

Clinical question

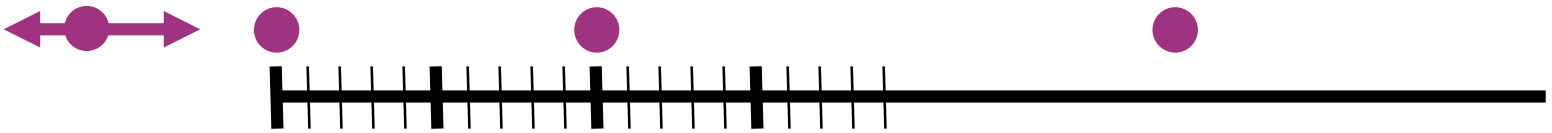
- Continue gefitinib?



Baseline imaging

Two strategies

- Diagnostic phase PET — Staging
- Real baseline PET — Quantification

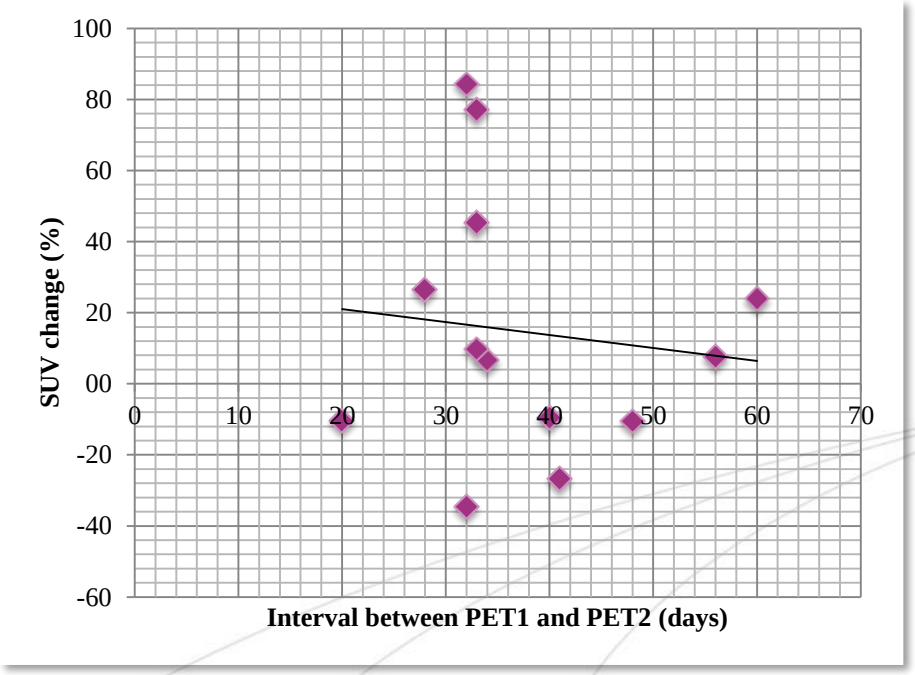


Diagnostic scan versus RT day 1

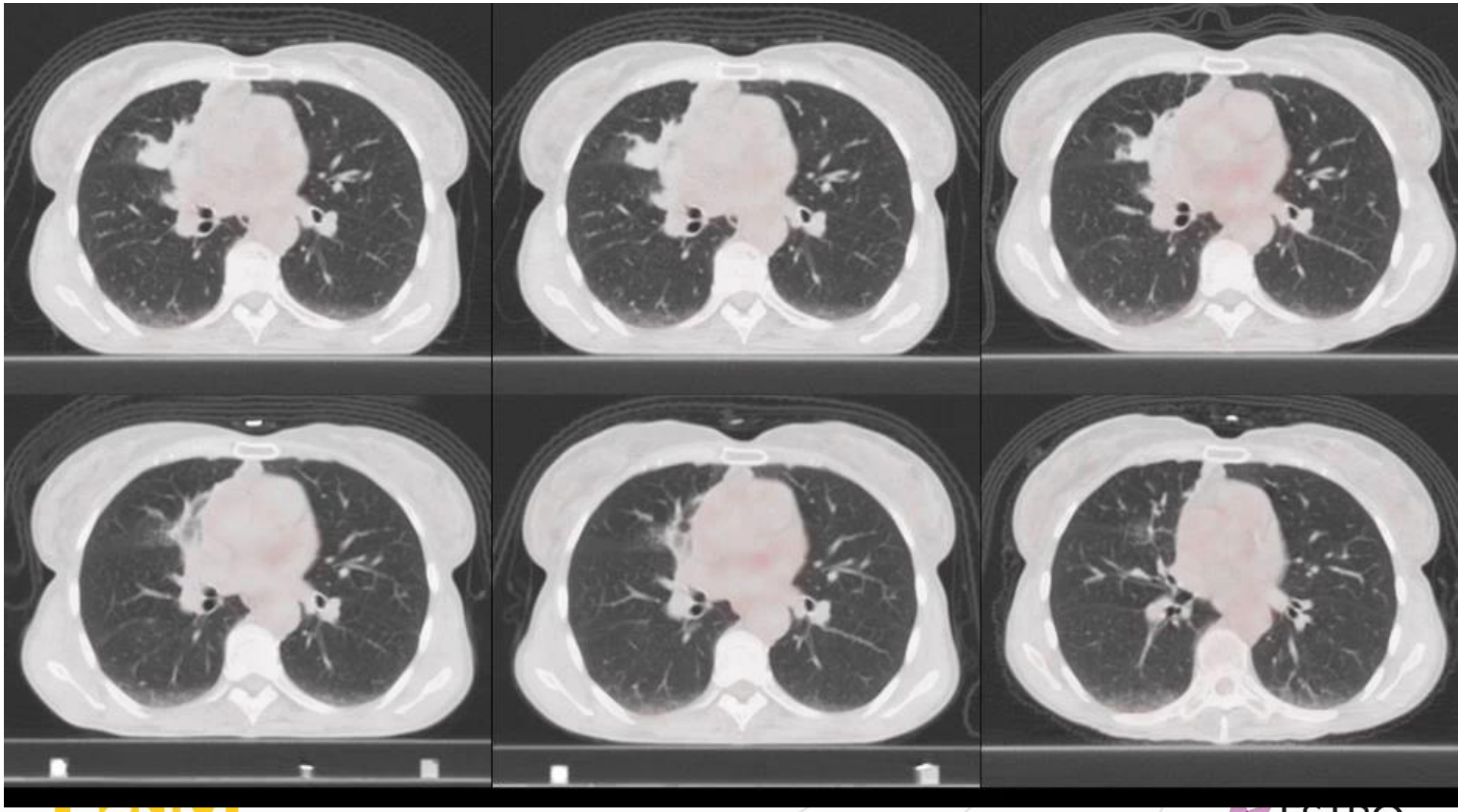
- Not in treatment position
- Sometimes different scanner brand / model
- ≥ 1 month old

- SUVmax differences
  - range -35% - +84%

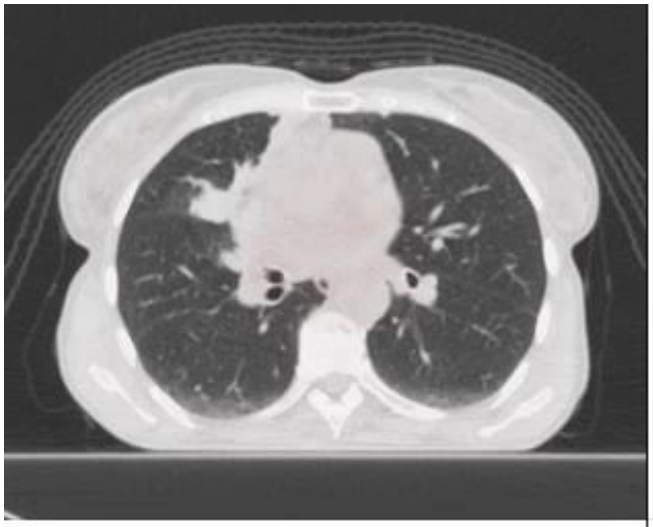
- Tumor progression (8)
- Stage progression (1)
- Calibration issues (3)



Serial metabolic response

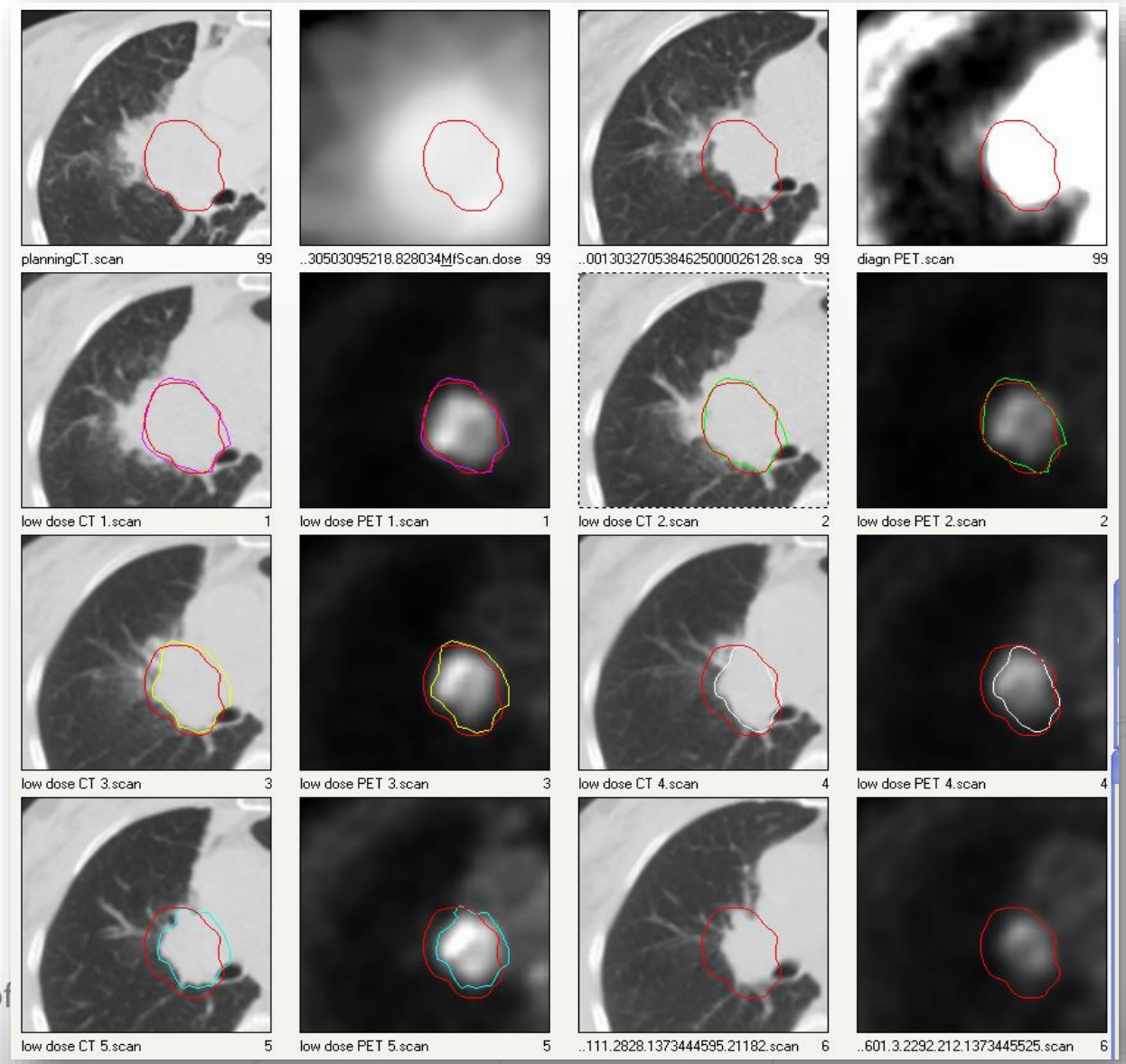


Serial metabolic response



Quantitative serial response evaluation

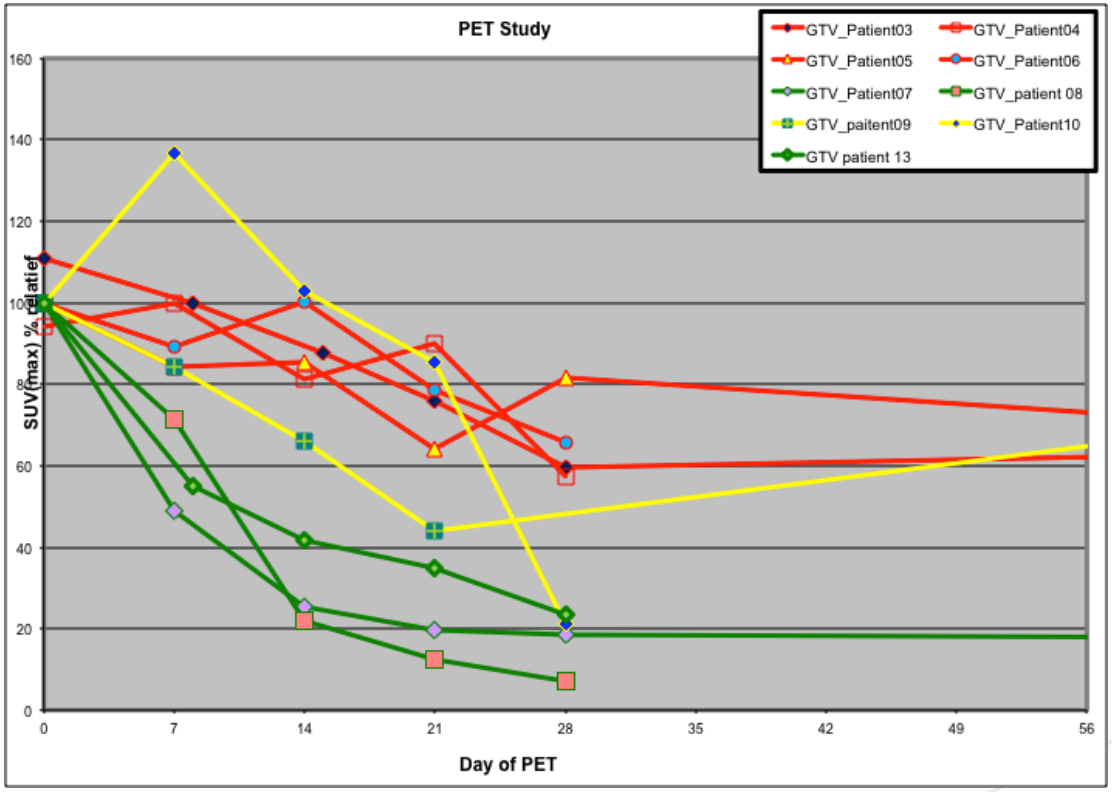
- NSCLC
- Weekly PET



ESNM European School of

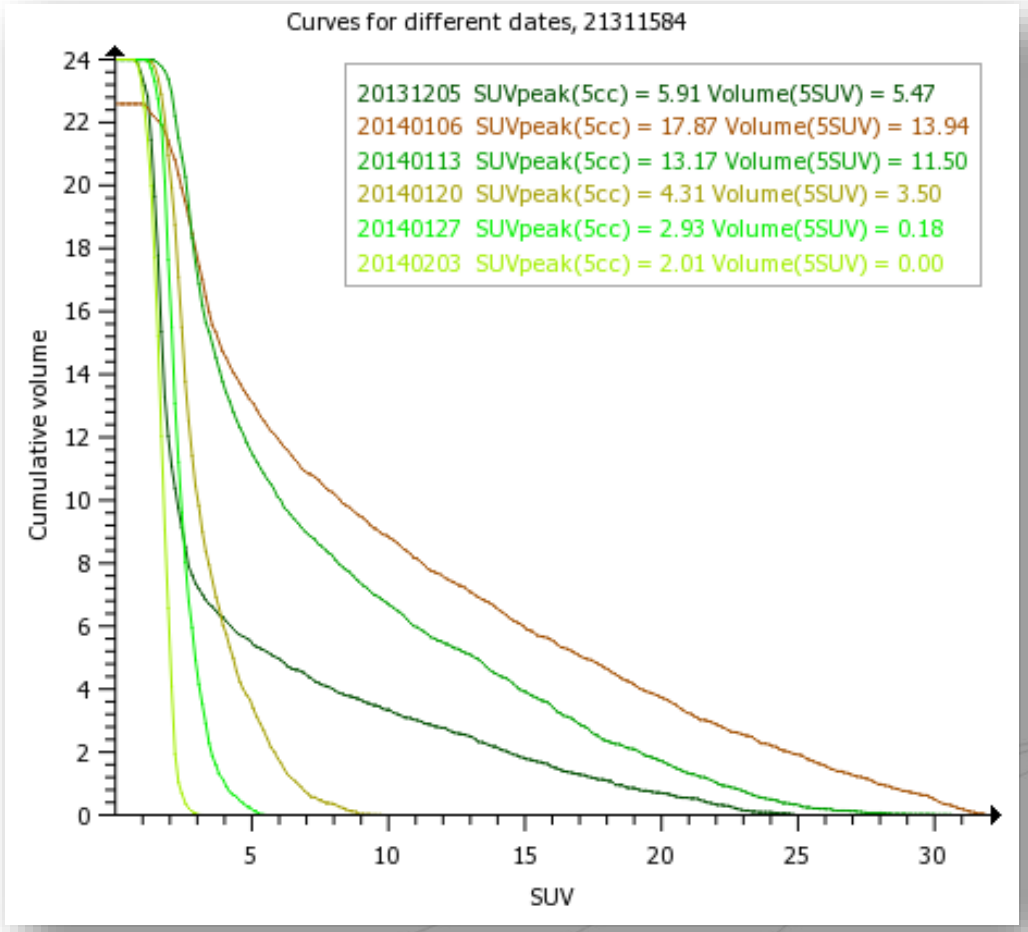
Quantitative serial response evaluation

- Weekly PET/CT during CCRT for NSCLC



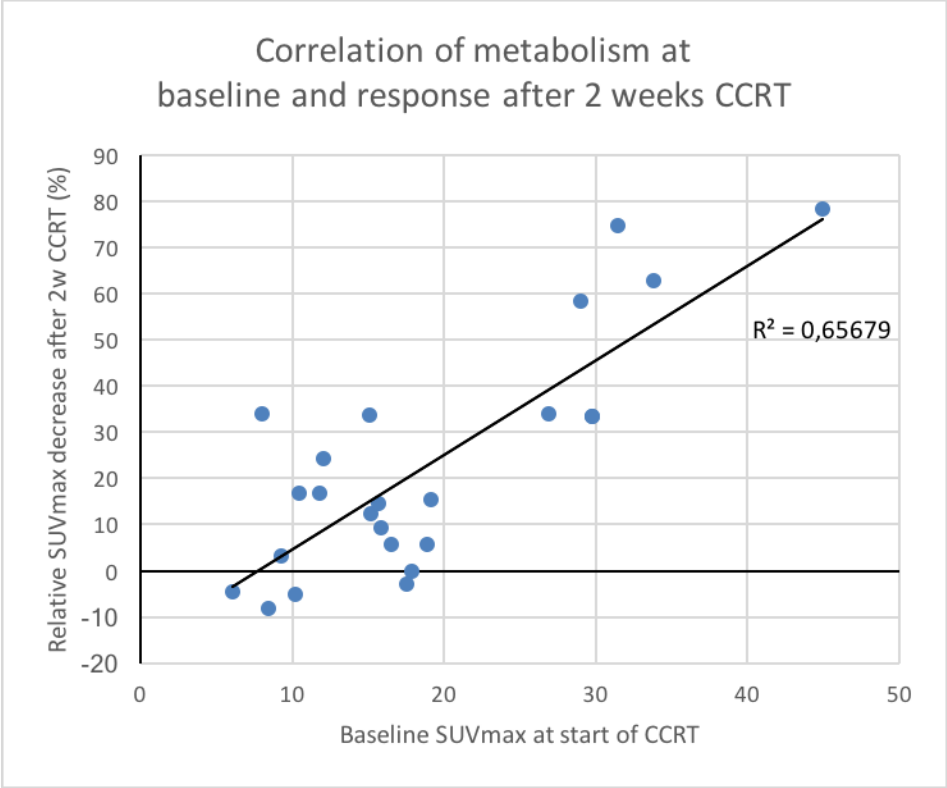
Quantitative serial response evaluation

- **SUV max**
- **SUV peak**
  - Volume?
- **SUV mean**
  - Manual?
  - 50% iso?
  - Watershed?



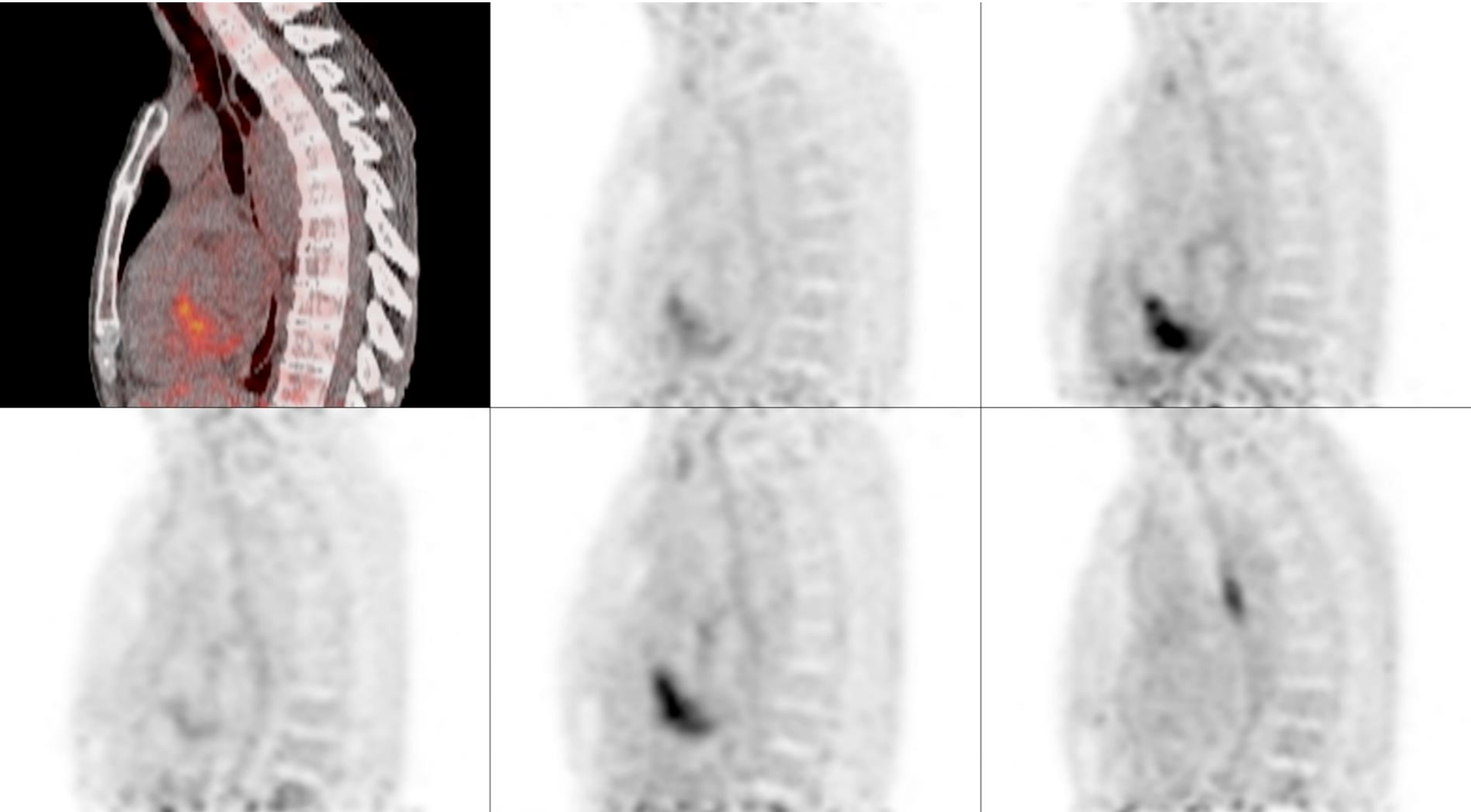
Baseline versus response

- **Related parameters?**



Normal tissue - toxicity

- Esofagus: Dmax = 101%



Conclusions

- There is a lot of biological data and potential
- But we do not have validated decision criteria yet

Thank you for your attention

Questions ?

FDG PET/CT
for follow-up of nodes in head and neck tumors

Dr. Wouter V. Vogel
Department of Nuclear medicine
Department of Radiation oncology

NKI-AVL
The Netherlands Cancer Institute
Antoni van Leeuwenhoek Hospital

Contents

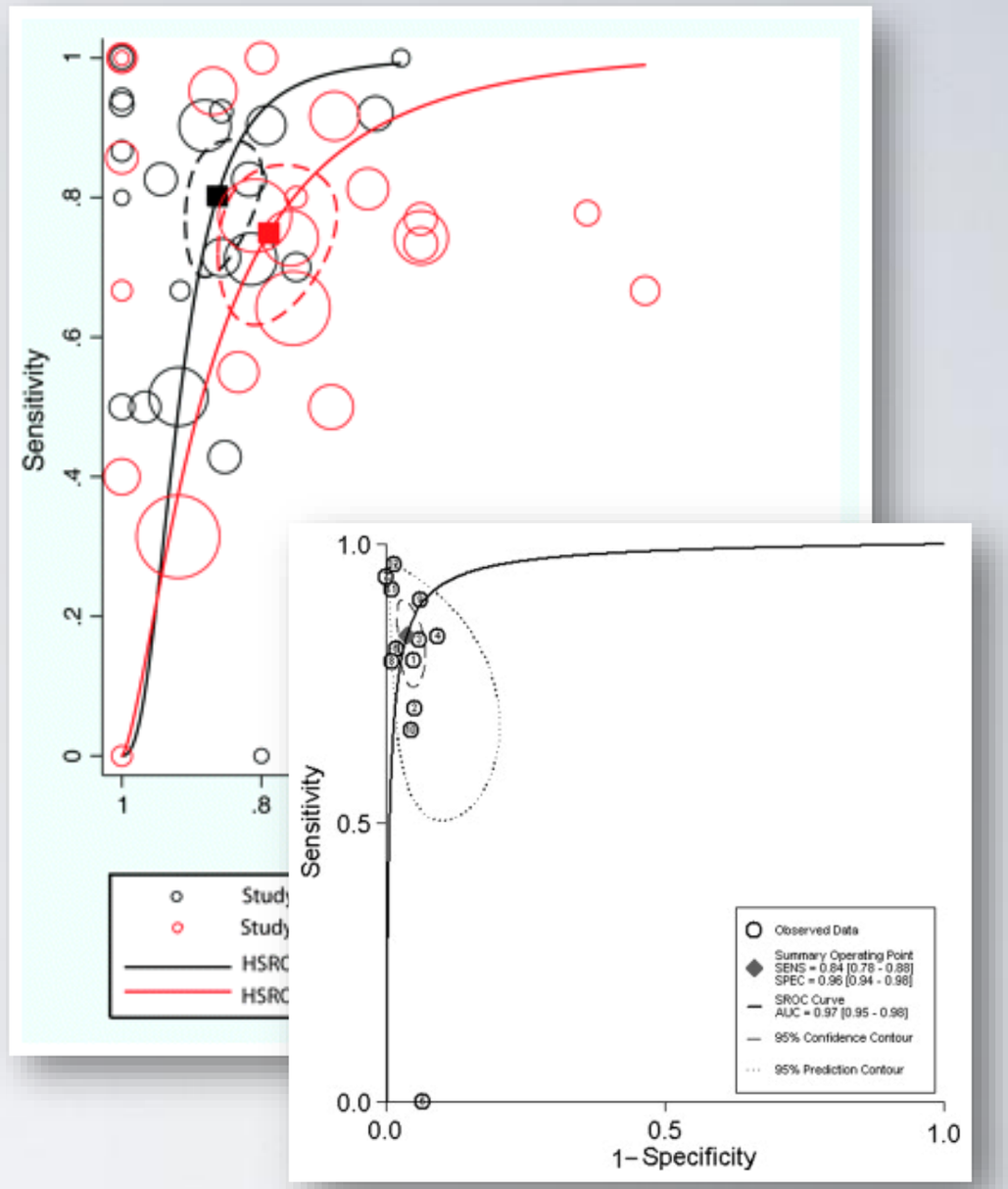
- Concept
- Retrospective evaluations
- Prospective evaluation
- Multicenter prospective randomised trial with cost effectiveness

FDG-PET for node metastases

- 32 studies
- 1236 patiënten

PET outperforms CT and MRI for detection of node metastases in the neck

PET is the best non-invasive instrument available



A meta-analytic evaluation of FDG PET in diagnosis of cervical node metastases
Kyzas et al., J Natl Cancer Inst 2008;100:712-720
Yongkui et al. Surg Oncol. 2013 Mar 25.

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Response evaluation

- In a previously treated area with distorted anatomy
  - Sensitivity for vital tumor remains good
  - Specificity remains good

Retrospective evaluation
follow-up of nodes

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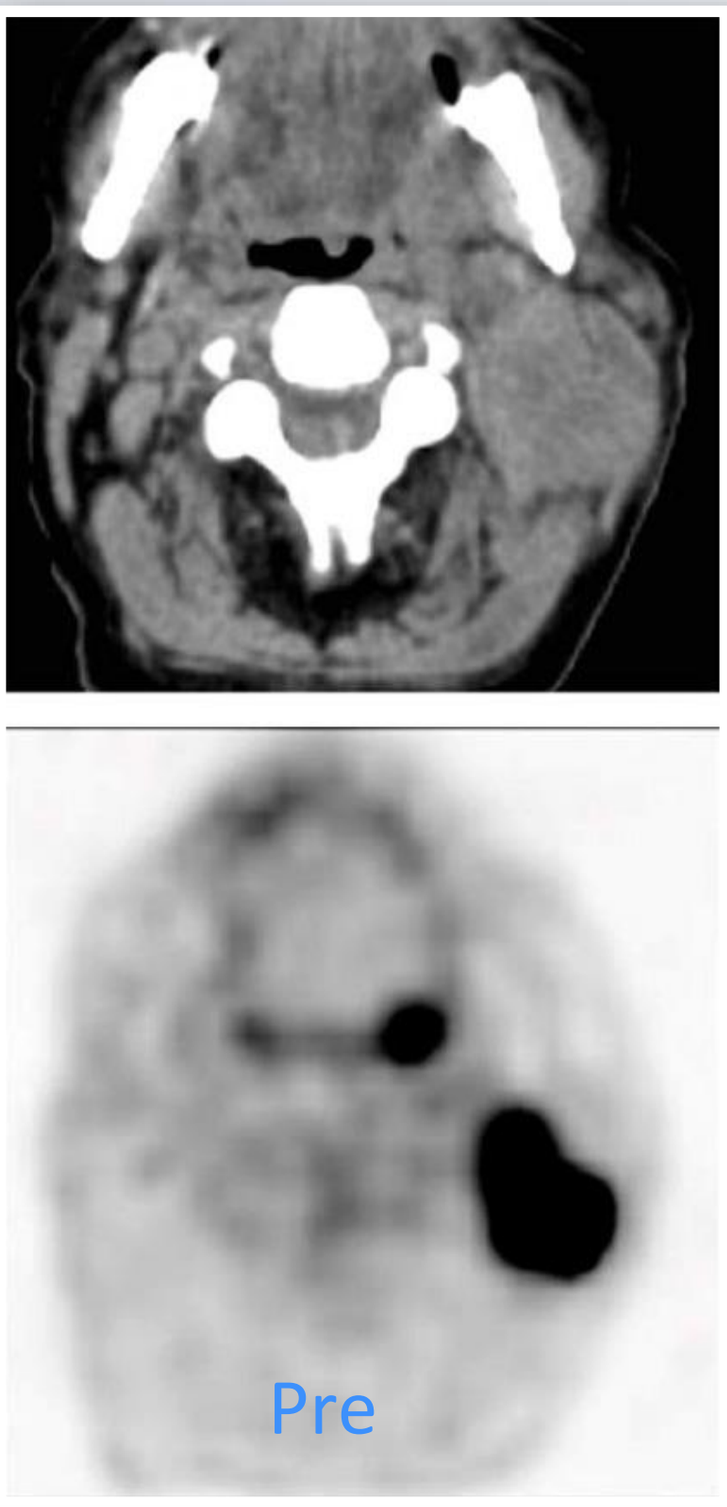
Example 2011



- T1 N2b oropharynx carcinoma

Standard treatment

- Chemoradiation
  - RT 70 Gy / 35 fractions
  - Cisplatin weekly

In case of residual nodes

- Additional neck dissection

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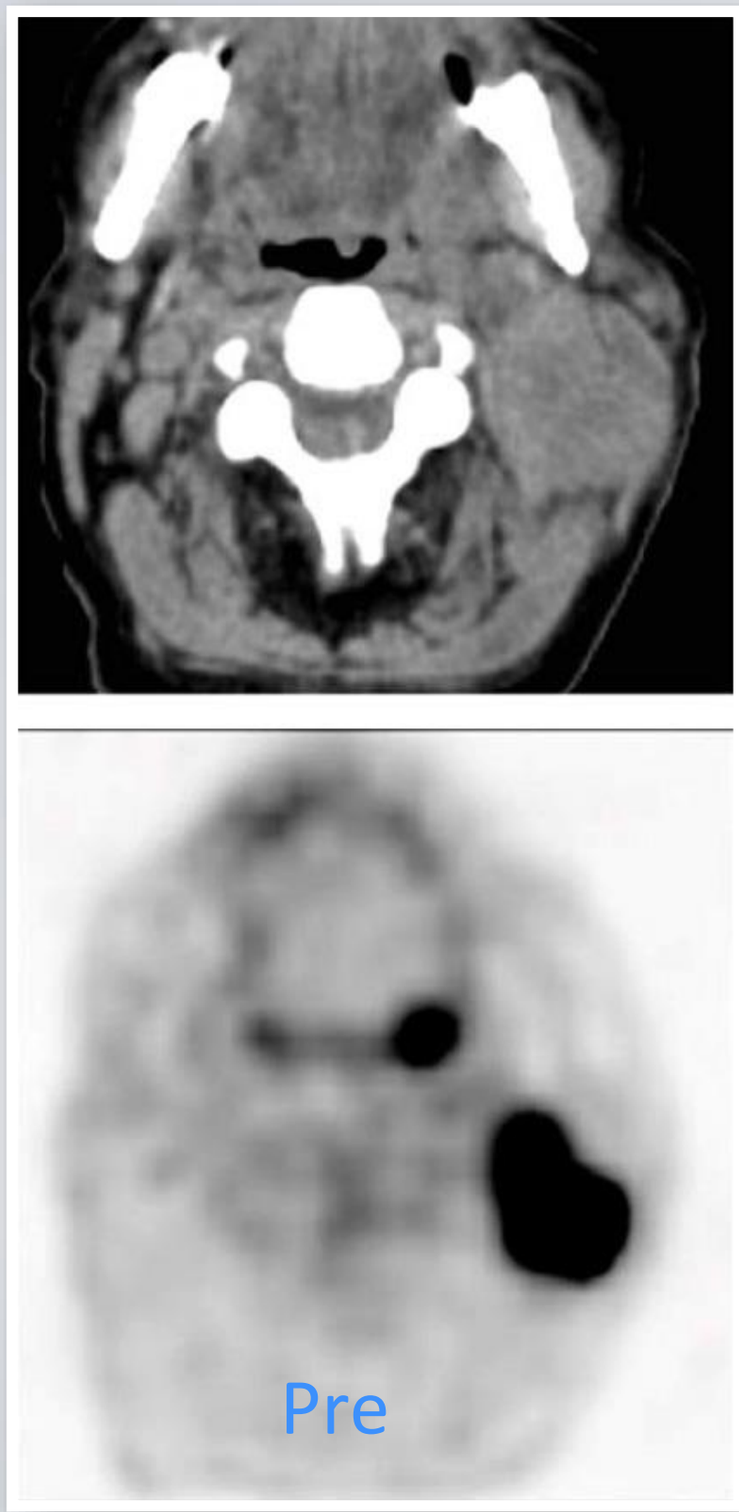
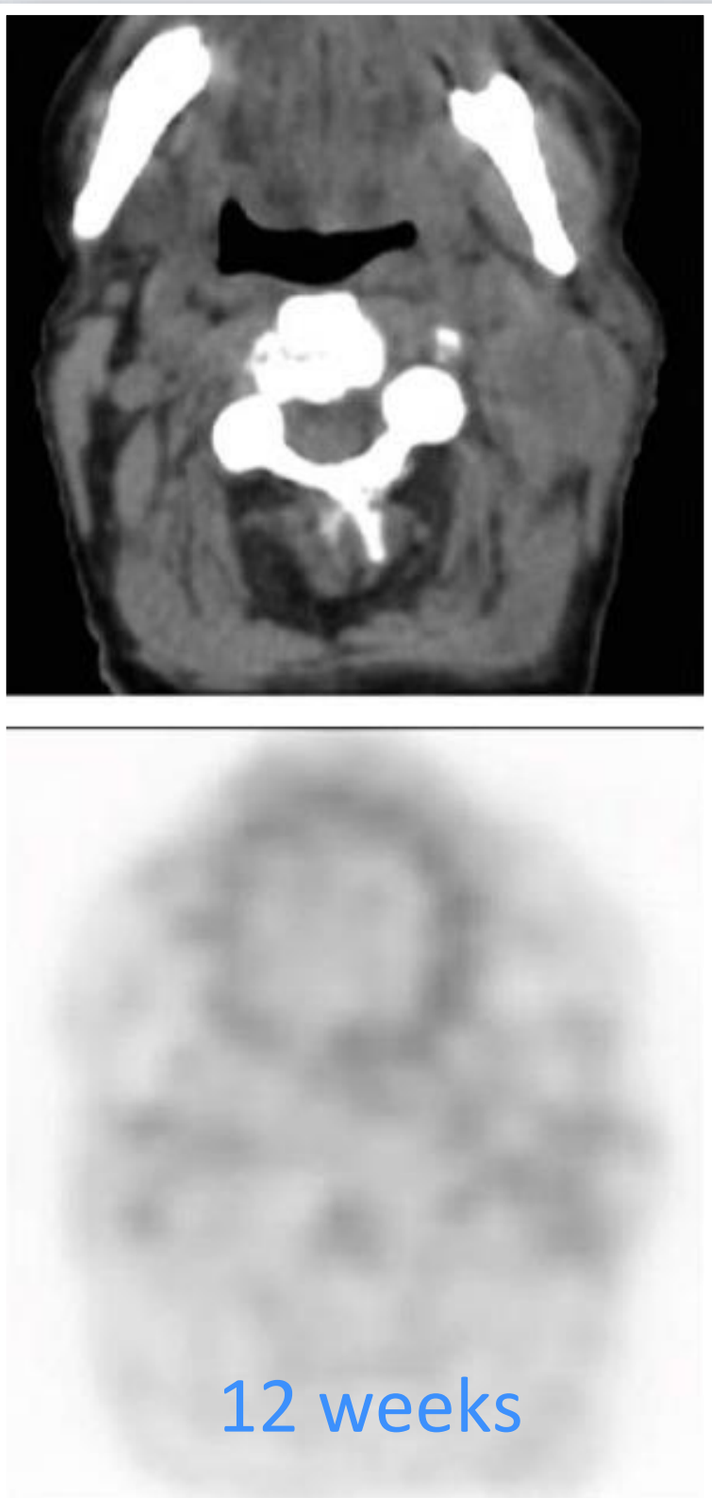
Example 2011





Complete metabolic response 12 weeks after treatment

What does this mean ?

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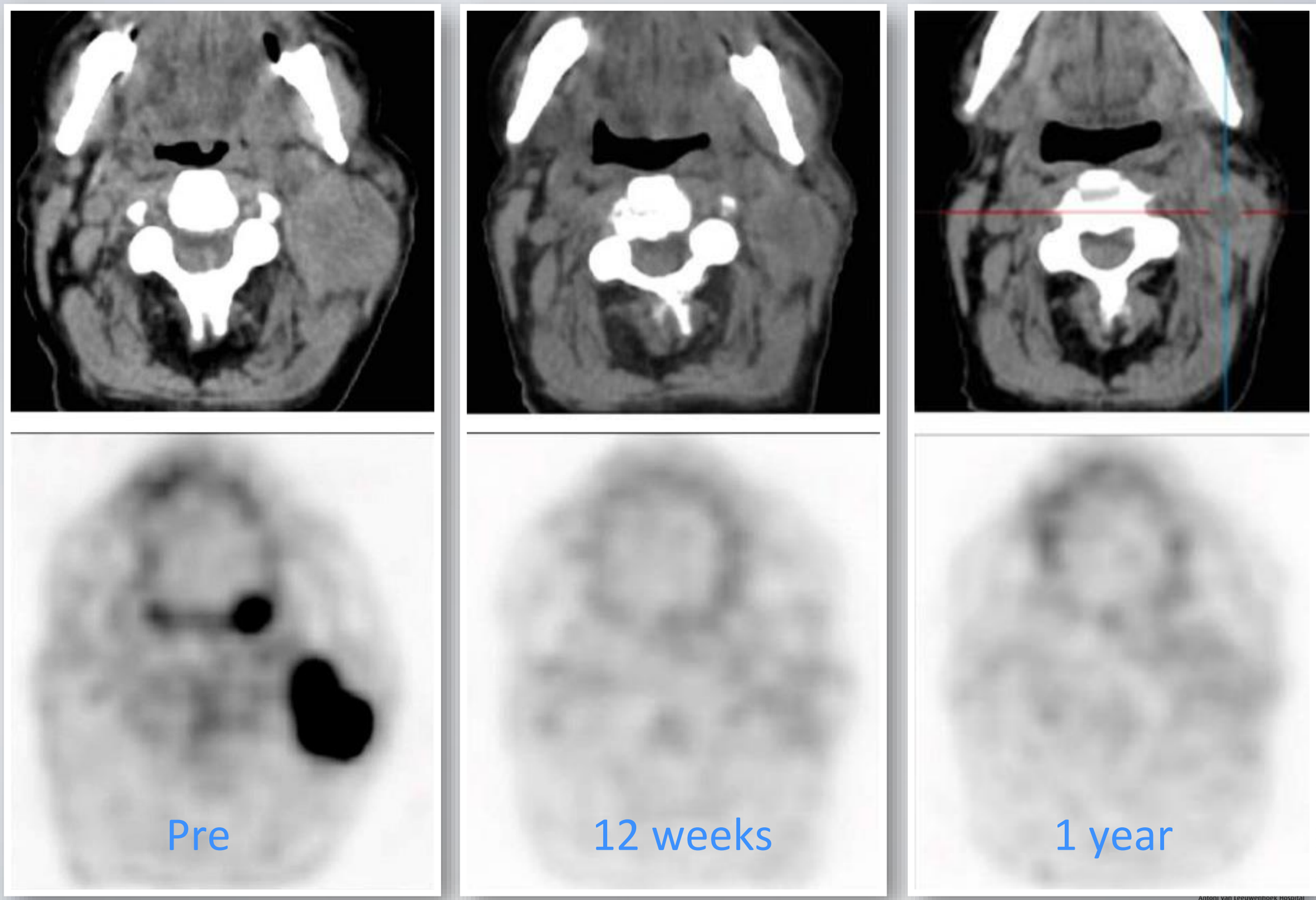
Example 2011



Supporting study #1

- 112 patients with (chemo)radiation for a N2 headneck tumor
- FDG-PET/CT scan 3 months after CRT
- Only FDG-positive necks received node dissection
- All others wait-and-see
- Average follow-up 2,5 years

Results

- 50 patients with residual nodes on CT
- 9 positive on PET: PPV = 22%
- 41 negative on PET: **NPV = 100%**

Results of a prospective study of positron emission tomography-directed management of residual nodal abnormalities in node-positive head and neck cancer after definitive radiotherapy with or without systemic therapy.
Porceddu SV et al., Head Neck 2011. (Aus)

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Supporting study #2

- 34 patients with (chemo)radiation for N2 headneck tumor
- FDG-PET/CT scan 3 months after therapy
- Only FDG-positive necks received node dissection
- All others wait-and-see
- Average follow-up 3 years

Results

- **NPV = 100%**

Neck Dissection can be avoided after Sequential Chemoradiotherapy and Negative Post-treatment Positron Emission Tomography-Computed Tomography in N2 Head and Neck Squamous Cell Carcinoma.
Loo SW et al., Clin Oncol 2011. (UK)

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Supporting study #3

- 52 patients with (chemo)radiation for N2 headneck tumor
- FDG-PET/CT scan 4-6 months after therapy
- Only FDG-positive necks received node dissection
- All others wait-and-see
- Average follow-up 4 years

Results

- **NPV = 100%**

Comparison of Physical Examination and Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography 4-6 Months After Radiotherapy to Assess Residual Head-and-Neck Cancer.
Zundel MT et al., IJROBP 2011.

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Potential impact

In treatment

- Large reduction in unneeded neck dissections after CRT ?

In clinical endpoints

- Survival May not make a difference
- QoL Should be better
- Costs Should be better

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Prospective evaluation
follow-up of nodes

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Study

Lessons from a standardized program using PET-CT to avoid neck dissection after primary radiotherapy for N2 squamous cell carcinoma of the oropharynx.
Hitchcock et al., Florida College of Medicine
Oral Oncol. 2015 Jul 8.

Design

- Changed clinical practice to LND, from $CT+_{(4wk)}$ to $FDG\text{-}PET+_{(12wk)}$
- Monitored in a prospective trial

Current evaluation: 50 first consecutive patients with:

- Oropharyngeal carcinoma (mainly tongue base / tonsil)
- N2a-b (retropharyngeal nodes included)
- Suitable candidates for neck dissection
- LND at positive or equivocal PET at 12 weeks
- Follow-up at least 1 year after PET (regular CT+palpation)

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Important considerations

Refraining from / delay in potentially curative LND

- Diagnostic accuracy of PET is not a complete result
- Compare with CT-based scenario
- Consider additional factors (resectability, local control, M1)

Procedure results

- All patients received prescibed RT dose (70-74.4 Gy, 96% IMRT)
- 92% received concurrent CCRT (82% weekly cisplatin)
- PET scans were made at median 13.5 weeks (range 9-23)

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Outcome

5 patients PET positive -> LND

- Histopathology unknown
- No recurrences at follow-up

45 patients PET negative -> no LND

- 4/45 = 8% neck recurrences (time after PET = 0.5, 0.6, 1.2, 2.0Y)

Comparison with CT strategy

- 1 additional recurrence (2%)
  - Was operable, recurrence in LND field
- 3 patients would have recurrence anyway (6%)
  - 1 = CT complete remission
  - 1 = Recurrent node was never operable (retropharyngeal)
  - 1 = Double sided neck recurrence

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Outcome rephrased

- 2% Neck recurrence “caused by PET strategy”
- 6% Neck recurrence “Not avoidable by CT”
- 92% NPV for $PET_{(12w)}$ “Very safe strategy”

Discussion

- ? % Saved LND relative to $CT_{(12w)}$?
- ? % PPV for $PET_{(12w)}$ -> still too many LND?

Conclusions

- Not many neck recurrences occur
- Introduction of PET(12w) for LND selection is very safe
- It also seems to save unneeded LND, but unknown how many

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Multicenter prospective phase III randomized controlled trial with cost effectiveness

ASCO 2015

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PET-NECK

A multi-centre, randomized, phase III, controlled trial (RCT) comparing PETCT guided active surveillance with planned neck dissection (ND) for locally advanced (N2/N3) nodal metastases (LANM) in patients with head and neck squamous cell cancer (HNSCC) treated with primary radical chemoradiotherapy (CRT).

Mehanna et al., University of Birmingham, J Clin Oncol 33, 2015 (suppl; abstr 6009)

Inclusion

- Patients with Tx-4 N2-3 cancer
- Eligible for CCRT and LND (before or after)

Randomization

- Arm 1: Planned LND before or after CCRT (control)
- Arm 2: CCRT with LND only based on PET (intervention)
- Primary outcome OS with follow-up 2Y
- Non-inferiority design

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Statistical considerations

- Intention to treat analysis
- Non-inferiority intervention arm = HR < 1.50
- 560 patients required at 80% power

Inclusion

- 564 patients in 43 centers in the UK (282 / 282)
- 85% orophagyngeal cancer, 75% p16+
- 17% N2a, 62% N2b, 18% N2c, 3% N3
- Median follow-up 36 months

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Outcome

Procedures

- Control: 221 x LND (78%), with 85 complications
- Intervention: 54 x LND (19%), with 22 complications

Outcome parameters

- HR for OS 0.92 (95% CI 0.65-1.32, p = 0.004)
- 2Y LC LND 93% versus PET/CT 92%
- 2Y RF LND 84% versus PET/CT 86%
- Quality of life similar

Conclusion

- PET/CT based strategy is non-inferior

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Cost-effectiveness

Is PET-CT guided management for patients with locally advanced head and neck squamous cell cancer (HNSCC) cost-effective? Results from a UK non-inferiority phase III randomized trial.
Smith et al., University of Leeds, J Clin Oncol 33, 2015 (suppl; abstr 6010)

Evaluation

- Individual patient data evaluation for NHS reimbursement (564).
- Comparison of randomized arms for 2Y cost-effectiveness.

Outcome for intervention arm

- Average health benefit 0.07 QALYs
- Average cost saving 1415 GBP
- Probabilities at 20.000 GBP per QALY
  - PET/CT = cheaper 99%
  - PET/CT = most effective 91%
  - PET/CT = most cost-effective 98%

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Conclusion

Response driven management of the neck

- LND in <20%
- Isolated failures in 4%
- Cost effective (over a short time horizon)

“These important data combined with large contemporary institutional series reporting excellent outcomes with response-based neck management strongly suggest response-based neck management should be the standard of care for patients with N2/3 selected to undergo radiation plus or minus chemotherapy,”

Dr. Waldon, Univ. Toronto, Discussion leader ASCO 2015

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The Netherlands Cancer Institute
Antoni van Leeuwenhoek Hospital

Thank you
for your attention

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PSMA PET/CT
for salivary gland evaluation

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A dry mouth after radiotherapy

- CCRT is standard of care
- IMRT improves sparing of salivary gland locations

Xerostomia remains a problem

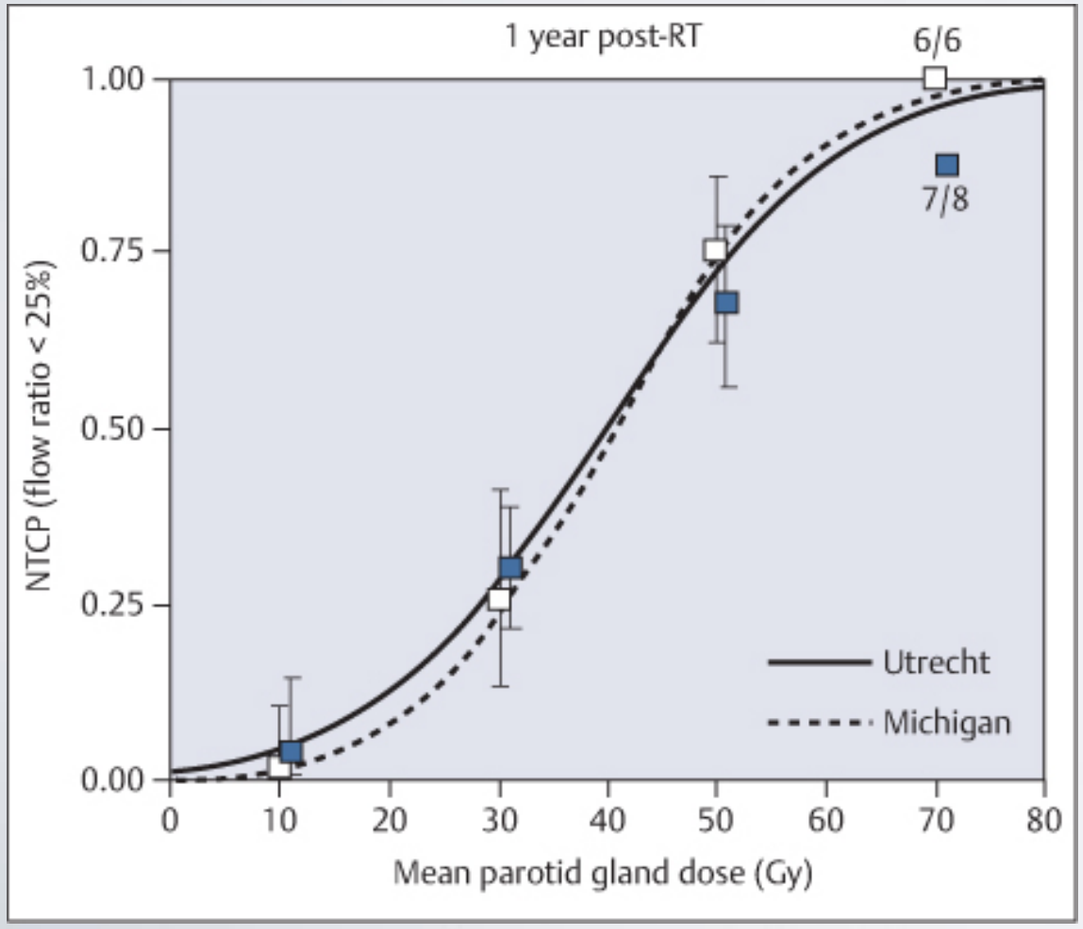
- Poor intake and taste
- Poor oral / dental hygiene
- Reduced quality of life

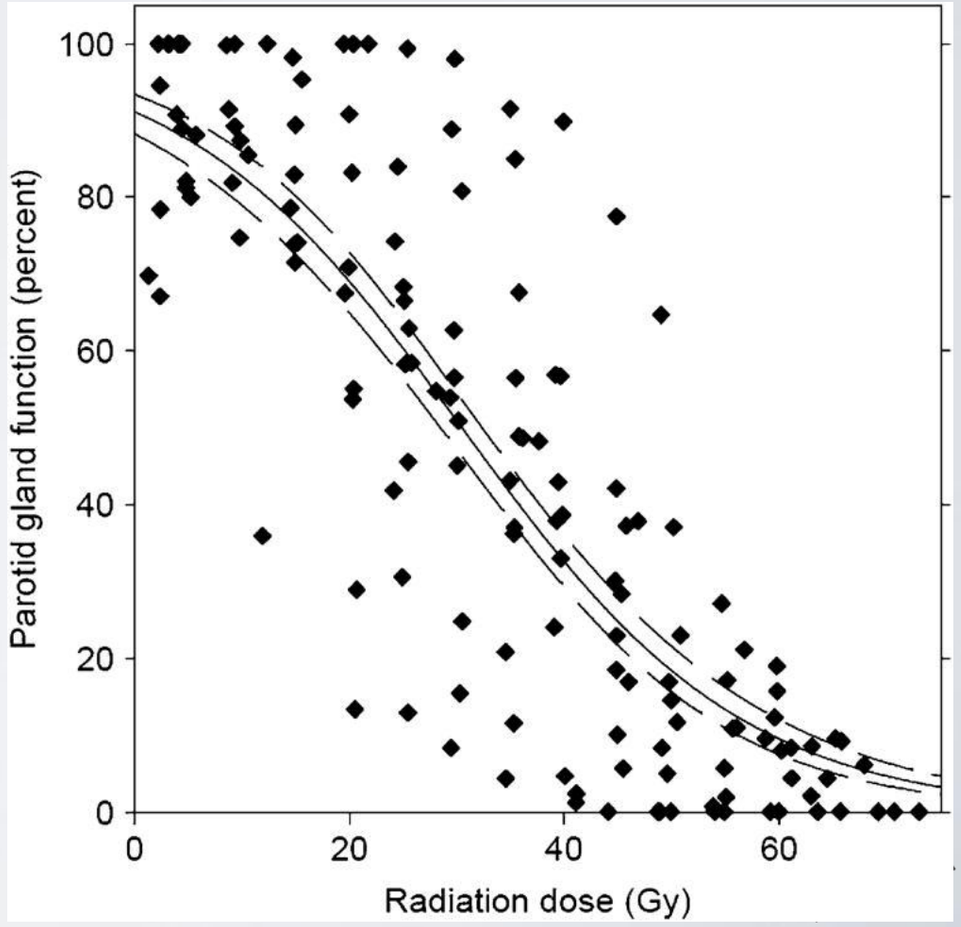
Current problems

- Where are the salivary glands located?
- Which glands function properly?
- Loss of which glands causes a subjective dry mouth?

Function loss after RT is hard to quantify

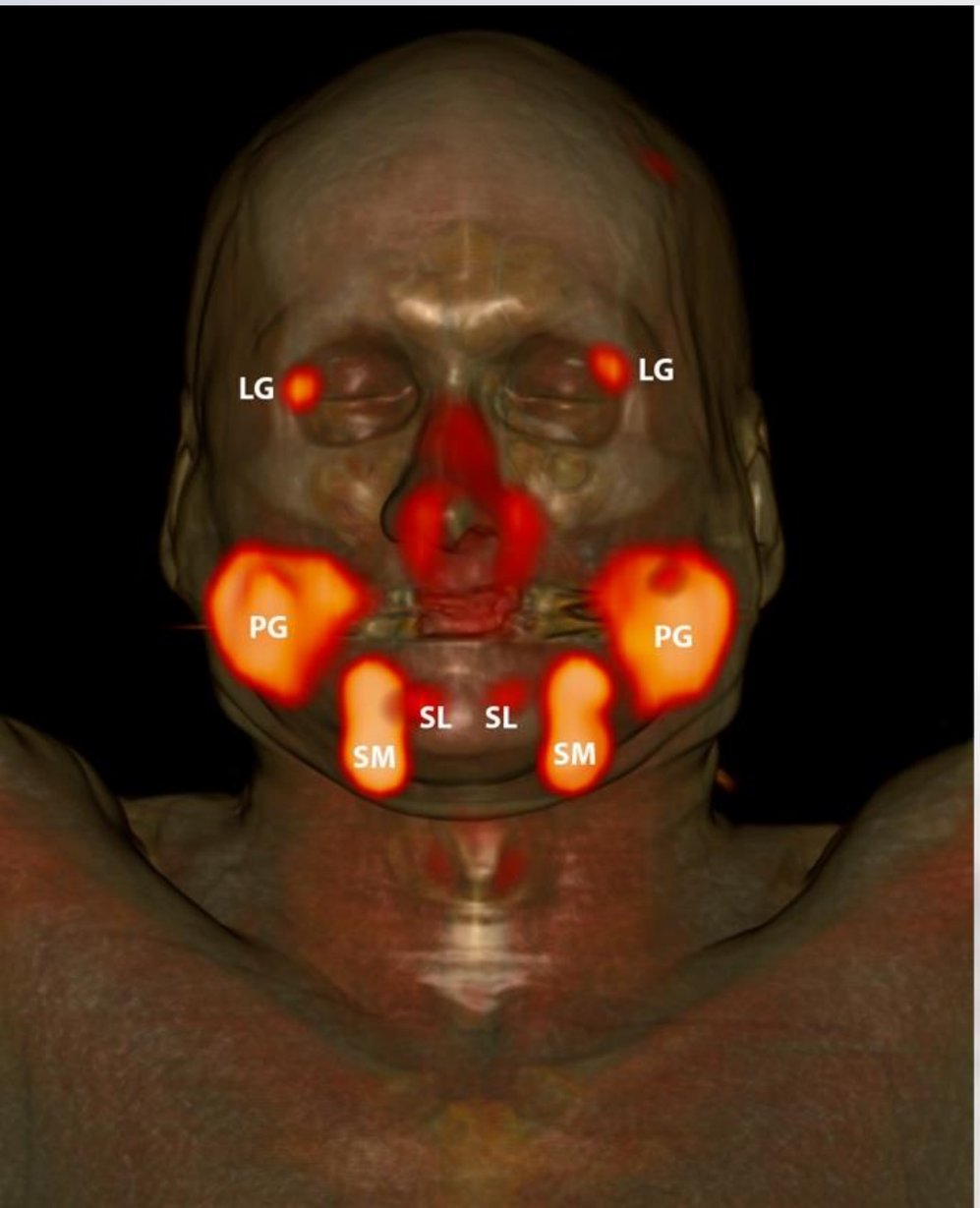
- Subjective questionnaires are the current standard
- Salivary flow rates are limited, poorly reproducible, uncomfortable
- Scintigraphy is limited, poorly reproducible
- Dose-effect relations are incomplete and inaccurate

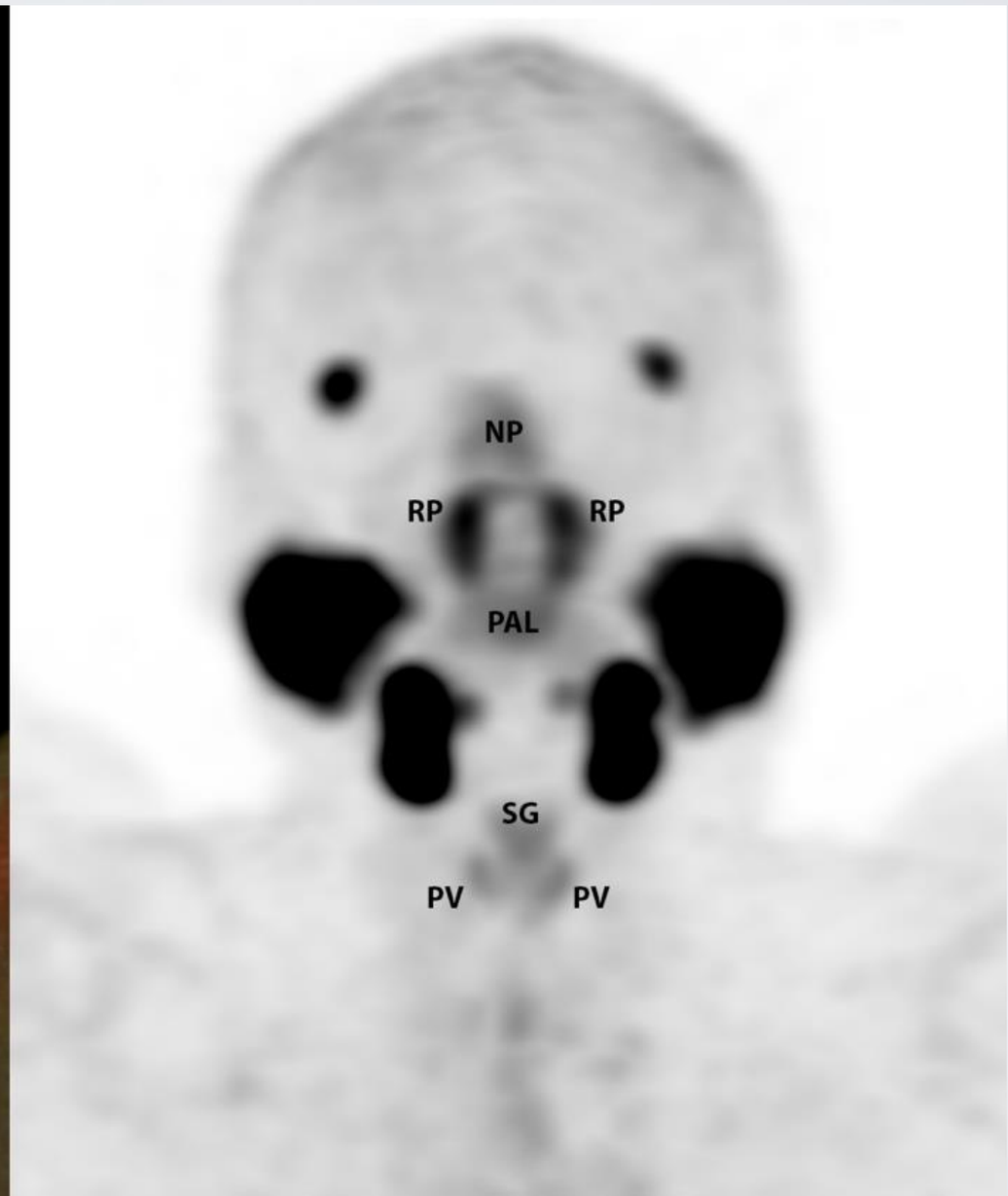




PSMA PET/CT for functional imaging

- Very high sensitivity: Detection of new glands
- Very high specificity: No issues with inflammation





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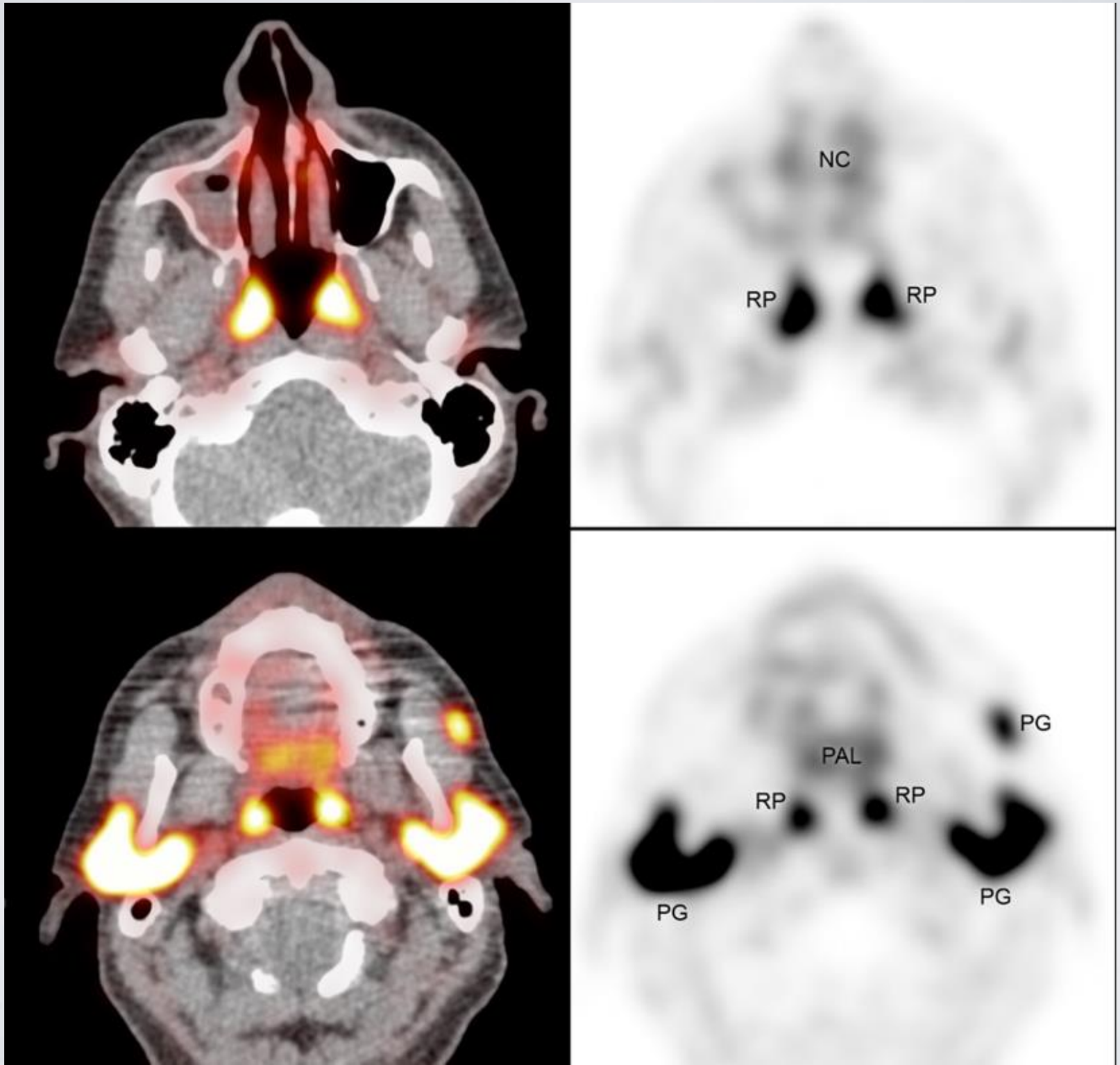
PSMA PET/CT for functional imaging



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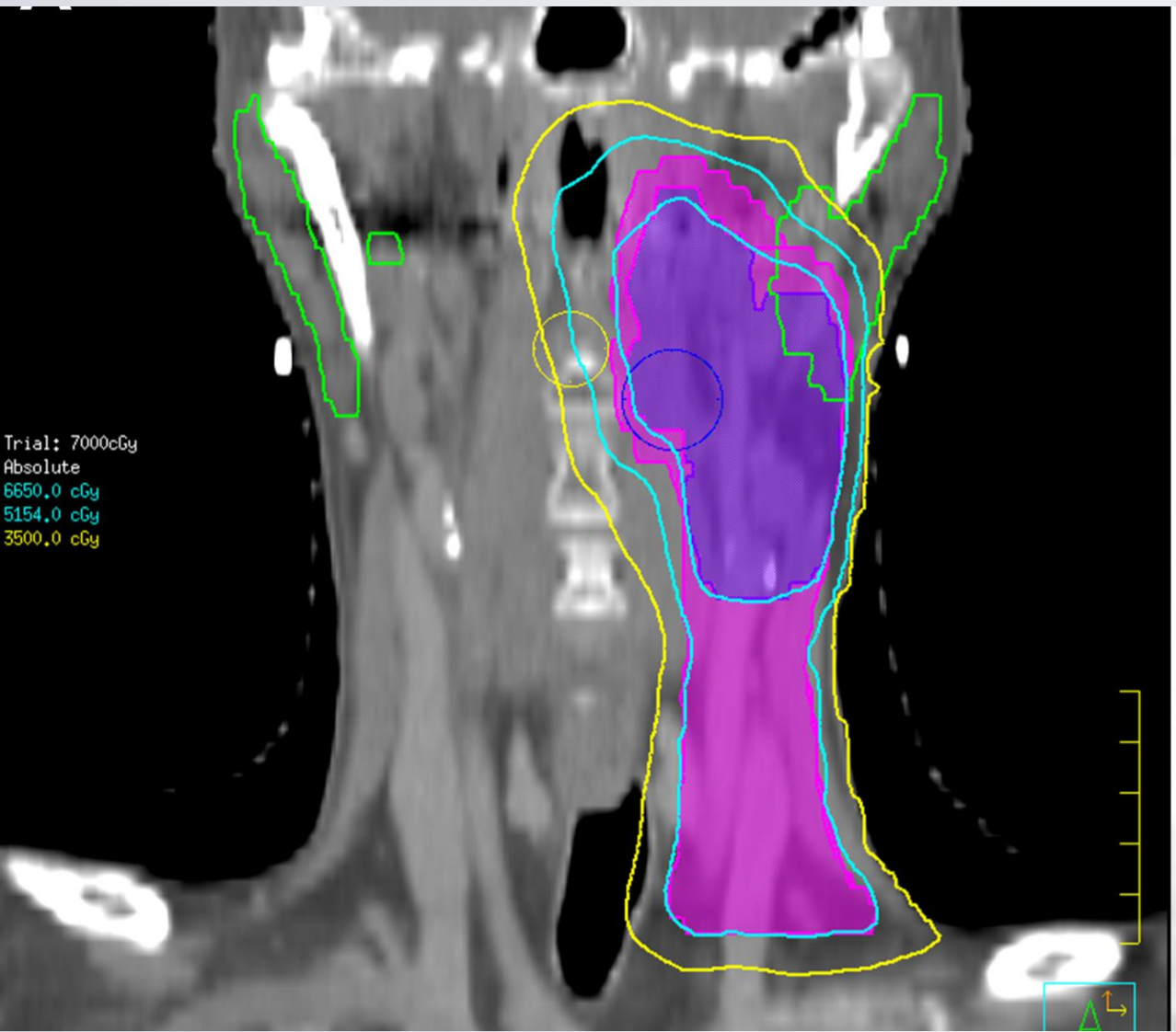
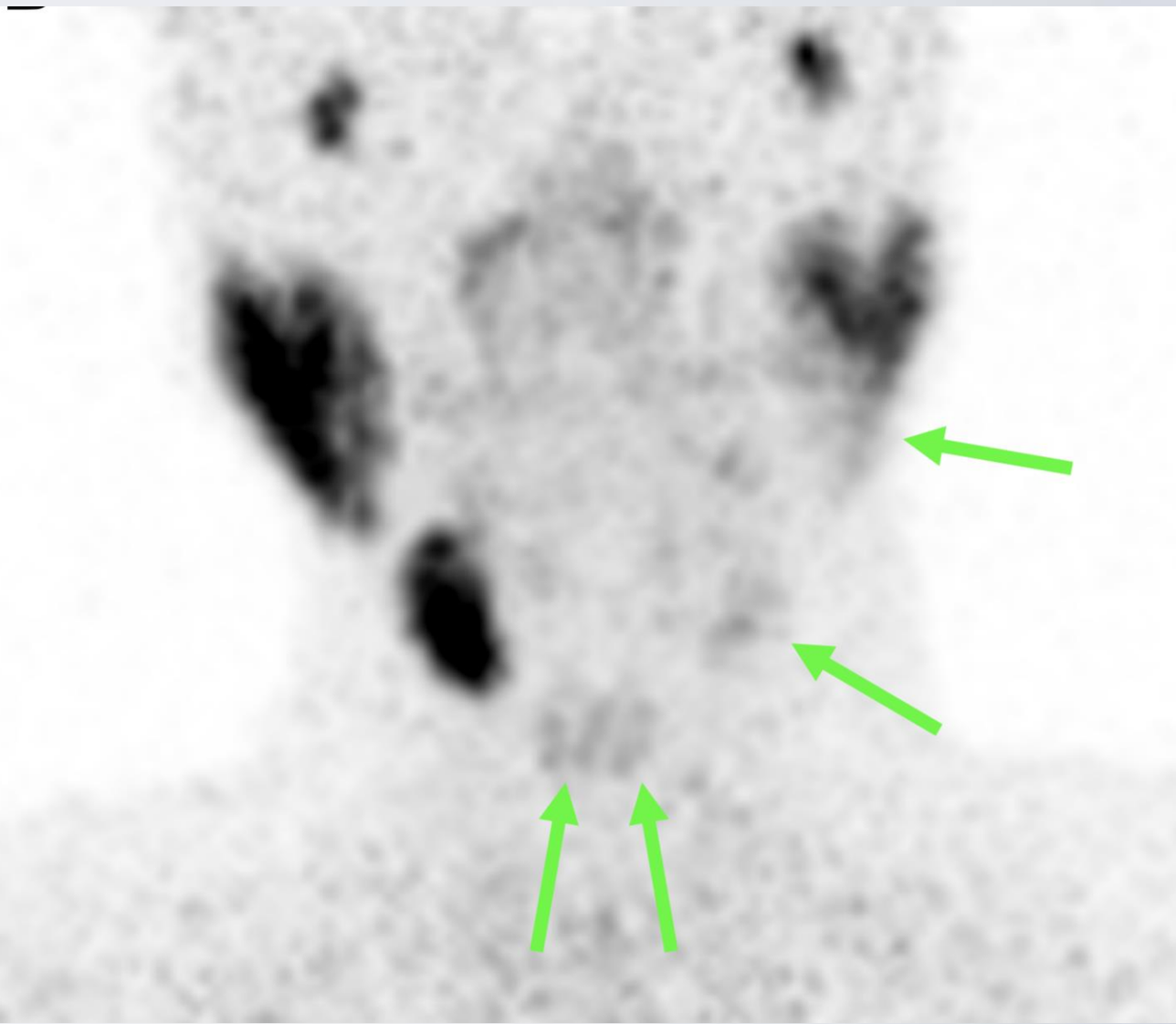
Relation with RT

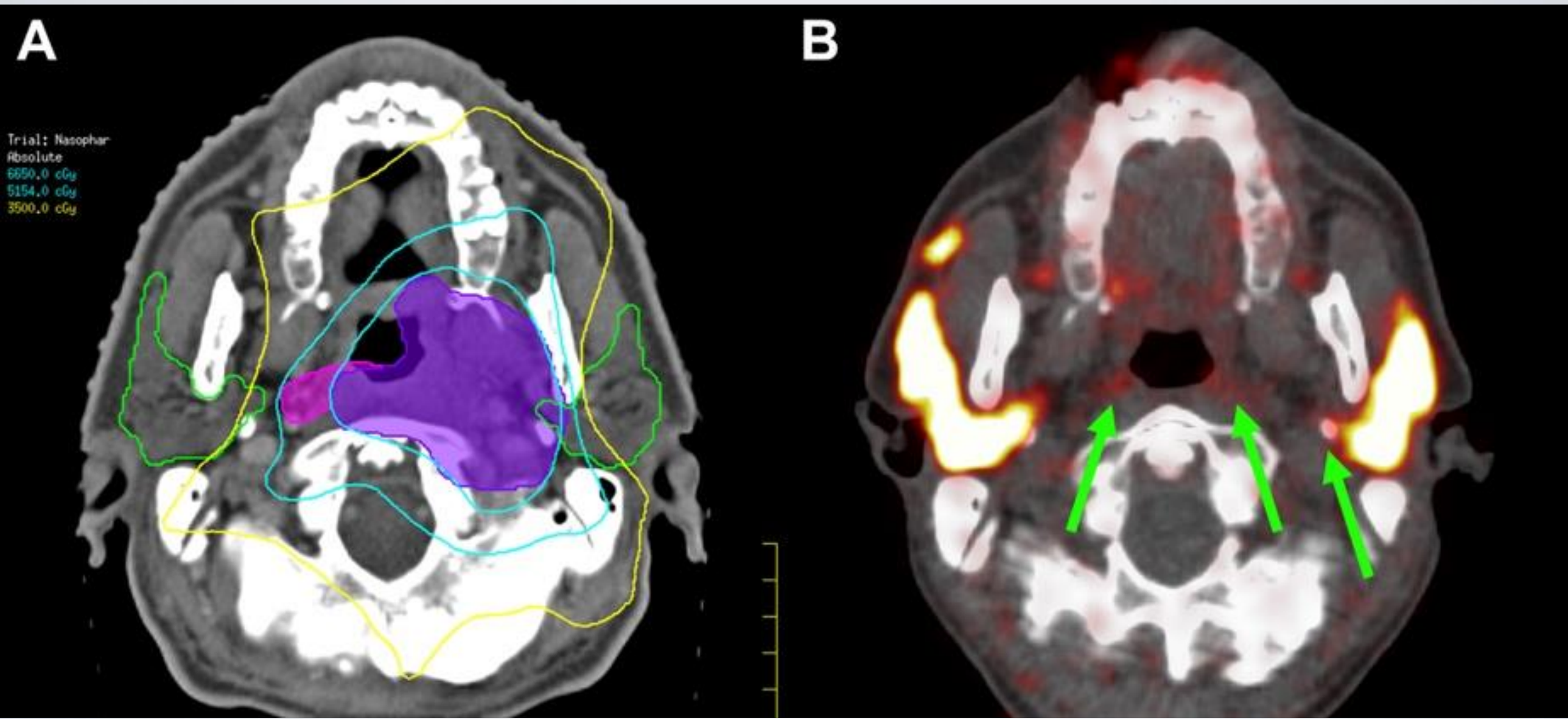
- Signal loss correlates with cell loss
- Voxel-based correlation of administered dose and signal loss
- An objective and reproducible biological parameter in 3D





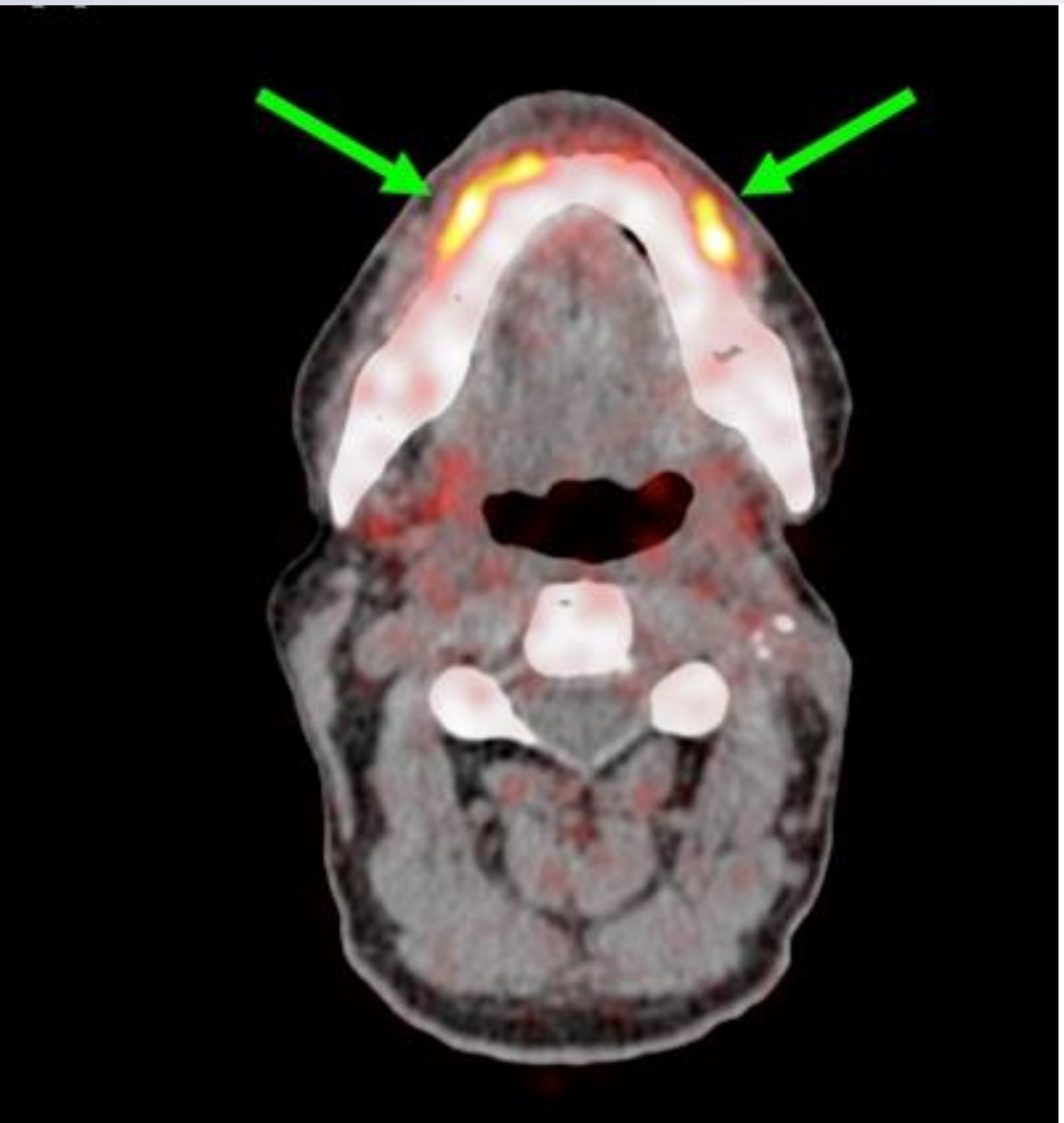
Relation with RT

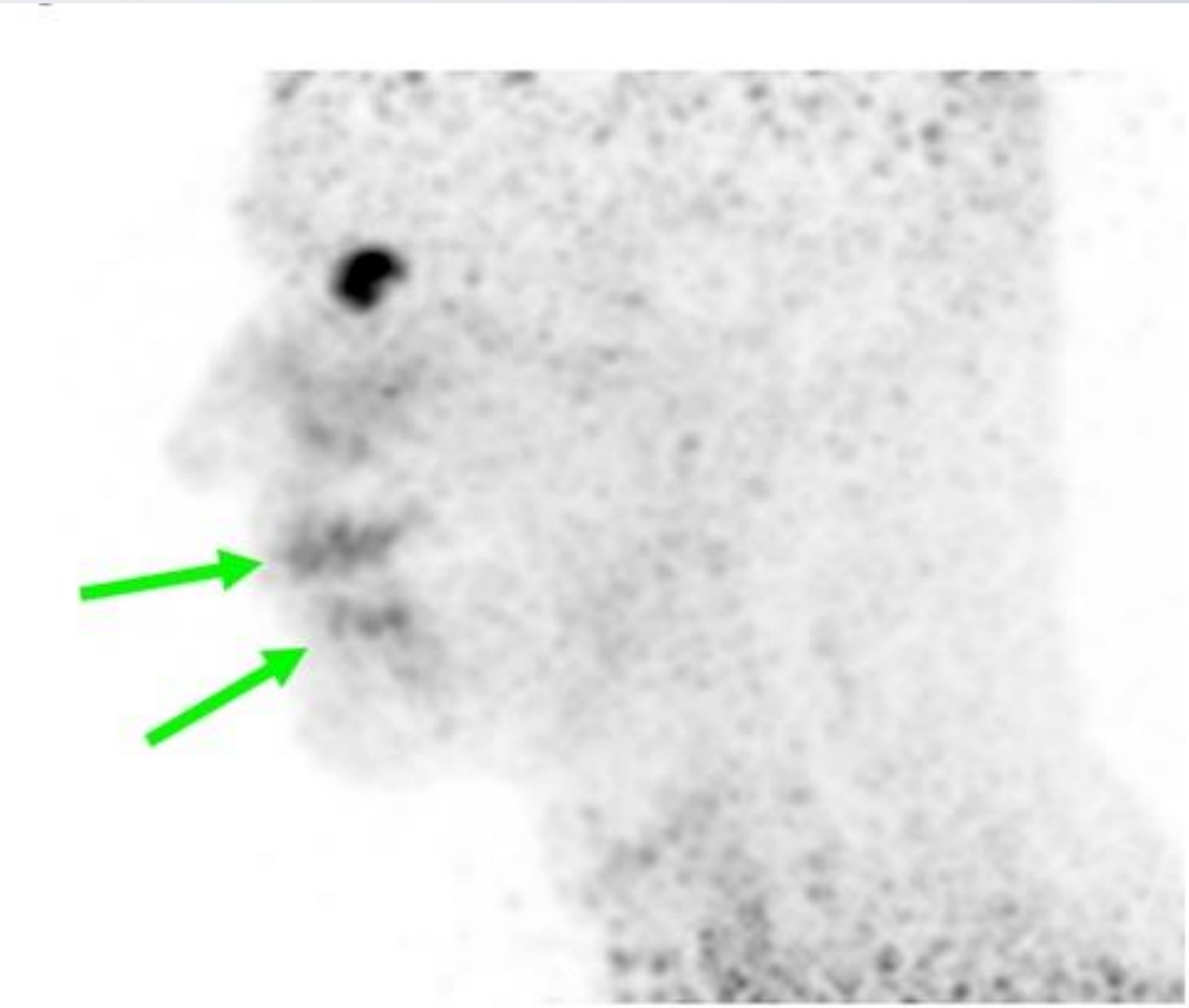
- Evaluation of glands that were never assessed before
- Functional / anatomical explanation for complaints



Relation with radiotherapy

- Visualisation of compensation mechanisms





Potential applications

- Avoiding dose to functional glands
- More accurate dose-constraints
- Gland type specific dose constraints
- Evaluation of concurrent chemotherapy

Thank you

Questions?

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ESNM/ESTRO COURSE
MOLECULAR IMAGING &
RADIATION ONCOLOGY
10-13 MAY 2017

MRI for Response Assessment

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KING'S College LONDON

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Learning Objectives

- To learn about response assessment using MRI
- To be aware of the limitations of current response assessment & other response criteria
- To be aware of the imaging appearance of side effects of therapies

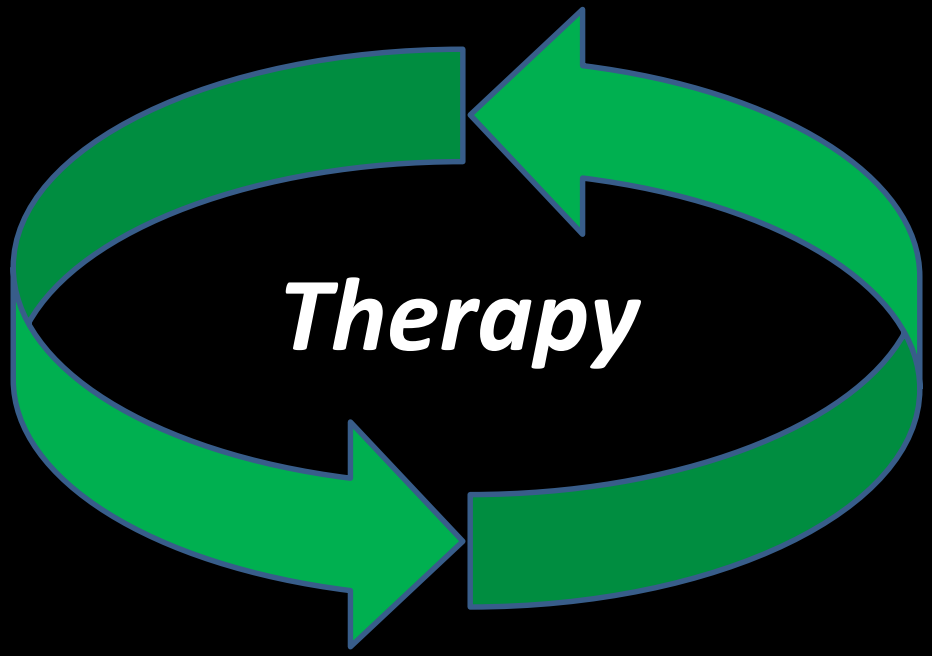
Therapy Assessment: Imaging

- Depicting disease burden accurately
- Selecting appropriate patients for therapy or therapy combinations
- Assessing therapy response/non-response
- Directing further management

Advantages of imaging:

- High patient acceptability
- Non-invasive
- Safe
- Robust
- Cost effective

Response Biomarkers: Imaging



Size & Morphology

Molecular & Physiological

Agnostic: Heterogeneity

MRI for Response Assessment: When ?

- Clinical trials:
  - MRI response assessment
    - RECIST 1.1 assessment
    - Other response criteria
  - Exploratory imaging
    - Phase I: Biological effect & Dose finding
- Clinical pathway:
  - MRI performed as part of standard imaging

Clinical Trials

Therapy Assessment: Clinical Trials

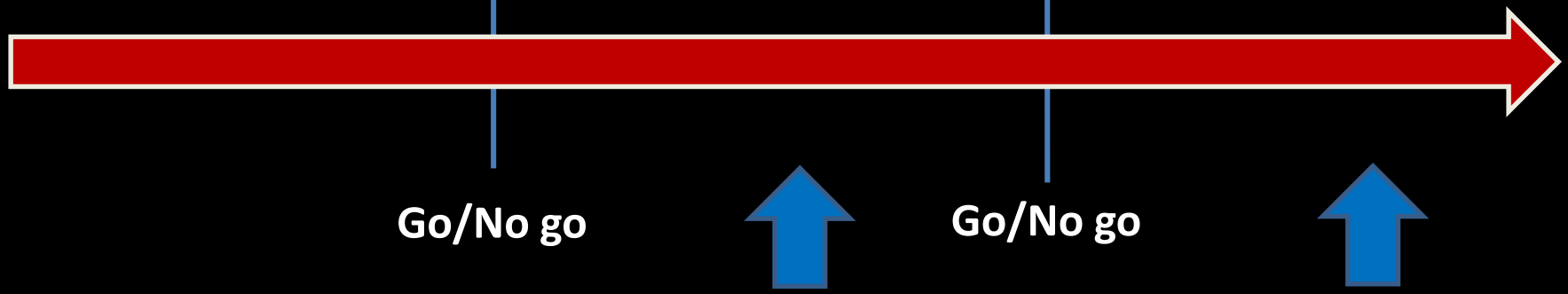
Clinical trials:

- Tool for screening new therapies
- Assessment of biological effect & effective dose
- Assessment of therapeutic effect
  - Objective response
    - Important trial endpoint & surrogate for clinical outcome
  - Response categorisation
    - Standardisation
    - Reproducible

Clinical Trials:

Phase I	Phase II	Phase III
▪ Safety/Toxicity/Dosage	▪ Therapy effectiveness ▪ Safety	▪ Randomisation ▪ Tested vs standard treatment

Question: Is the therapy safe & is there biological activity?	Question: Does the therapy work sufficiently well?	Question: How well does the therapy compare to what we have?

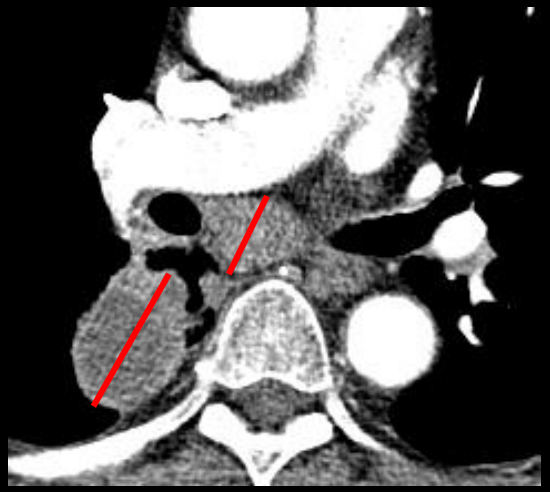


Response Categorisation

- **Classification of Response:**
  - Complete remission
  - Partial remission
  - Stable disease
  - Progressive disease

Response Criteria in Solid Tumours: RECIST 1.1

Validated response biomarker:
Clinical trial end point that has proven useful for screening new therapeutic agents



- **Response classification:**
  - **Complete remission (CR)**
  - **Partial remission (PR)**
  - **Stable disease (SD)**
  - **Progressive disease (PD)**

Target lesions:

- Longest dimension except nodes (short axis)

Eisenhauer et al. Eur J Cancer 2009;45:228-47
Therasse P et al. J Natl Cancer Inst 2000

Response Categorisation

Response criteria for evaluation of target lesions
Complete Response (CR): Disappearance of all target lesions (TL) All nodes <10 mm i.e. non-pathological
Partial Response (PR): **>30% decrease** in the sum of TL diameters
Stable Disease (SD): Neither PR nor PD
Progressive Disease (PD): **> 20% increase** in the sum of TL diameters Absolute increase of at least 5 mm **New lesions**

Eisenhauer et al. Eur J Cancer 2009;45:228–47

RECIST Measurable Disease

Target lesions:

Maximum 5, 2 per organ

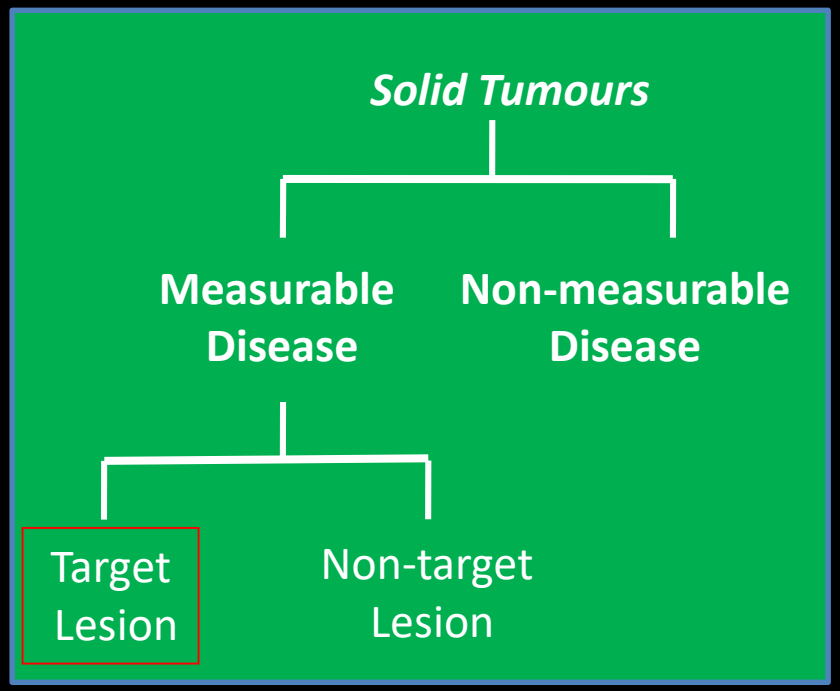
- >10mm lesion or 15mm node (short axis)

Non-target lesions:

- >10mm lesion

Non-measurable disease:

- <10mm lesions
- Pleural effusion, ascites, lymphangitis, bone metastases



Eisenhauer et al. Eur J Cancer 2009;45:228–47

Overall Response

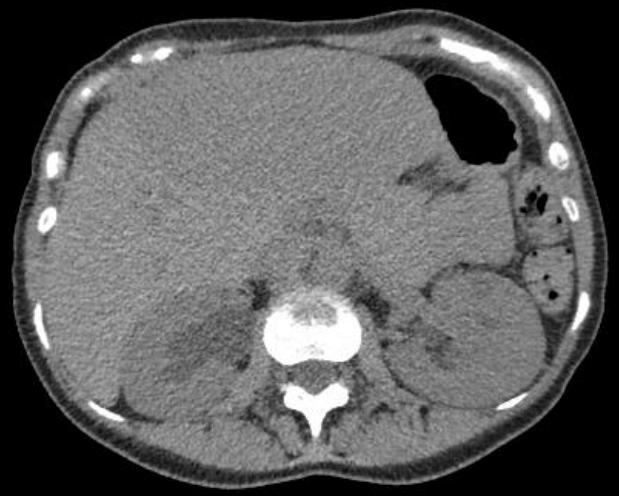
Target Lesion	Non-target	New Lesion	Overall Response
CR	CR	No	**CR**
CR	Non-CR/PD	No	**PR**
PR	Non-PD	No	**PR**
SD	Non-PD	No	**SD**
PD	Any	Yes/No	**PD**
Any	PD	Yes/No	**PD**
Any	Any	Yes	**PD**

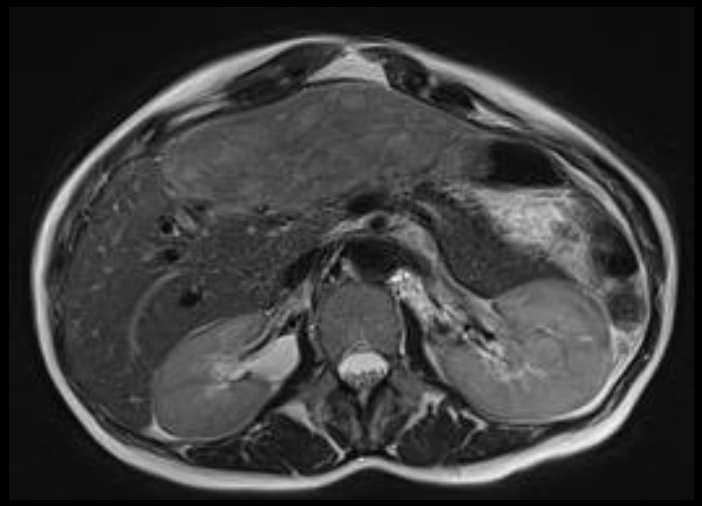
CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease

MRI or CT for RECIST?

Advantages of MRI over CT:

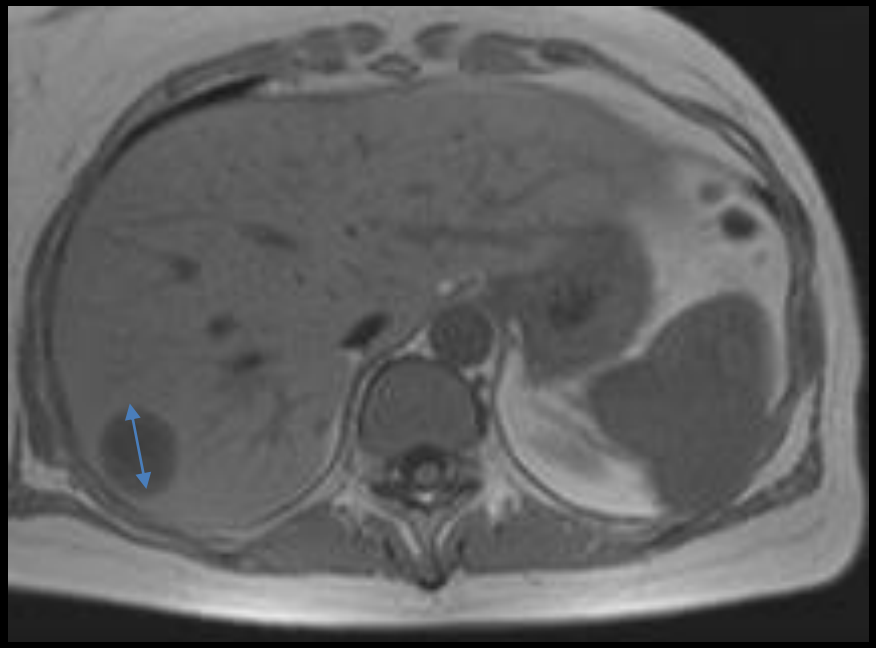
- Higher contrast to noise
- Better lesion delineation
- Specific sites:
  - Liver
  - Pelvis
  - Brain

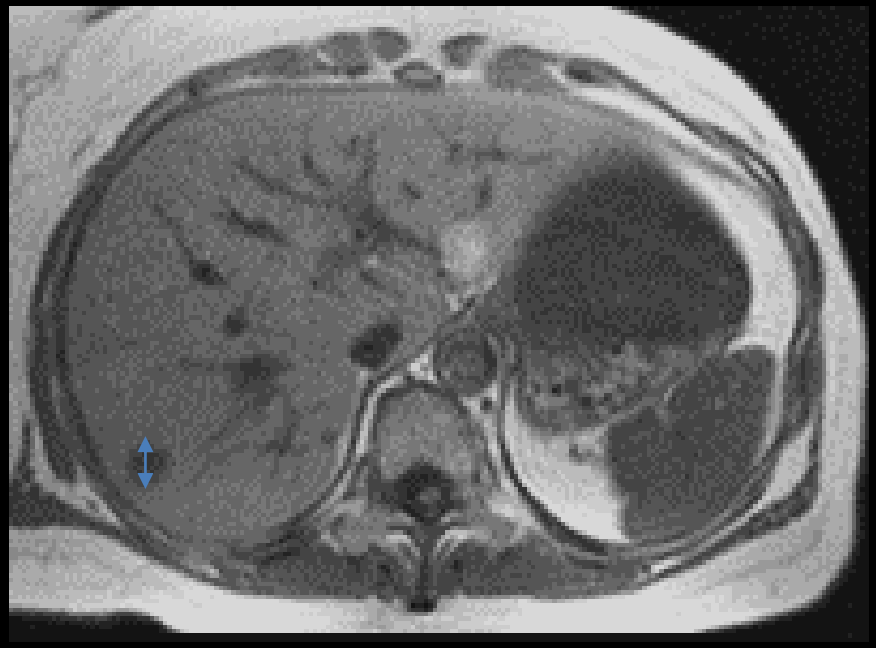




RECIST 1.1

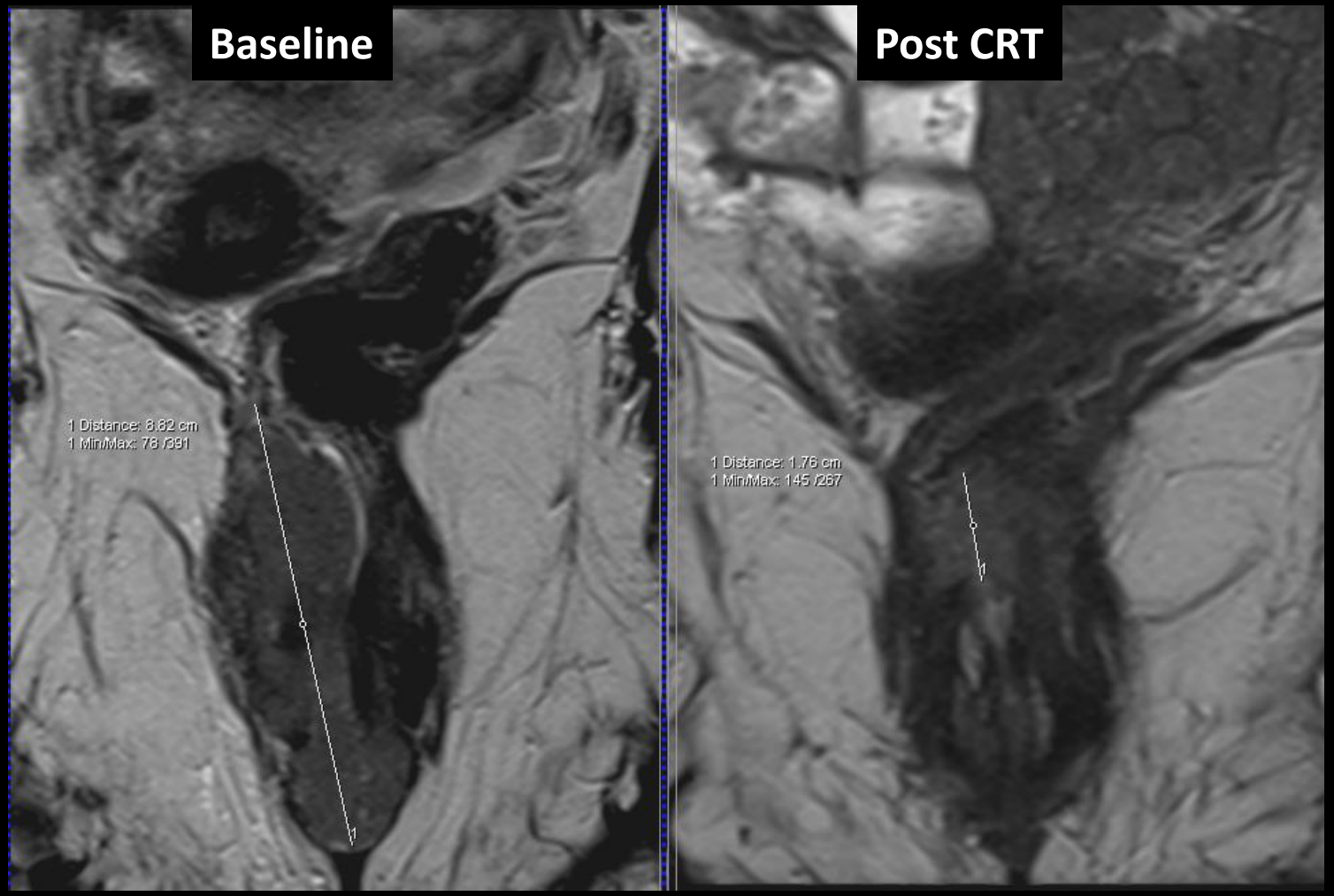
Liver metastasis:





Partial response: >30% reduction in maximum size

RECIST 1.1

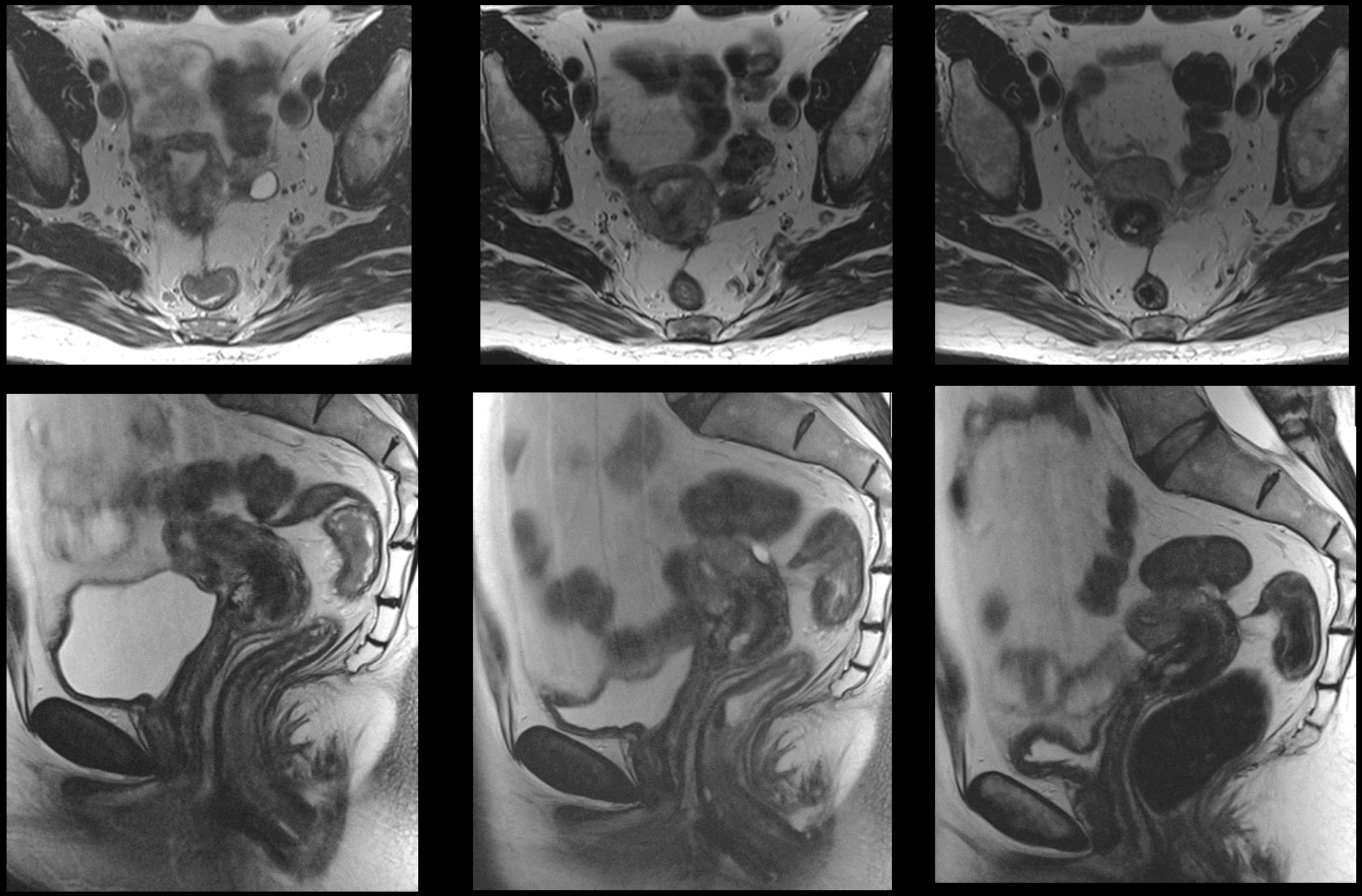


Partial response: 8.8-1.8/8.8*100= -79.5%

Baseline

Post C3

Post C6



Limitations of RECIST

- Not all therapies result in initial shrinkage yet are effective e.g. anti-angiogenic therapies, immunotherapies
- Side effects of some therapies can hamper response assessment
- Not all lesions are best evaluated in portal venous post contrast phase e.g. hepatocellular carcinoma, renal cell carcinoma

Modified RECIST: HCC

Modified RECIST Criteria:

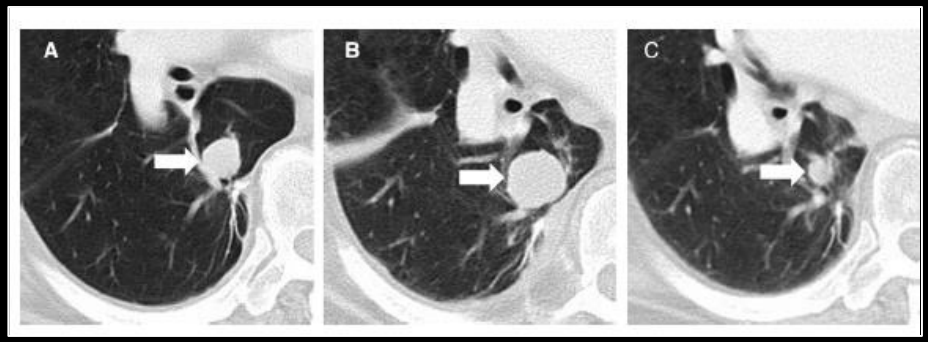
CR	PR	SD	PD
Resolution of arterially enhancing target lesions	At least 30% reduction in sum longest diameter of arterially enhancing target lesions	Response not fulfilling PR or PD category	At least 20% increase in sum longest diameter of arterially enhancing target lesions or new lesions

Lesions measured in the arterial phase: Max 2 lesions

Hepatocellular Carcinoma

Immune Response Criteria

- Different patterns seen in response to treatment due to antitumor effects by inducing cancer specific immune responses or by modifying native immune processes



Baseline **12wks** **24wks**

From:Nishino M et al. Eur J Radiol 2015; 84: 1259–1268

Immune Response Criteria

iRC: Bidimensional; Max 5/organ; Up to 10 visceral & 5 cutaneous lesions

CR	PR	SD	PD
Resolution of target lesions & all nodes <10 mm in short axis	>50% decrease from baseline	Neither PR not PD	≥25% increase from the nadir

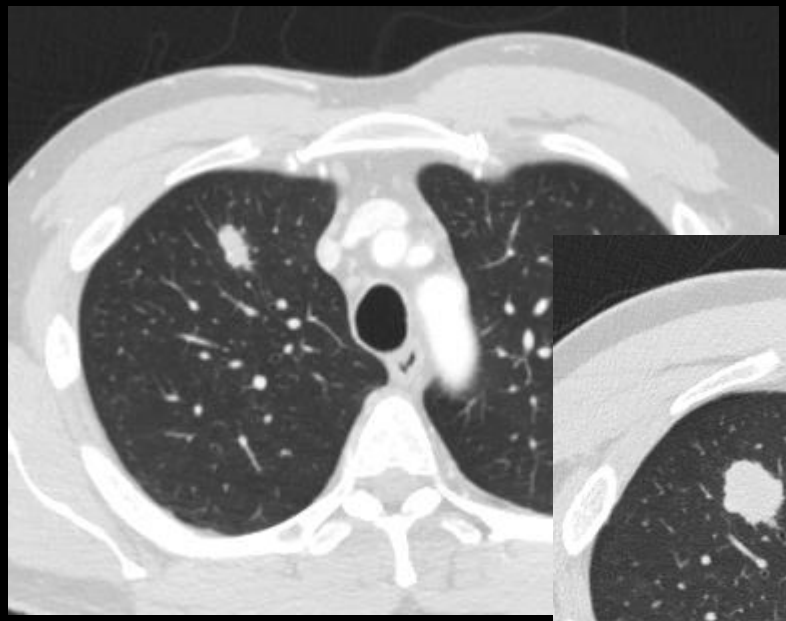
iRC: Unidimensional simulating RECIST 1.1; Max 2/organ & 5 total

CR	PR	SD	PD
Resolution of target lesions & all nodes <10 mm in short axis	>30% decrease from baseline	Neither PR not PD	≥20% increase from the nadir

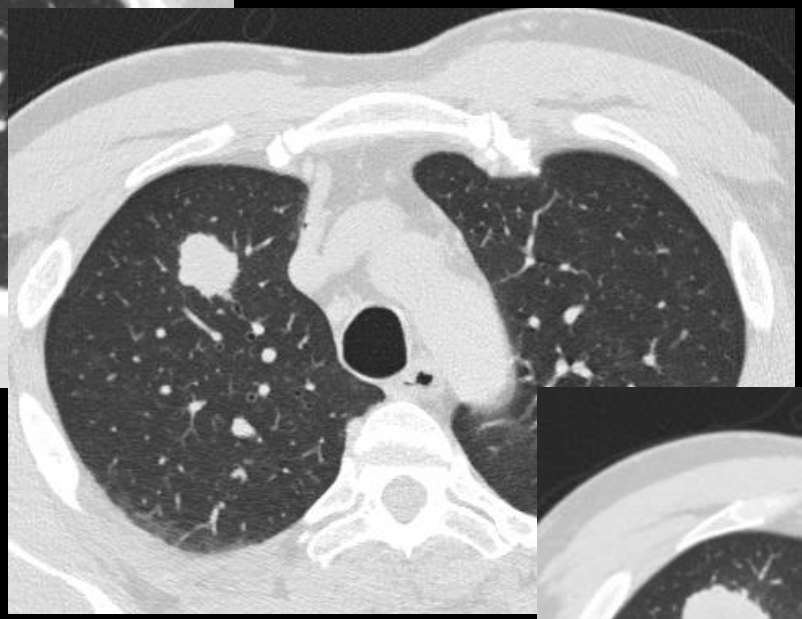
New lesions do not define progression & measurements are included in TL; PD or PR must be confirmed by 2 consecutive observations >4wks apart

Wolchok JD et al. Clin Cancer Res 2009;15(23):7412–20
Nishino M et al. Eur J Radiol 2015; 84: 1259–1268

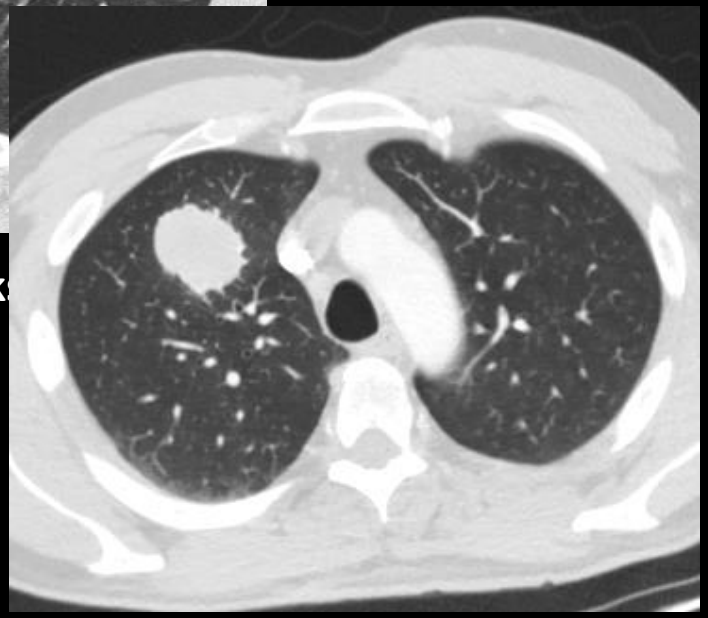
Nivolumab in metastatic RCC



Baseline



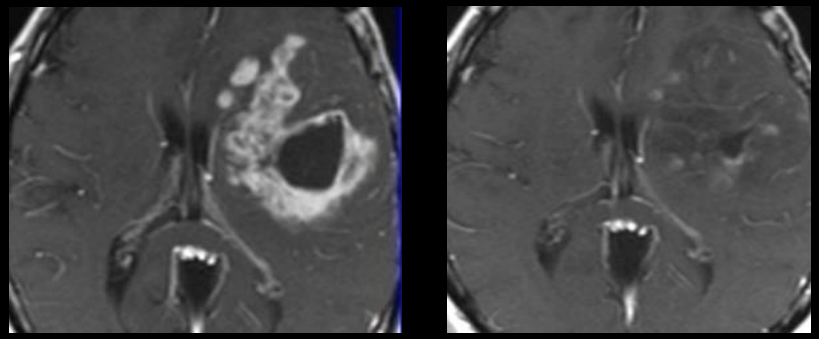
12 week



24 weeks

High Grade Gliomas

RANO criteria



- Post contrast T1W: >10mm
- Bidimensional measurement excluding cystic cavity

- **Response classification:**
  - **Complete remission (CR)**
  - **Partial remission (PR)**
  - **Stable disease (SD)**
  - **Progressive disease (PD)**

- PR: >50% decrease in enhancing lesions; stable/improved non-enhancing T2/flair lesions
- PD: >25% increase in enhancing lesions; increase in non-enhancing T2/flair lesions; new lesions

Wen et al. J Clin Oncol 2010; 28: 1963-72

Clinical Trials of Novel Agents:

Phase I	Phase II	Phase III
▪ Safety/Toxicity/Dosage	▪ Drug effectiveness ▪ Safety	▪ Randomisation ▪ Tested vs standard treatment

Question: Is the agent safe & is there biological activity?

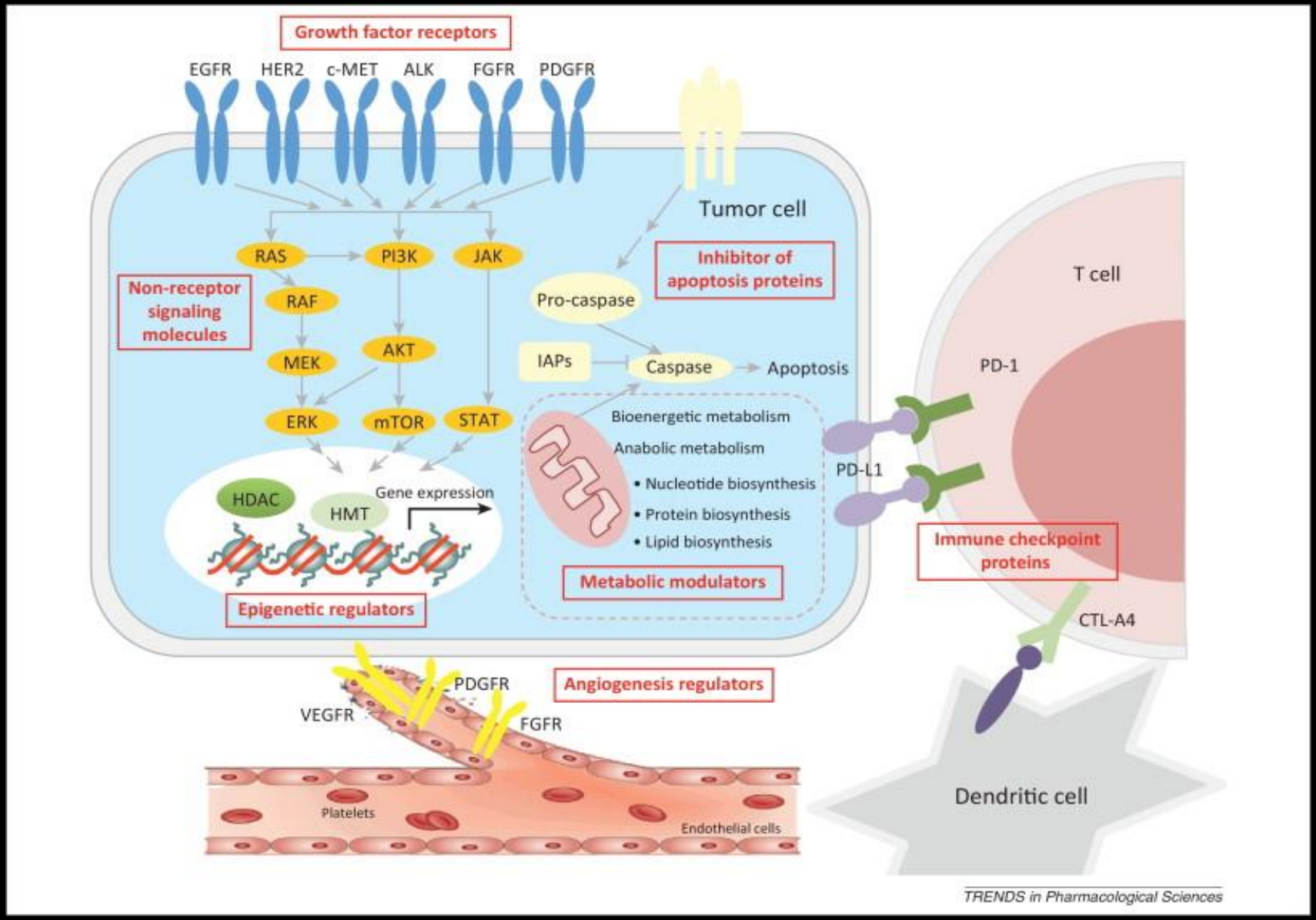
Question: Does the drug work sufficiently well?

Question: How well does the drug work compared to what we have?

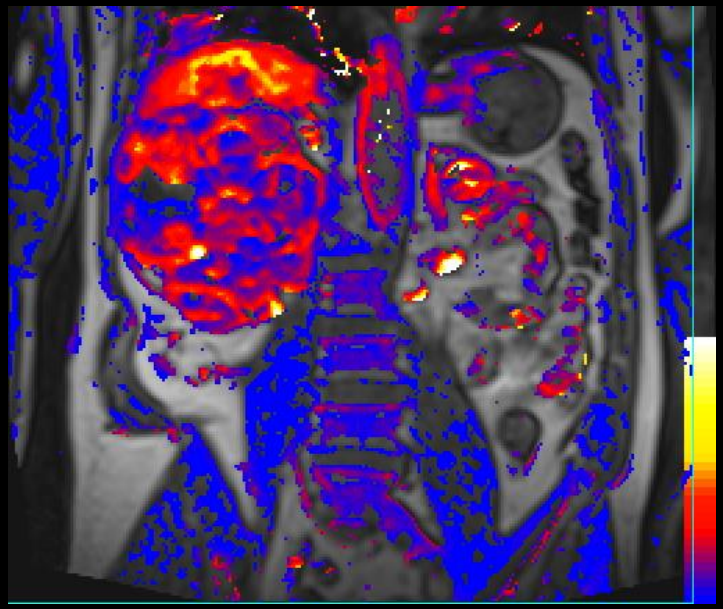
Go/No go

Go/No go

Targeted imaging


Growth factor receptors
EGFR
HER2
c-MET
ALK
FGFR
PDGFR
Tumor cell
RAS
PI3K
JAK
RAF
MEK
AKT
ERK
mTOR
STAT
Non-receptor signaling molecules
Inhibitor of apoptosis proteins
Pro-caspase
IAPs
Caspase
Apoptosis
Bioenergetic metabolism
Anabolic metabolism
• Nucleotide biosynthesis
• Protein biosynthesis
• Lipid biosynthesis
Metabolic modulators
HDAC
HMT
Gene expression
Epigenetic regulators
T cell
PD-1
PD-L1
Immune checkpoint proteins
CTL-A4
Dendritic cell
PDGFR
VEGFR
FGFR
Angiogenesis regulators
Platelets
Endothelial cells
TRENDS in Pharmacological Sciences

Vascular Response Markers



- DCE-MRI or CT used in >100 early phase trials of anti-vascular drugs
- ΔK^{trans} & $IAUC_{60}$:
  - Proof-of-principle
  - Optimum drug dose & schedule e.g. cediranib*, brivanib**

O'Connor JP et al. Nat Rev Clin Oncol 2012; 9: 167-77
*Drevs J et al. J Clin Oncol 2007; 25: 3045-54; **Jonker et al. Ann Oncol 2011; 22: 1413-9

Vascular Response Assessment

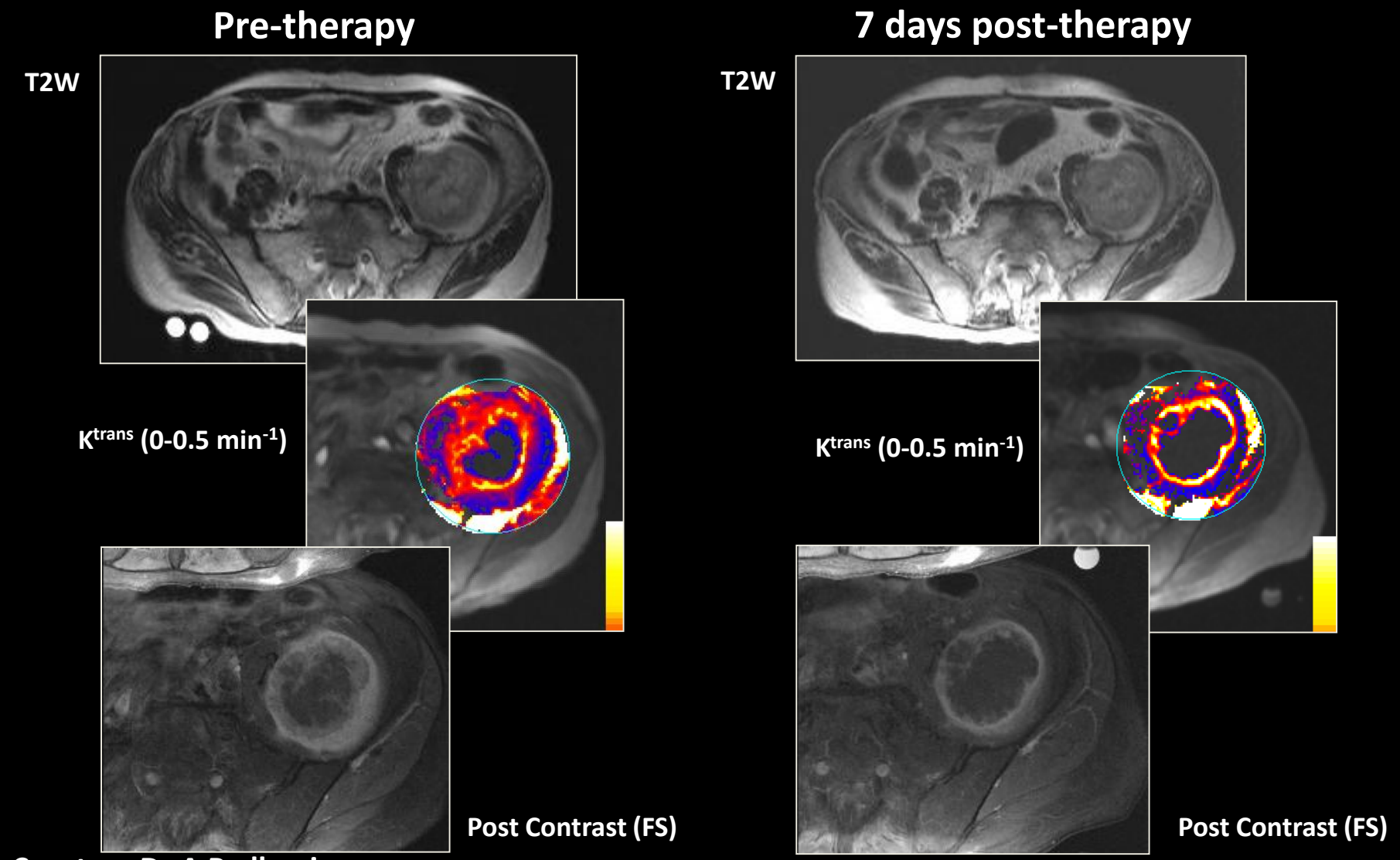
Effects measured by T1 DCE-MRI

Therapy	Measured effect
Chemotherapy	↓ IAUGC, K^{trans}
Radiation	↑ IAUGC, K^{trans} initially, then ↓
Anti-angiogenic agents	↔↑ IAUGC, K^{trans} initially, then ↓
Ablative therapy	↓ IAUGC, K^{trans}

IAUGC = Initial area under the Gadolinium curve; K^{trans} = transfer constant

Extent of changes depends on therapy evaluated & timing to therapy

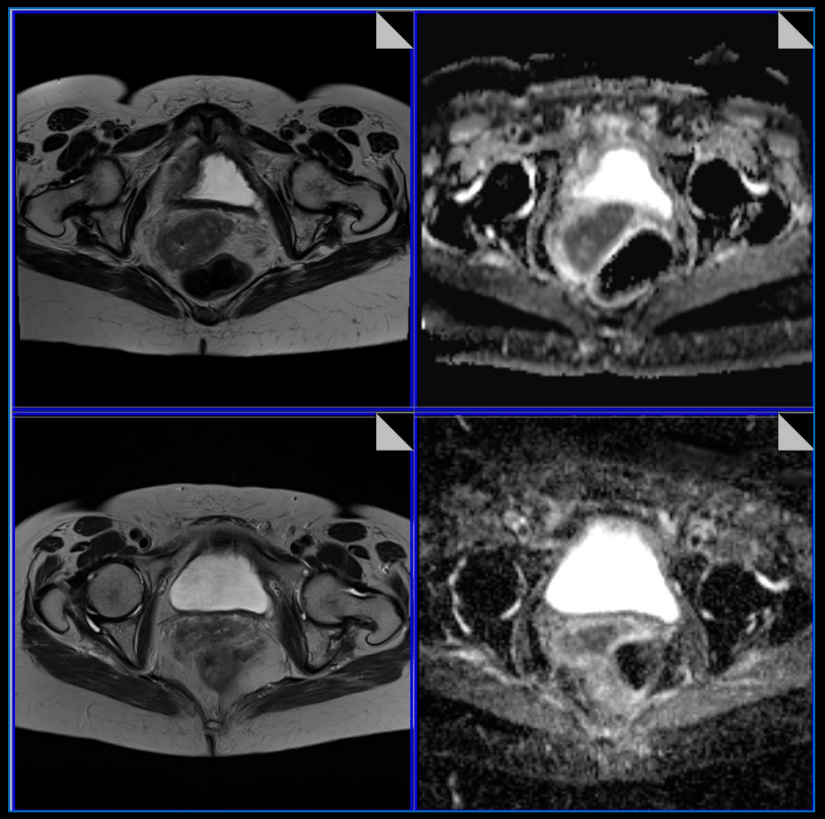
Vascular Pruning with anti-VEGF TKRi



Courtesy Dr A Padhani

Diffusion Response Markers

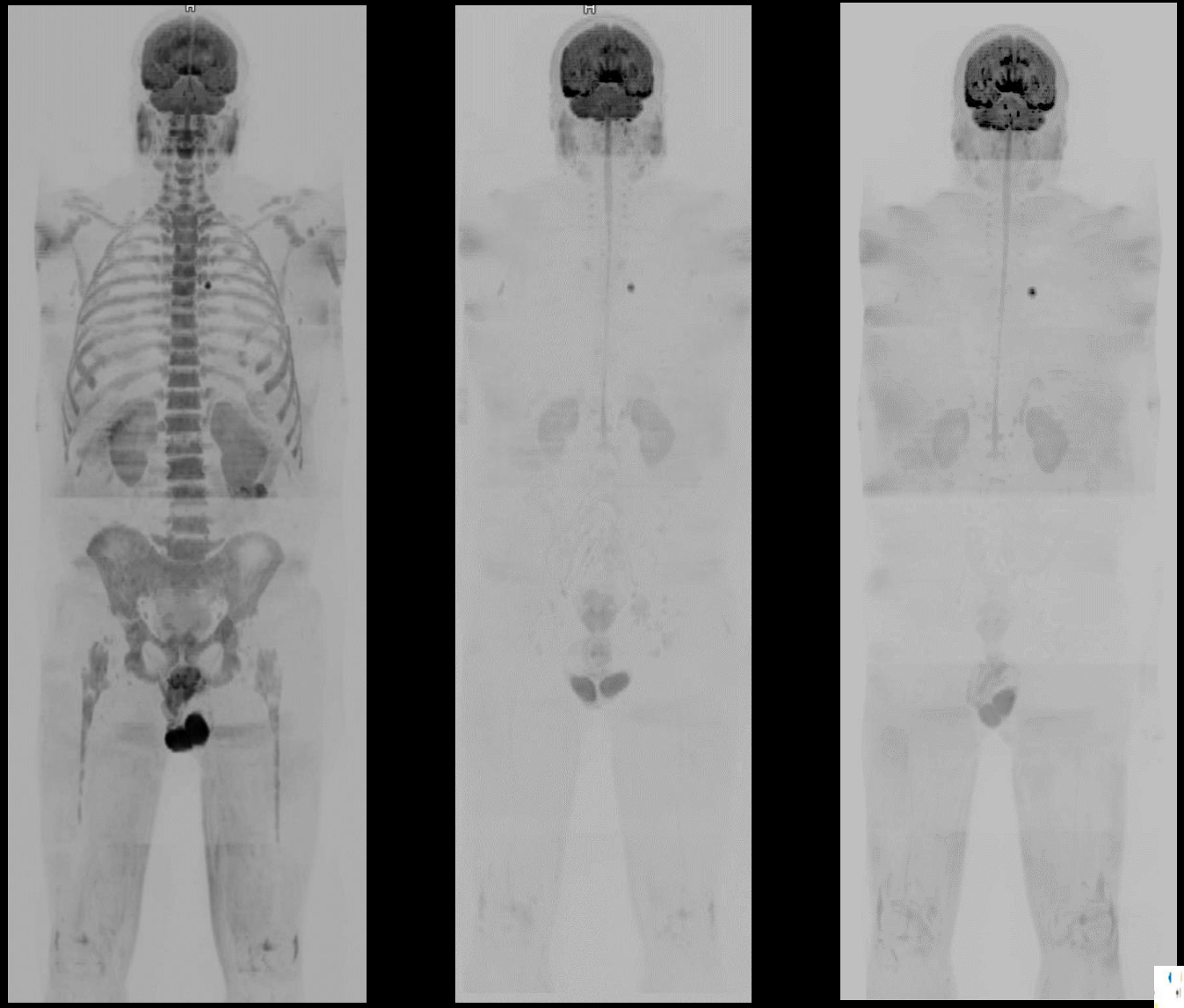
- Diffusion MRI used in >60 therapy studies
- Therapy effects:
  - Decrease in high b-value signal intensity
  - Increase in tumour ADC ≥30%
  - Early response (14d) assessment achievable



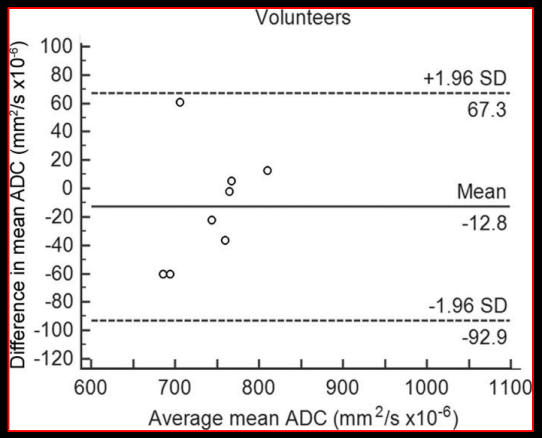
ADC: 0.74 to 1.05 x10^{-3} mm^2/s

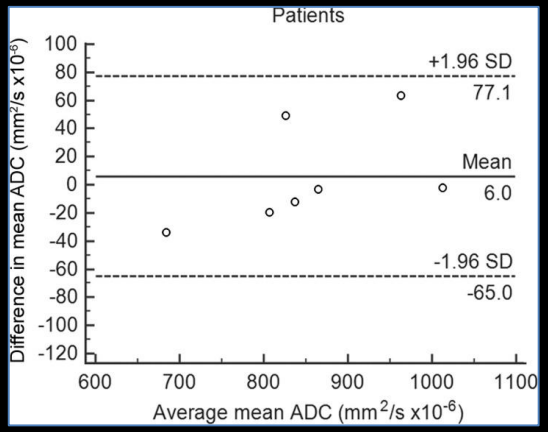
Afaq A et al. Cancer Imaging 2010; 10: S179-188;
Bains LJ et al. Cancer Imaging 2012; 12:395-402

Myeloma



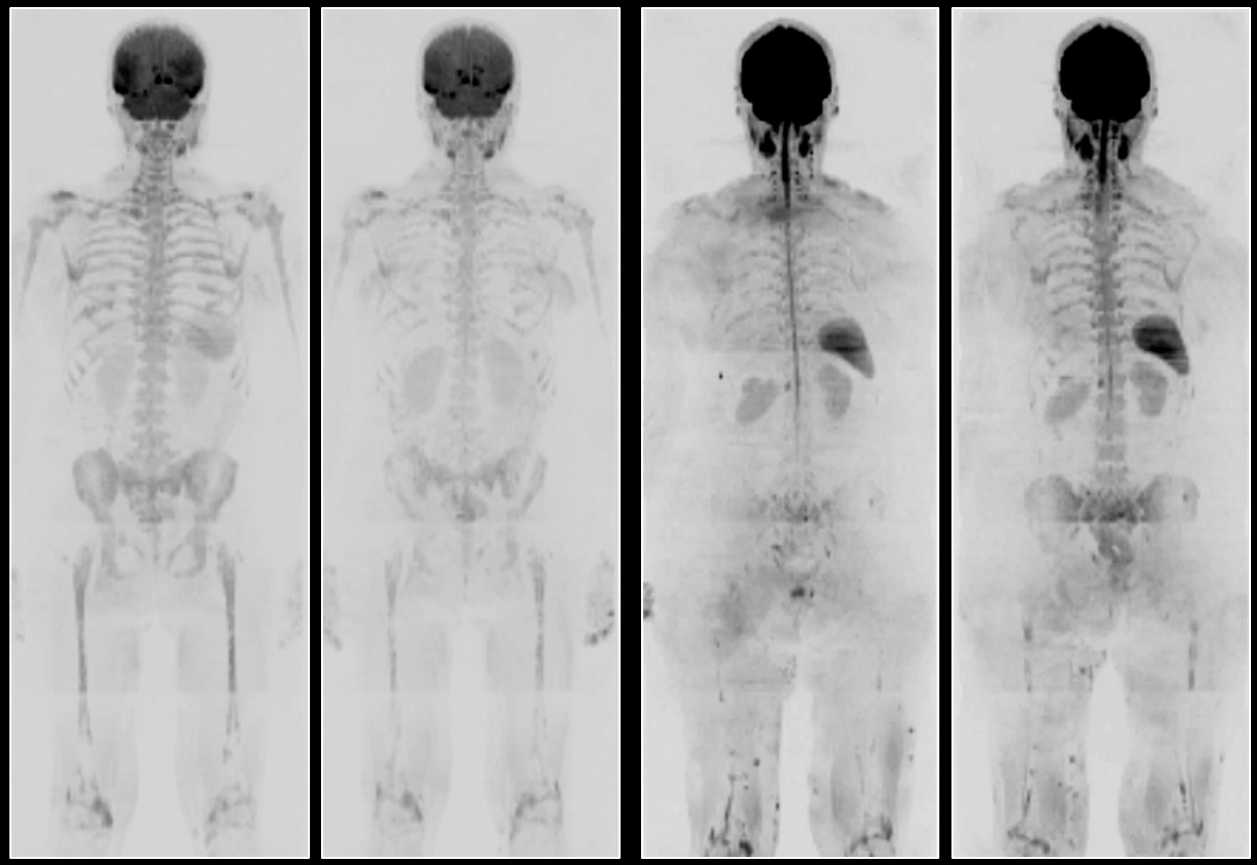
Treatment Response Assessment





Bland Altman Plots

Repeatability: CoV 2.8-3.8%



Responder **Non-Responder**

From: Giles et al. Whole-Body Diffusion-weighted MR Imaging for Assessment of Treatment Response in Myeloma. Radiology. 2014

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Treatment Response Assessment

Tumour Type	Treatment	Imaging	Findings	Author, Year
Symptomatic Myeloma: Mixed population n=34 13 weeks	Cyclophosphamide Lenalidomide , Bortezomib, Dexamethasone	$DWI_{50\text{-}900}$ T1, STIR	**Increase in ADC with treatment** SN: 86%, SP: 80%, PPV_{adj}: 94.5%, NPV_{adj}: 59%; prevalence of response: 80%	Giles et al, 2014
Symptomatic Myeloma n=12 3 weeks	Treatment not stated	$DWI_{50\text{-}800}$ T1, STIR	**Increase in ADC with treatment**	Horger et al, 2011
Symptomatic Myeloma n=20 4-6 weeks 20 weeks	Cyclophosphamide Thalidomide Dexamethasone	DWI T1, STIR	**Increase in ADC with treatment**	Messiou et al 2012

Imaging Biomarkers: Challenges

Imaging biomarkers in clinical trials

- Good QA & QC required
- Technical standardization required
- Minimum standards for measurement, analysis, & display
- Central review
- Baseline reproducibility should be part of study design

Leach M et al. Eur Radiol 2012;22(7):1451-64
Padhani AR et al. Neoplasia. 2009;11(2):102-25.
O'Connor J et al. Nat Reviews Clin Oncol 2016 (In press)

Imaging Biomarkers: Challenges

Discovery

Validation

Qualification

Preclinical study /Safety

al Gap 1

al Gap 2

Clinical Trials

Health Benefit


nature REVIEWS CLINICAL ONCOLOGY

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NATURE REVIEWS CLINICAL ONCOLOGY | CONSENSUS STATEMENT OPEN

Imaging biomarker roadmap for cancer studies

James P. B. O'Connor, Eric O. Aboagye, Judith E. Adams, Hugo J. W. L. Aerts, Sally F. Barrington, Ambros J. Beer, Ronald Boellaard, Sarah E. Bohndiek, Michael Brady, Gina Brown, David L. Buckley, Thomas L. Chenevert, Laurence P. Clarke, Sandra Collette, Gary J. Cook, Nandita M. deSouza, John C. Dickson, Caroline Dive, Jeffrey L. Evelhoch, Corinne Faivre-Finn, Ferdia A. Gallagher, Fiona J. Gilbert, Robert J. Gillies, Vicky Goh, John R. Griffiths + et al.

Affiliations | Contributions | Corresponding author

Nature Reviews Clinical Oncology (2016) | doi:10.1038/nrclinonc.2016.162

O'Connor JP et al. Nat Rev Clin Oncol. 2017;14(3):169-186

In clinical trials
Alters patient care
Cost effective

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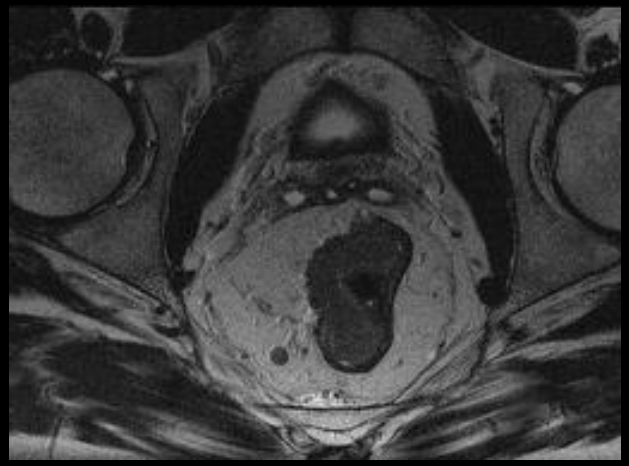
Clinical Pathways

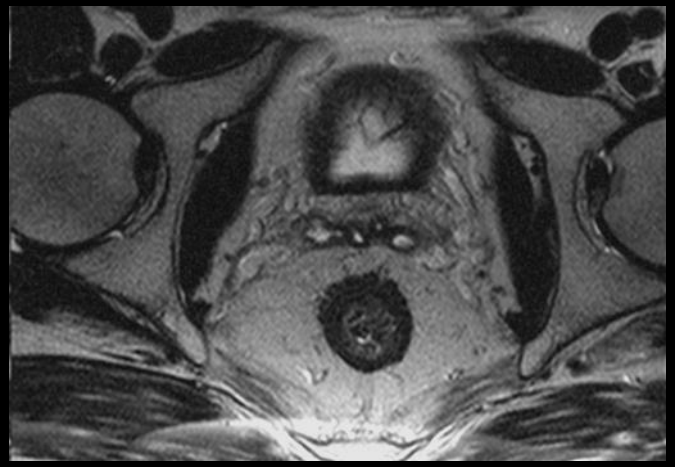
Assessing Therapy: Rectal Cancer

- MRI provides objective response assessment & judgement of whether R0 resection is viable following pre-operative therapy
- Selection of patients with imaging CR following pre-operative therapy for 'watch & wait'
- Increasing importance of accurate MRI assessment: Extraluminal/nodal disease

Habr-Gama et al. Semin Radiat Oncol 2011
Chawla S et al. Am J Clin Oncol 2014

Assessing Therapy: Rectal Cancer





Post surgery
Surveillance
Year 1

Baseline

12 weeks
Post CRT

6 & 12
months

Watch & Wait Approach

cCR, n=21

Year	Endoscopy	MRI	CT
1	4x	4x	2x
2	2x	2x	1x
3	2x	2x	1x
4	2x	2x	1x
5	2x	2x	1x

Maas M et al. J Clin Oncol 2011; 29: 4633-40

Definition of cCR:

- Downsizing with no residual tumour
- Residual fibrosis only
- Residual mural oedema
- No suspicious lymph nodes
- Negative tumour biopsy

MRI DWI - negative

Therapy Response Assessment: DWI

Added value of DWI:

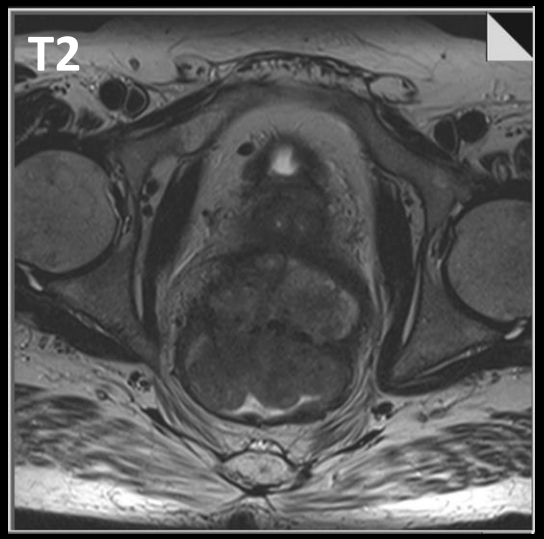
- Assessment of CR post CRT
- n=40
- 1.5T
- DWI: b0, 1000
- Qualitative assessment: Residual high signal intensity?

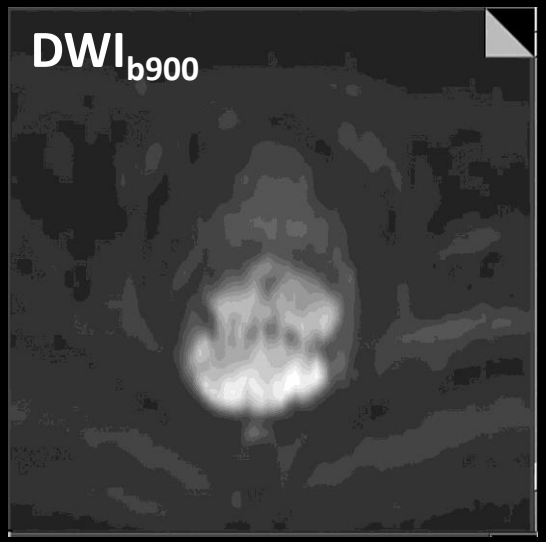
DWI better than T2 alone:

T2 (%)*				
Sens	Spec	Acc	PPV	NPV
45-55	77-79	70	45-46	79-81
DWI (%)*				
Sens	Spec	Acc	PPV	NPV
82-91	83	82-85	64-67	92-96

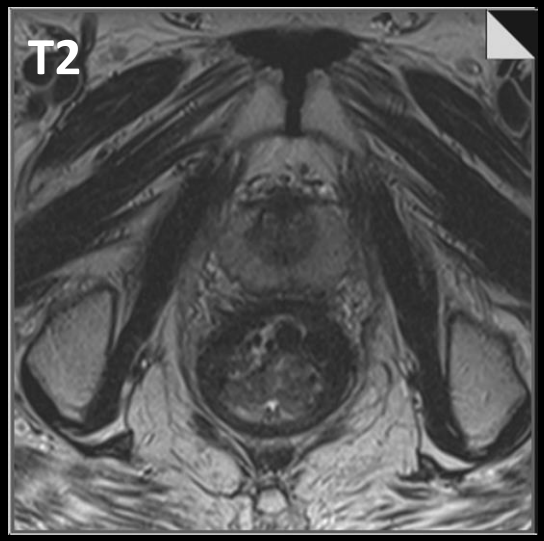
*** >1 reader**

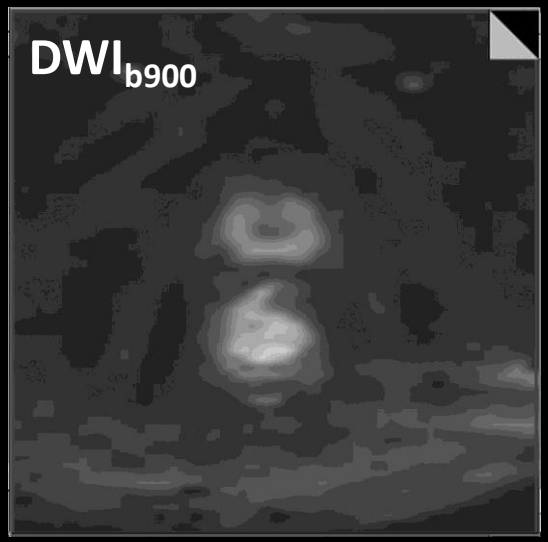
Kim SH et al. Radiology 2009; 253 (1): 116-25





Baseline





Immediate
Post CRT

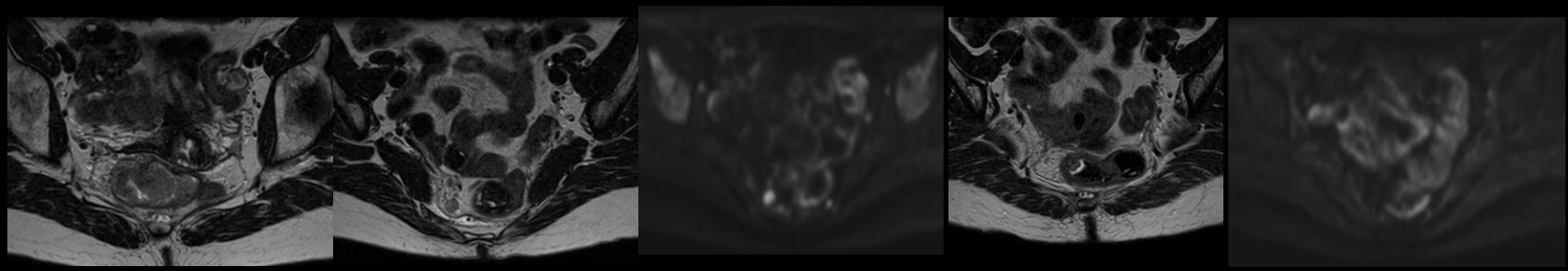
Qualitative assessment: Presence of DWI high b signal indicative of active tumour

Therapy Response Assessment: Nodes

Author, Yr	Pts	B values	Nodes	Findings: Qualitative
Post chemoradiation therapy: Qualitative				
Mizukami et al 2011	n=59	1.5T: 0,1000	Total: 1250 Met: 220	DWI+T2: Sn 97%, Sp 81%, PPV 52%, NPV 99%, Acc 84%
Ryu et al 2015	n=95	1.5T: 0,1000	Total: 199 Met: 30	DWI+T2: Sn 88%, Sp 73%, PPV 88%, NPV 73%, Acc 83%

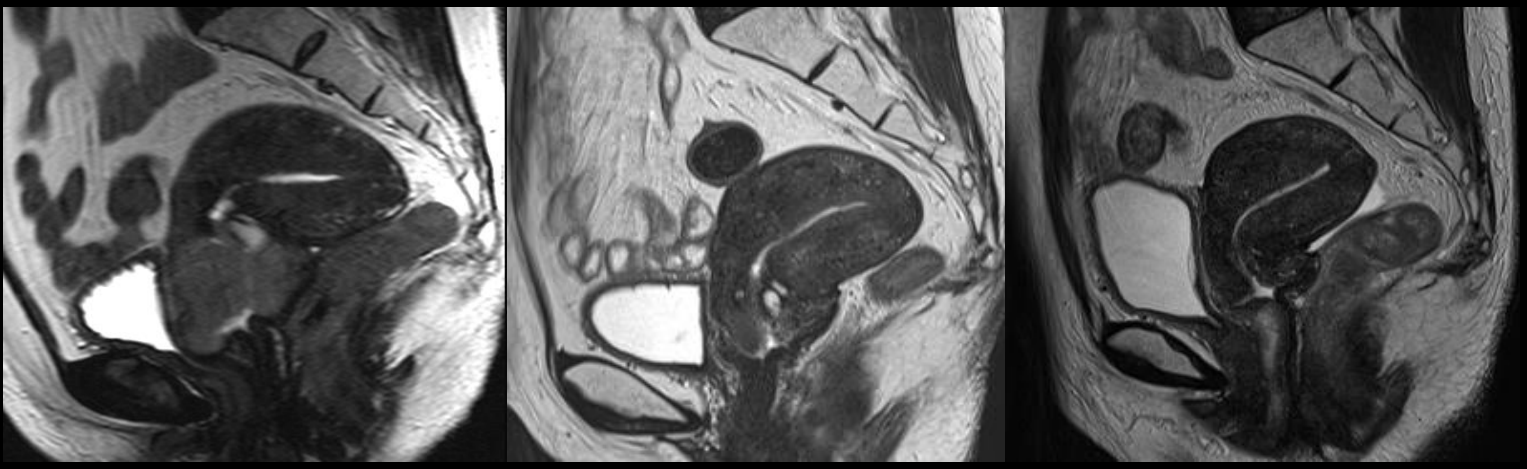
Mizukami Y et al. World J Surg 2011; 35: 895-9; Ryu KH et al. Acta Radiol 2015; Jan 30 Epub

Good Sensitivity & NPV



Baseline **Post CRT**

Assessing Therapy: Cervical Cancer



Surveillance Yr1,2

Baseline → 5wks Post CRT → Post BT → 3-6 monthly

Somoye et al. Eur Radiol. 2012;22(11):2319-27; Papadopoulou et al. Radiographics. 2016 Mar-Apr;36(2):538-53; Vincens et al s 2008;113(8):2158–2165.

Assessing Therapy: Cervical Cancer

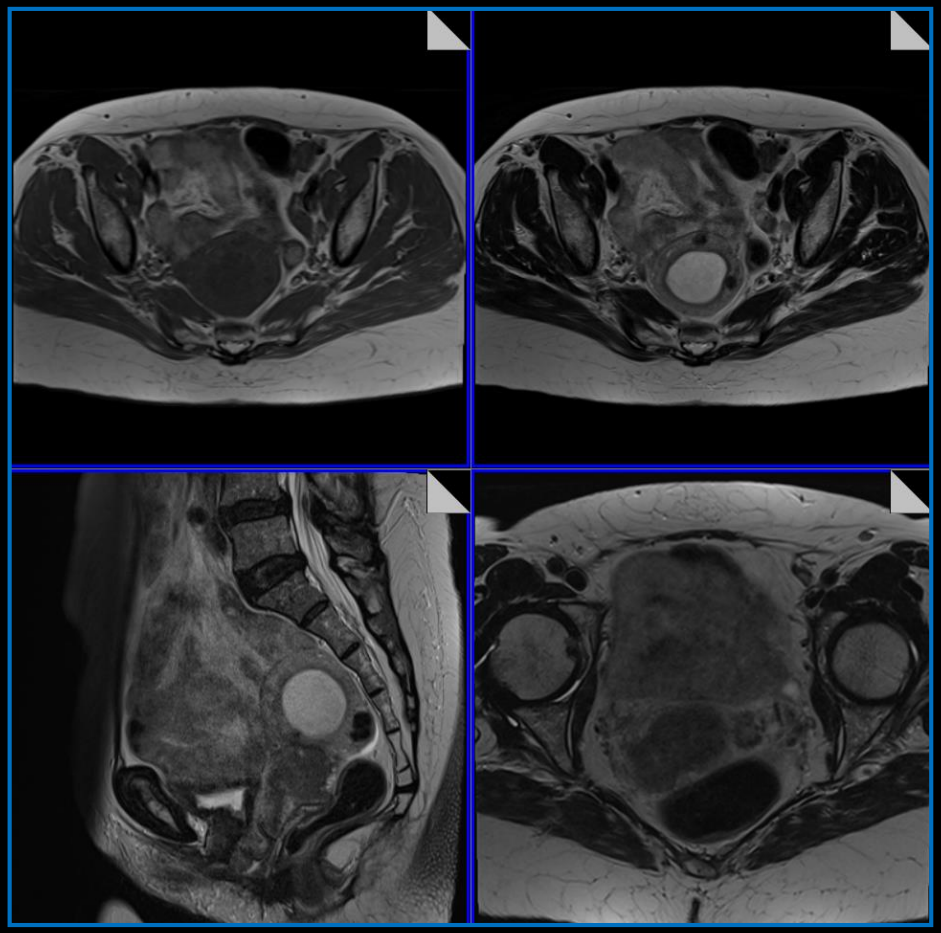
- n=60
- IB_2-IVB/recurrent
- Tumor **regression rate** (fast vs. slow) at mid-RT (45–50 Gy) best outcome **prediction for local control** (84% vs. 22%, $p < 0.0001$) & **disease-free survival** (63% vs. 20%, $p = 0.0005$)

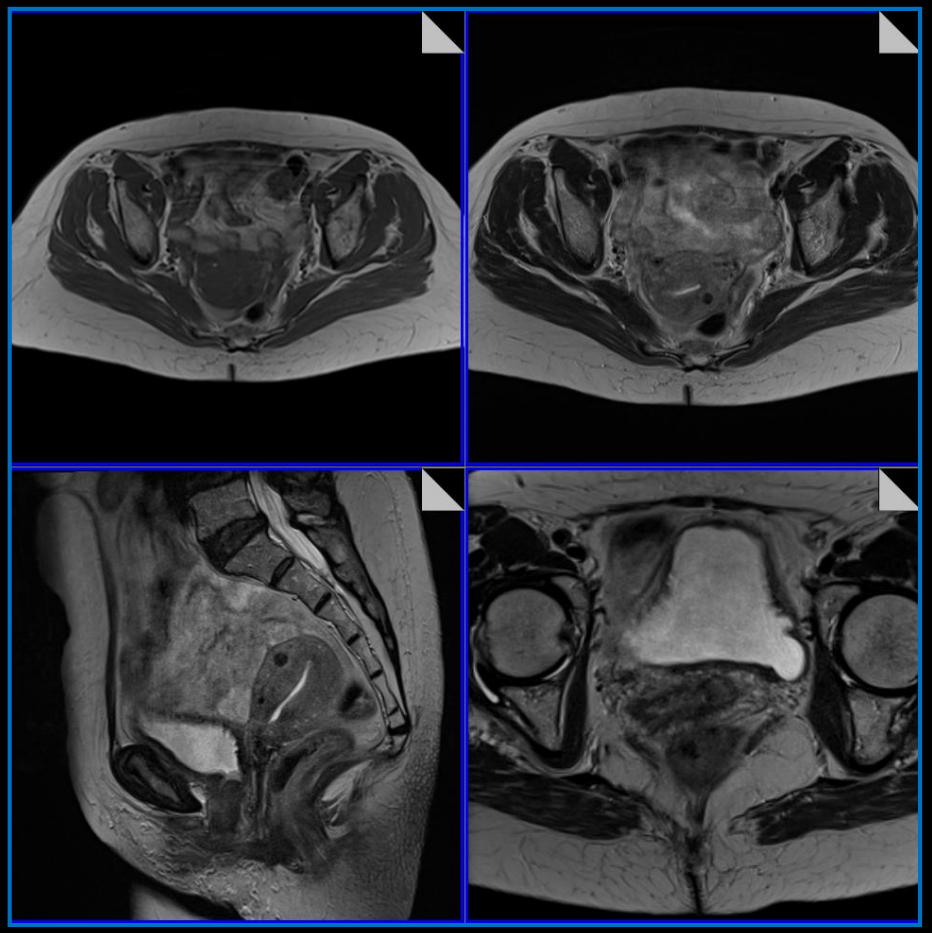
Mayr et al. Int J Radiat Oncol Biol Phys 2002;52(1):14-22

- N=80
- IB2 through IVA
- Combination of **pre RT tumour volume & MRI regression ratio 4-5 weeks post CRT** best predictor of local control: 89% sensitivity, 87% specificity, 88% accuracy for LR

Wang et al. Cancer 2010;116(21) 5093-101.

Assessing Therapy: Cervical Cancer





Baseline
FIGO IIIA

Post therapy:
Concurrent platinum based chemoradiotherapy
Intracavitary brachytherapy

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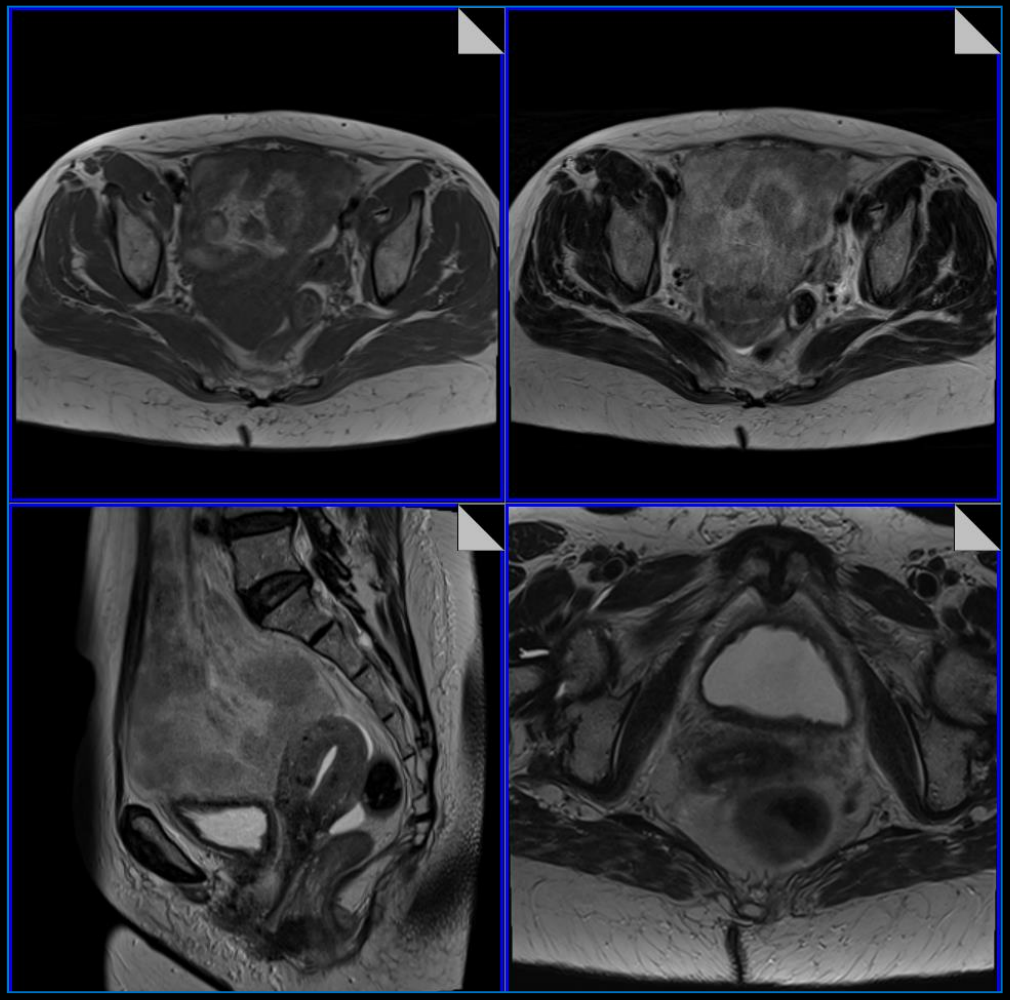
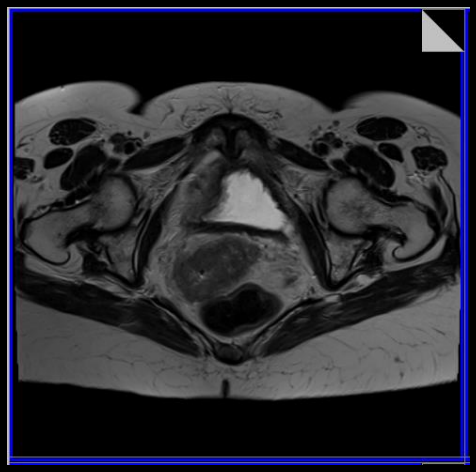
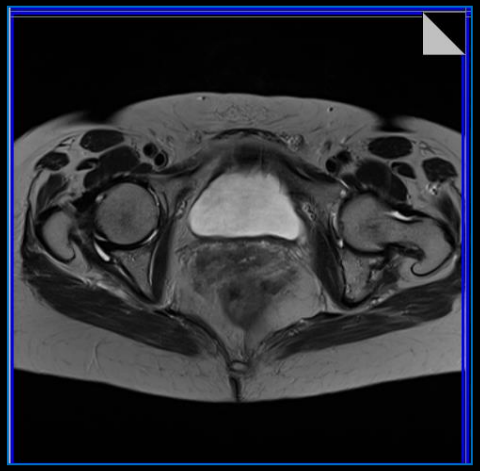
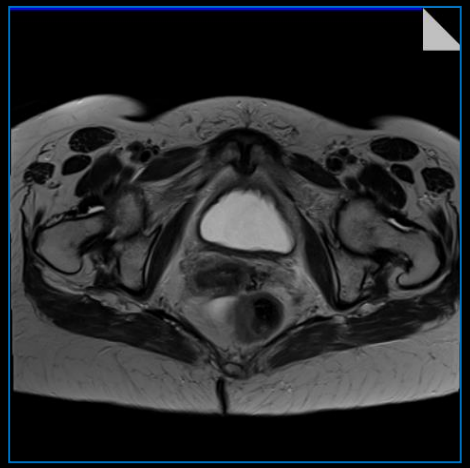
Assessing Therapy: Cervical Cancer



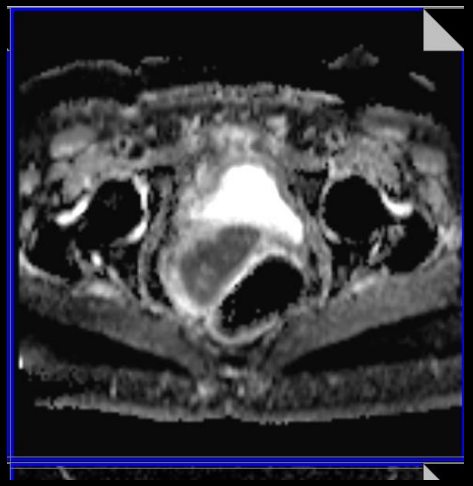
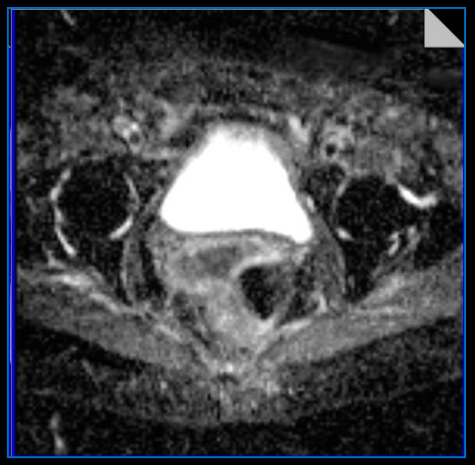
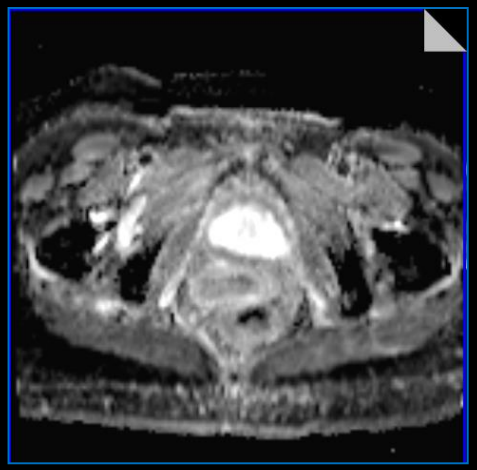
3 months
Post therapy

Assessing Therapy: Cervical Cancer

T2
Ax

DWI
ADC

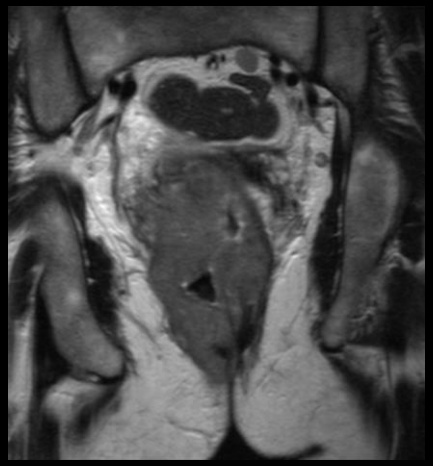




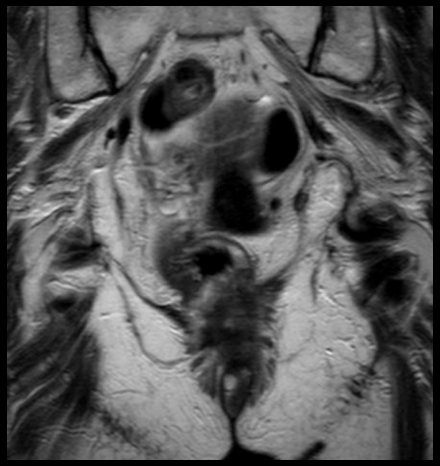
Assessing Therapy: Cervical Cancer

- n=50
- Pathological reference standard
- DWI & DCE MRI associated with incomplete response
- Mean ADC <1.40 X 10^{-3} mm^2/s (HR = 8.3), low ADC signal intensity (HR = 7.3), high DWI signal intensity (HR = 7.1) & time-signal intensity curve type B (initial rise > myometrium (HR = 4.3) associated with earlier recurrence (P < .05)

Jalaguier-Coudray et al. Radiology 2017 Mar 14 [Epub ahead of print]

Assessing Therapy: Anal Cancer



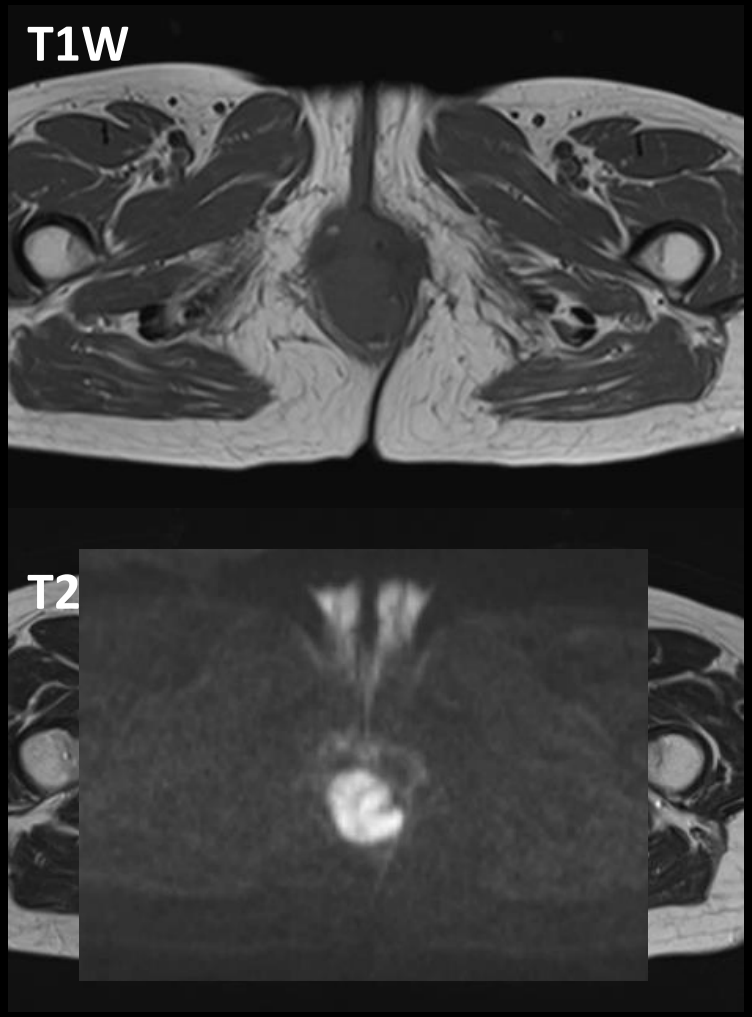


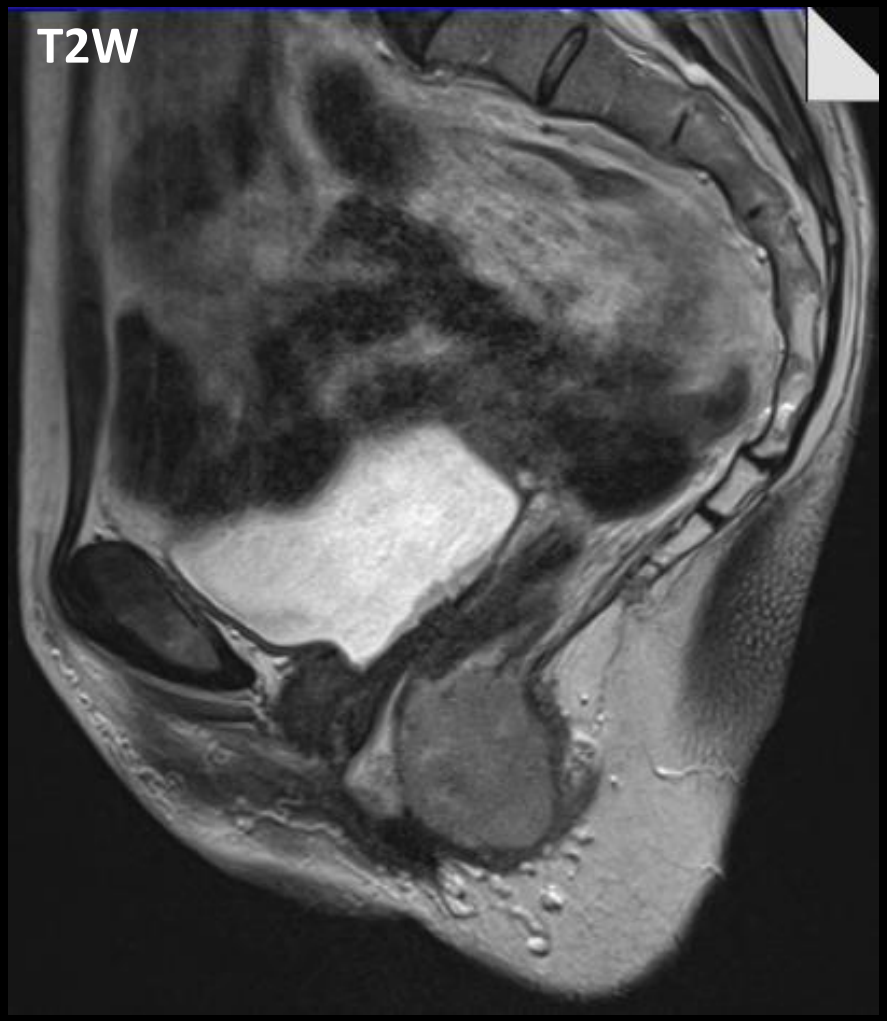
Surveillance
Yr 1,2

Baseline → 12 weeks Post CRT → 3-6 monthly

Jones CM et al. Br J Cancer. 2017;116(2):156-162; Glynne-Jones et al. Radiother Oncol. 2014;111(3):330-9; Gourtsoyianni et al. Abdom Imaging. 2014 ;39(1):2-17. ; Goh et al. Int J Radiat Oncol Biol Phys. 2010 Nov 1;78(3):715-21

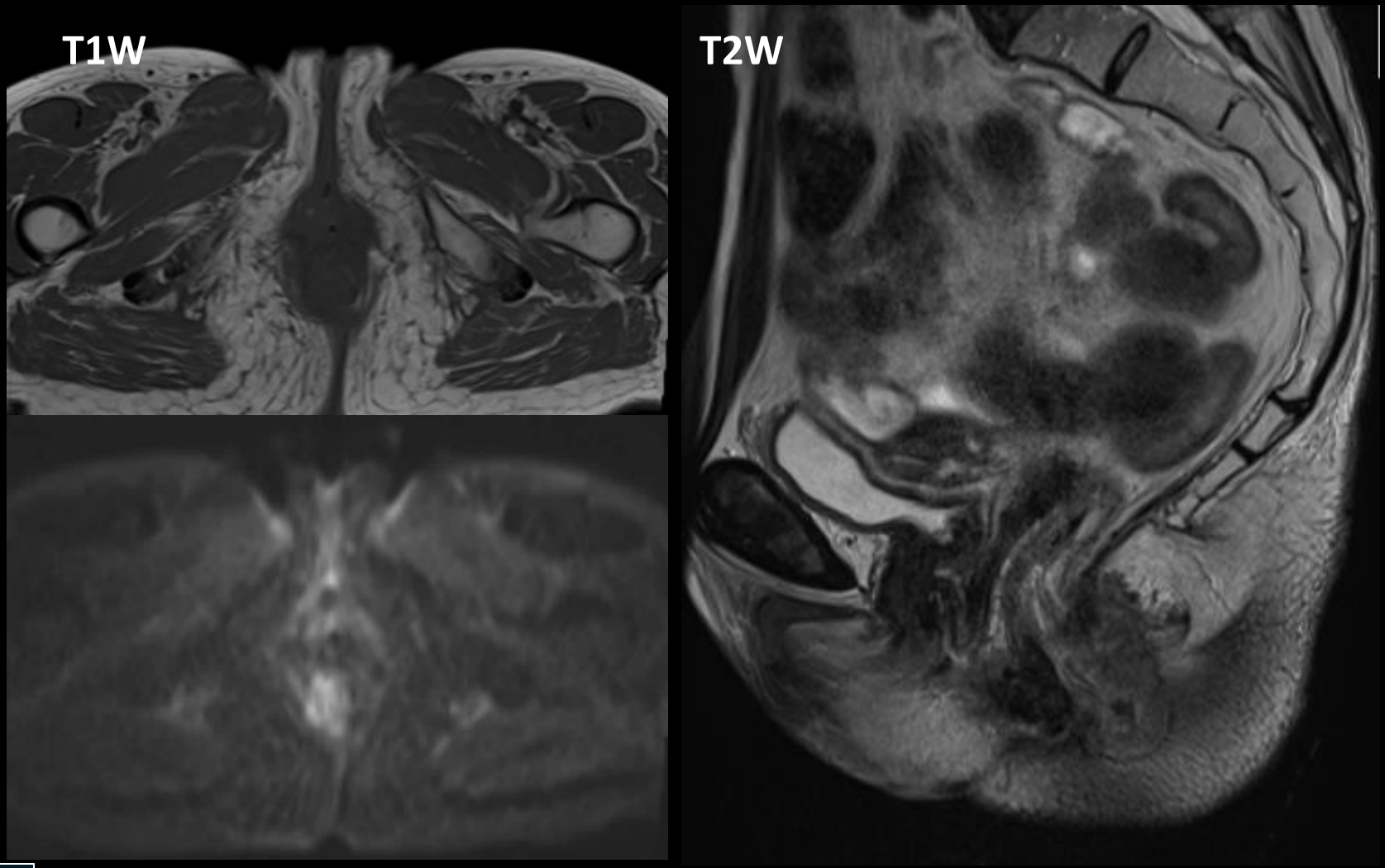
Assessing Therapy: Anal Cancer





Baseline

Assessing Therapy: Anal Cancer



Post CRT 3 months

PLATO: Eligibiilty

T1-2 (<=4cm) N0/X

T2 N1-3, T3/4 N any

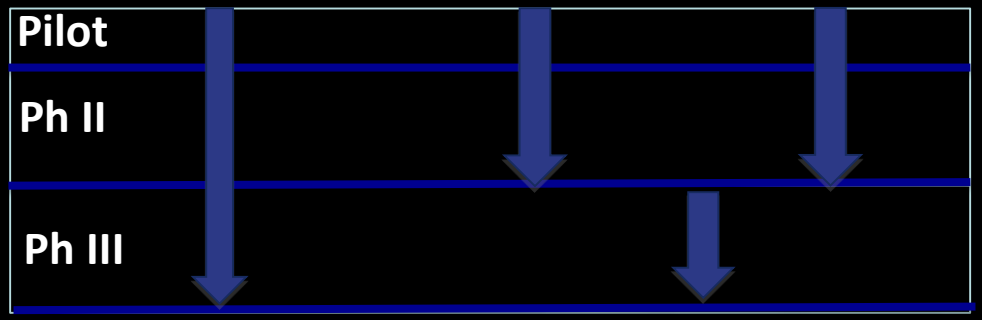
ACT4

- 41.4Gy 23F (CTV 34.5Gy)
- 50.4Gy 28F (CTV 40Gy)

Randomised 2:1 Phase II N=162
Control is a calibration arm
Primary end point 3yr LRF

ACT5

- 53.2Gy 28F GTV
- 58.8Gy 28F GTV
- 61.6Gy 28F GTV



Seamless Pilot / Phase II / Phase III N=640
Primary end point 3yr LRF

Imaging (Baseline): Pelvic MR + DWI; CT TAP; PET-CT recommended
Imaging (Post CRT): Pelvic MR + DWI at 3 & 6 months; CT TAP yrs 1,2,3
Toxicity assessment:- Acute toxicity CTCAE; Baseline and sequential PROMS (EORTC QLQ C30 and Anal cancer module)

Chief Investigators: Renehan, Muirhead, Adams, Harrison, Hawkins, Sebag Montefiore

Therapy: Effects & Complications

Acute effects:

- Proctitis, Enteritis
- Bullous edema of the bladder, urethritis, haematuria
- Sepsis

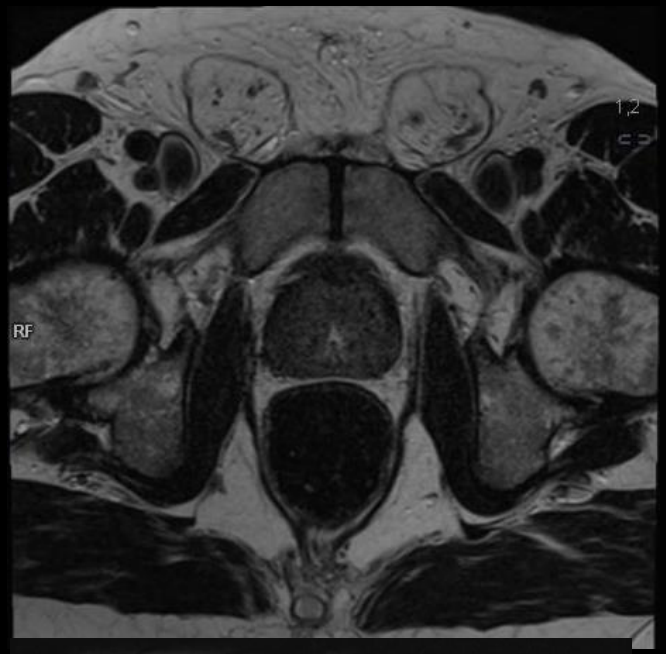
Sub-acute effects:

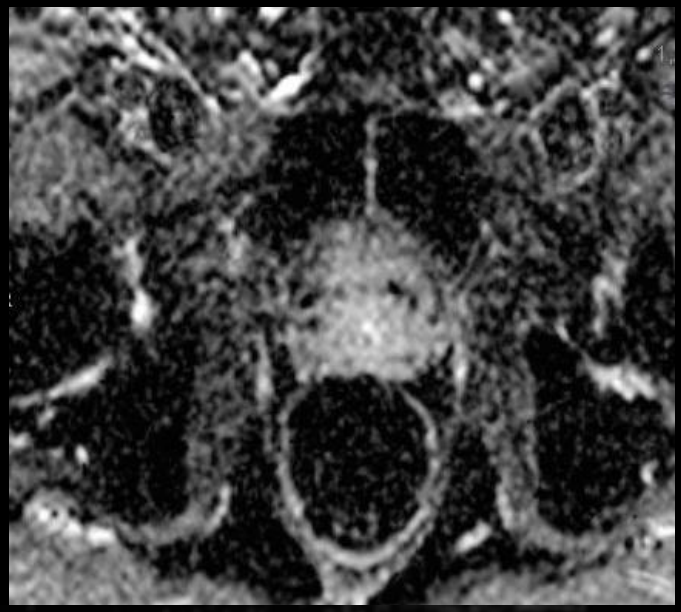
- Frequency of defecation
- Chronic perineal dermatitis
- Dyspareunia
- Impotence

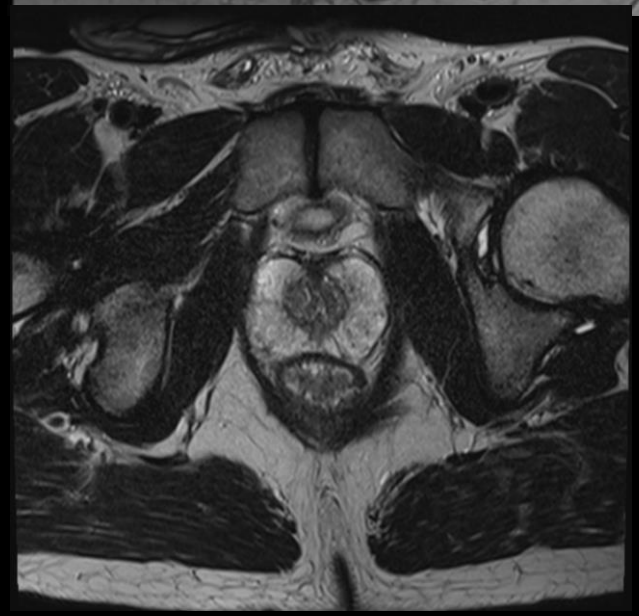
Late effects:

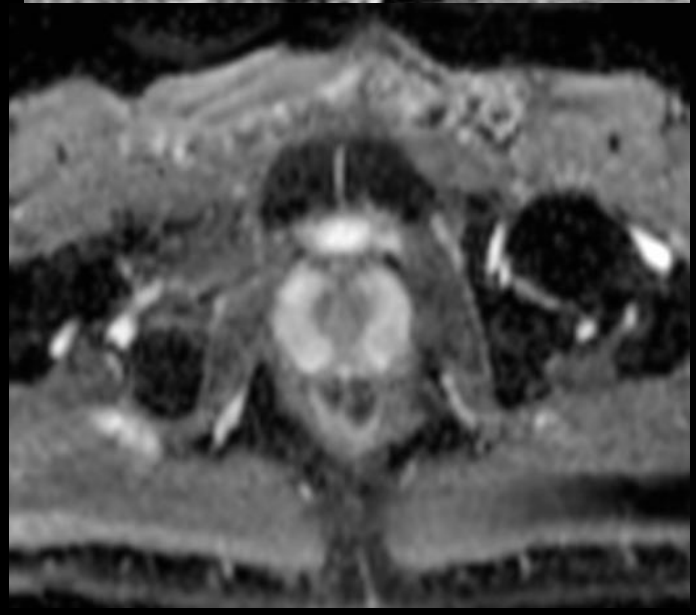
- Pelvic fracture: Avascular necrosis, pelvic insufficiency fractures
- Ulcers, fistulas
- Stenosis

Brachytherapy



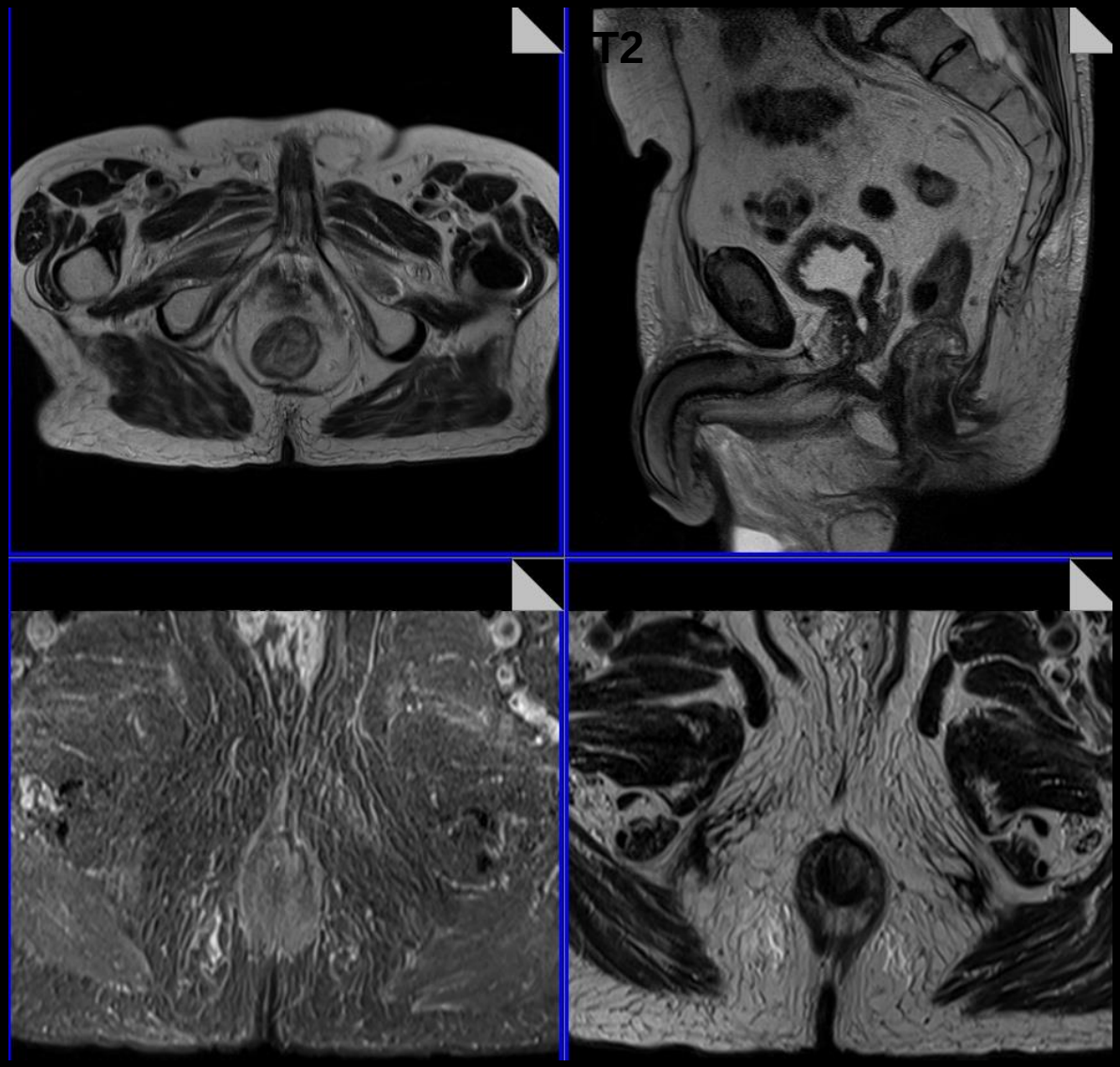






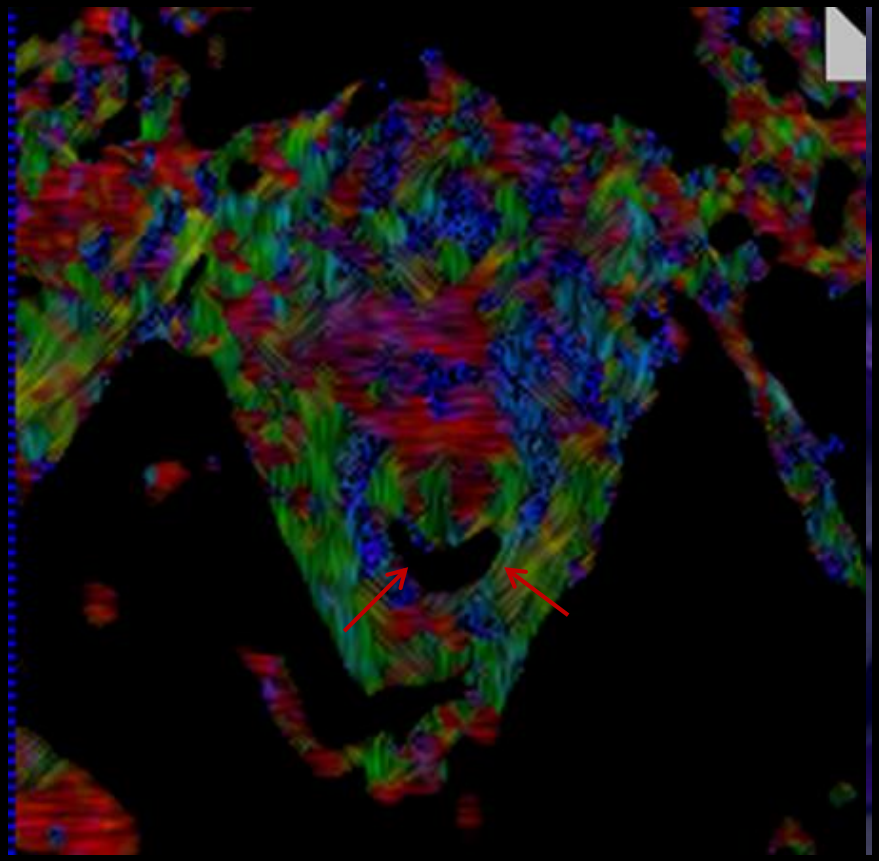
Normal

Therapy: Effects & Complications



- Proctitis
- Mesorectal & presacral oedema
- Increase in T1 marrow signal within radiotherapy field
- Fibro-fatty proliferation of pelvic & subcutaneous fat

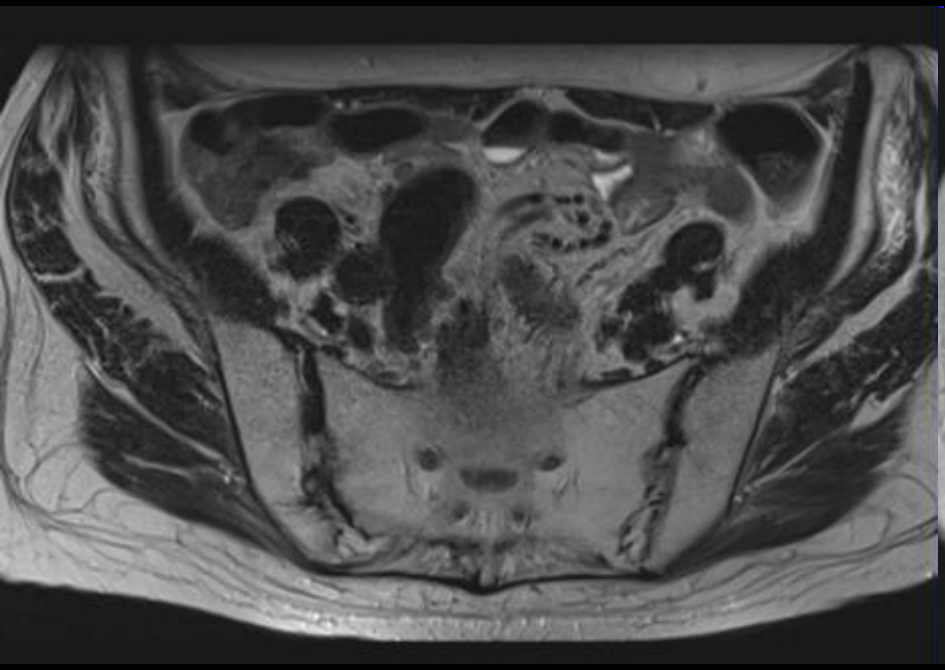
Therapy: Effects & Complications

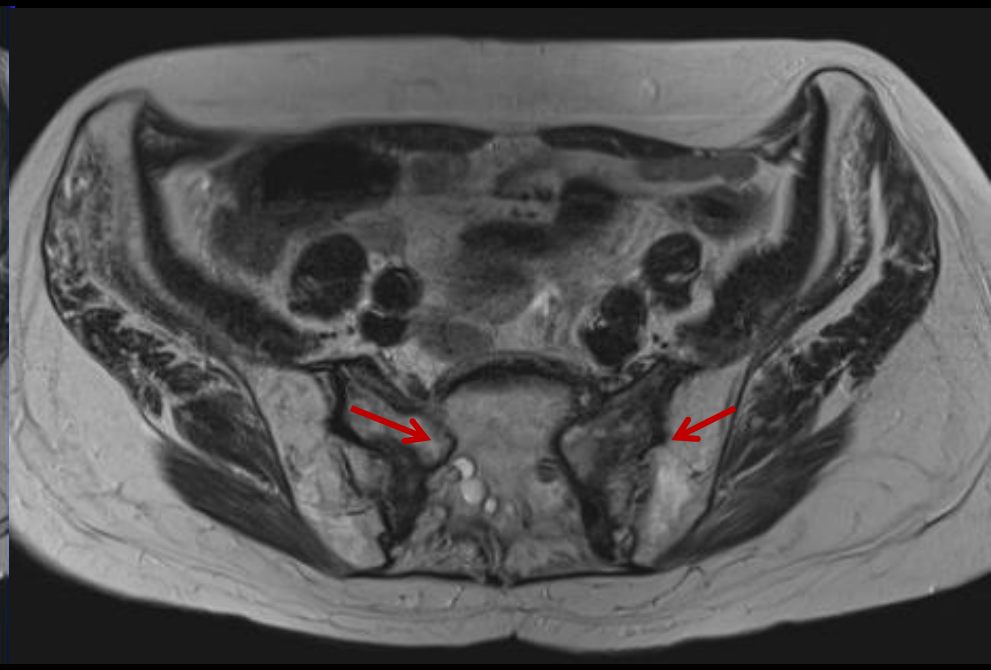


- Anal sphincter microstructural damage
- Anal sphincter fibrosis

Sequelae of Pelvic Radiotherapy

Therapy Complications: Late Effects



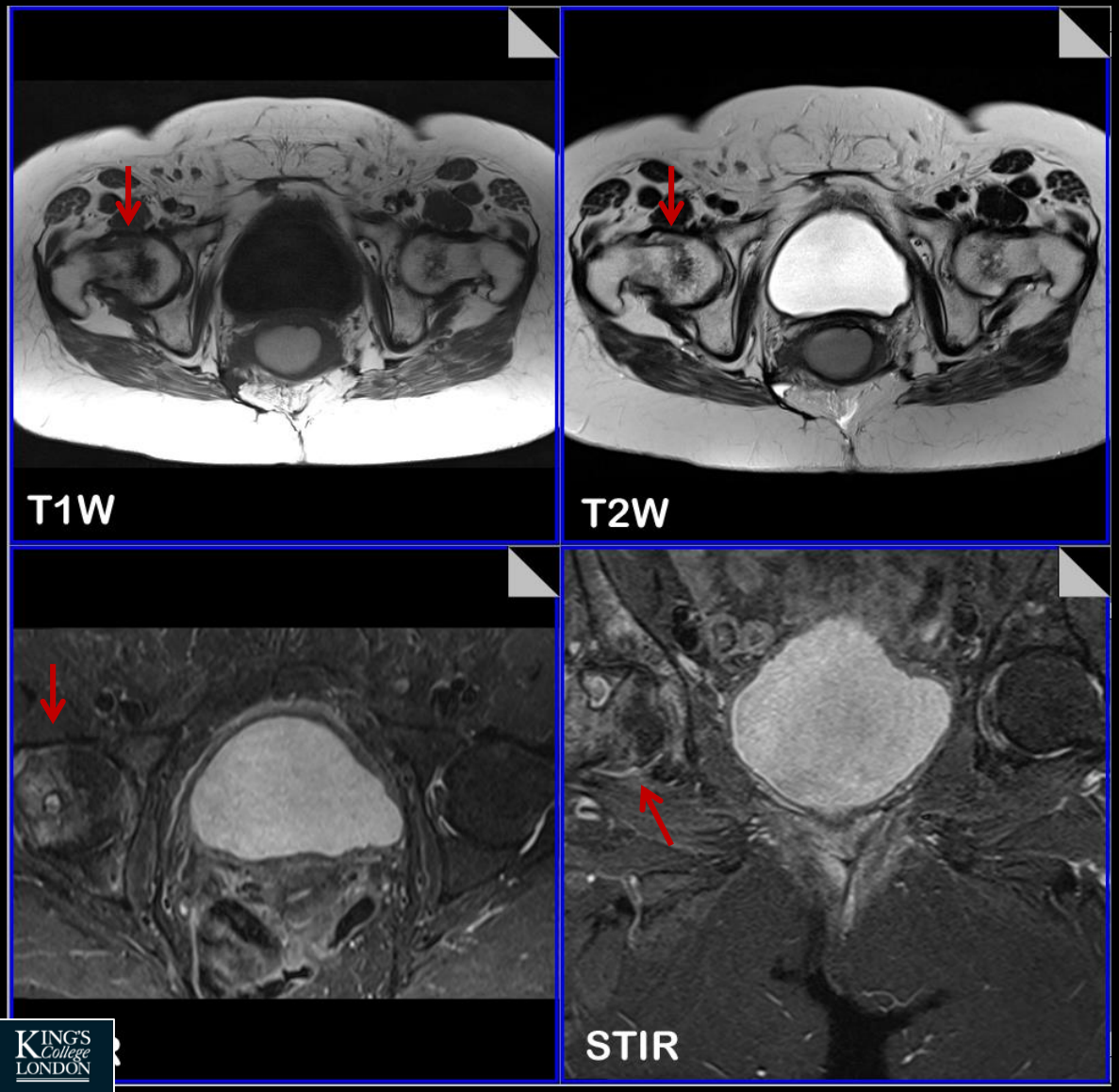


Baseline

2 yrs post treatment

Development of pelvic insufficiency fractures following CRT

Therapy Complications: Late Effects



Late effects

Development of avascular necrosis of R femoral head following CRT & subsequent salvage surgery

Summary

- MRI preferred to CT where greater tissue contrast is required, or where no contrast agent administered
- Response criteria allow standardised reporting in clinical trials but have limitations
- Physiological sequences may be helpful in Phase I trials to demonstrate biological effect e.g. anti-vascular
- MRI has a role in response assessment in the clinical pathway

Dose Painting

ESTRO Teaching Course on Advanced Molecular Imaging

Bordeaux, April 9-13, 2017

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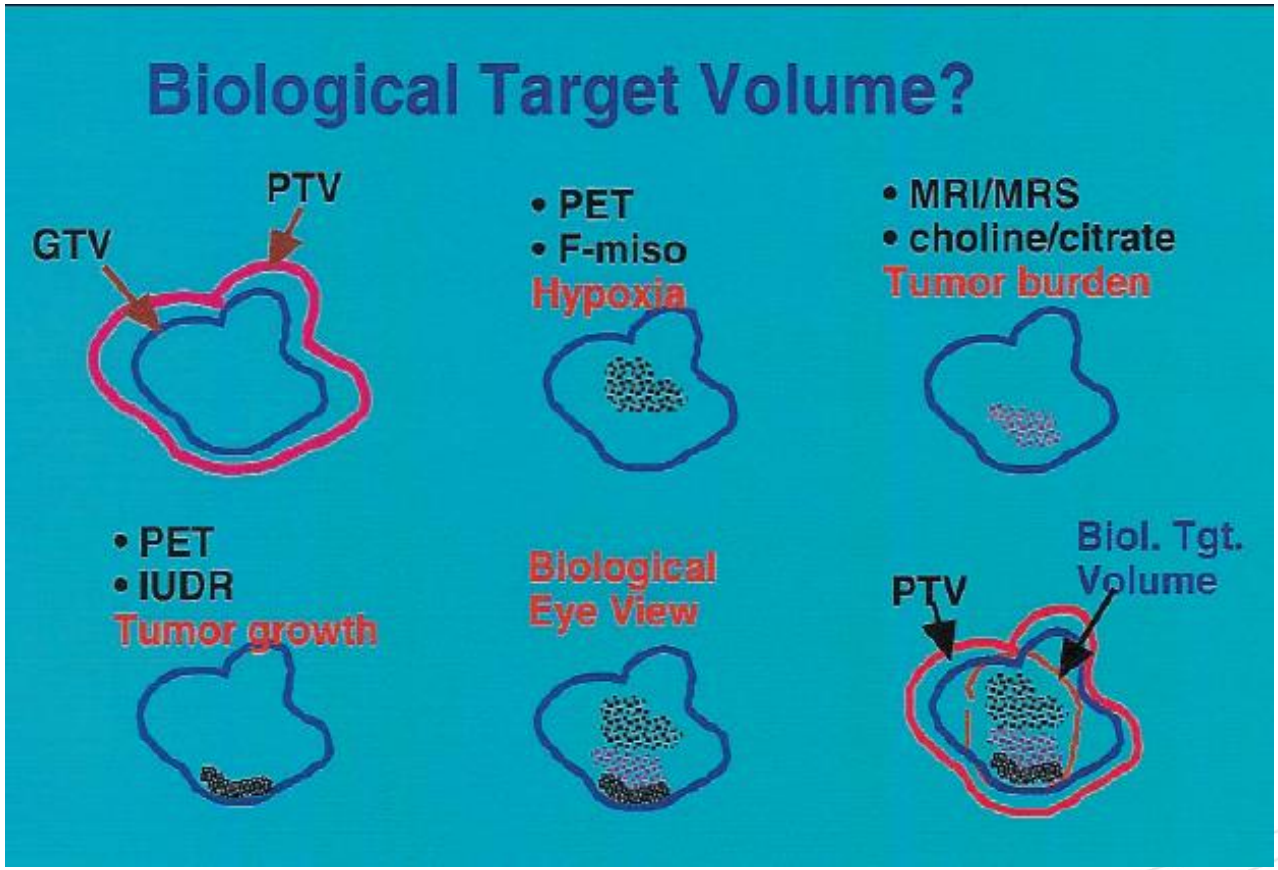
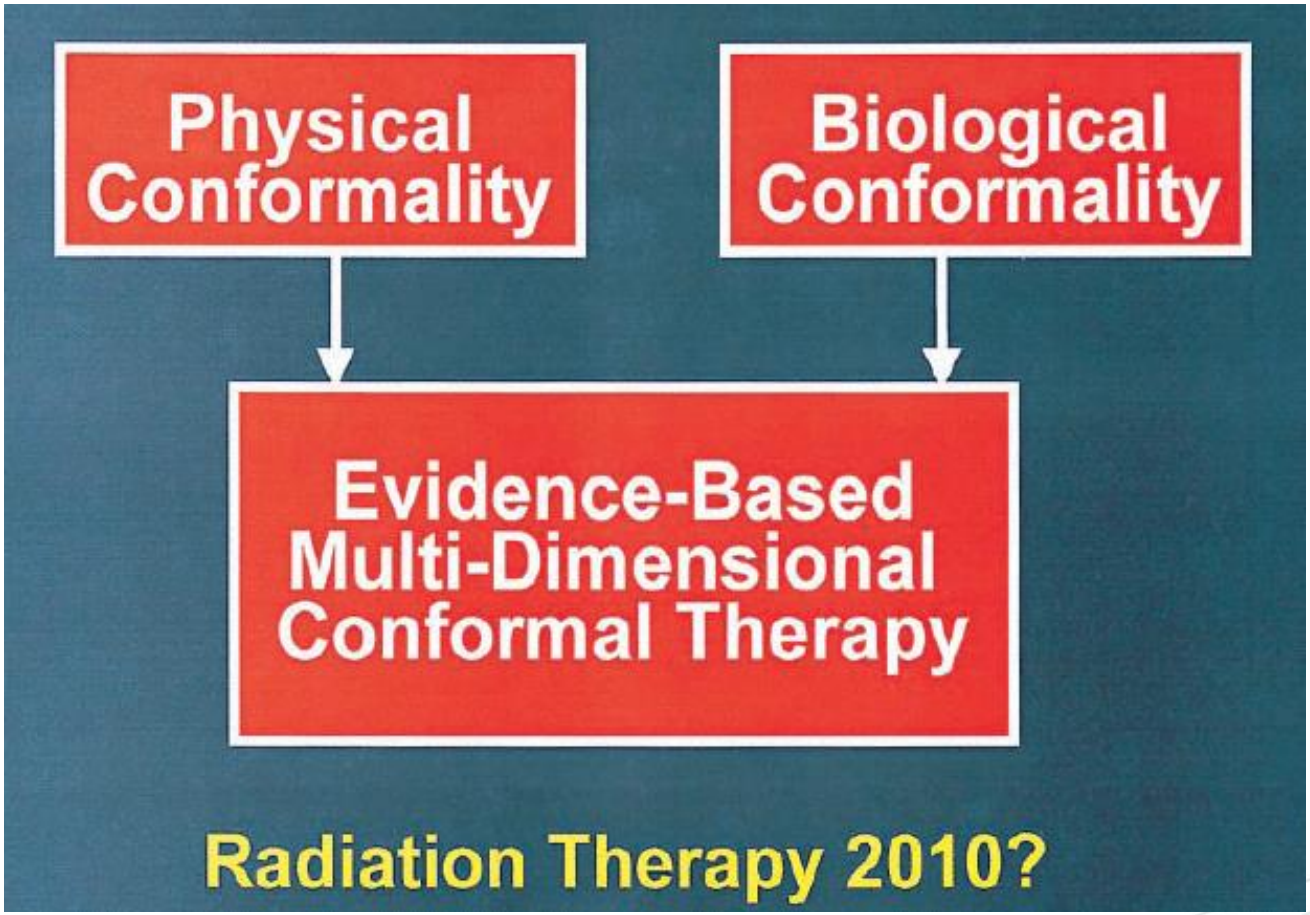
Biologically adapted RT: Dose Painting



Ling et al. IJROBP 2000

Vision Dose Painting 2010



Ling et al. IJROBP 2000

Dose Painting Trials

- Small number of active trials (n=9/10)
- PET, functional MRI to guide dose painting

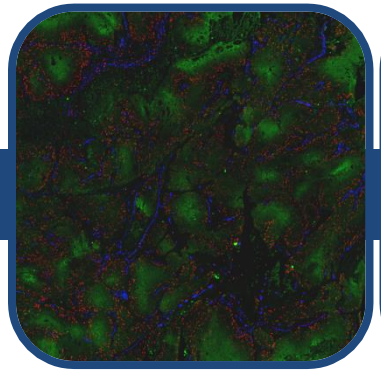
Source: www.clinicaltrials.gov

Key word: dose painting

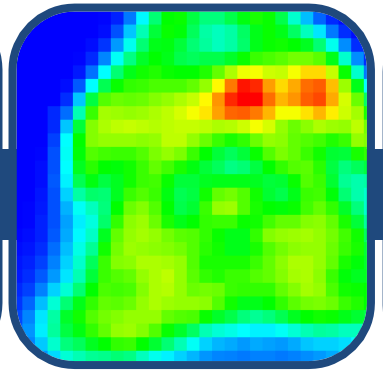
2016 / 04/2017

2	Recruiting	**A Study Comparing Adaptive Biological Imaging - Voxel Intensity - Based Radiotherapy (Adaptive Dose Escalation) Versus Standard Radiotherapy for Head and Neck Cancer** **Condition:** Primary Non-operated Squamous Cell Carcinoma of the Oral Cavity, Oropharynx, Hypopharynx and Larynx. **Interventions:** Radiation: Adaptive dose-painting-by-numbers; Radiation: standard intensity-modulated radiotherapy (IMRT)
3	Recruiting	**A Feasibility Study on Adaptive 18F-FDG-guided Radiotherapy for Recurrent and Second Primary Head and Neck Cancer in the Previously Irradiated Territory.** **Conditions:** Recurrent and Second Primary Squamous Cell Carcinoma of the Oral Cavity in the Previously Irradiated Territory in Case of Primary Unresectable Tumor.; Recurrent and Second Primary Squamous Cell Carcinoma of the Oropharynx in the Previously Irradiated Territory in Case of Primary Unresectable Tumor.; Recurrent and Second Primary Squamous Cell Carcinoma of the Hypopharynx in the Previously Irradiated Territory in Case of Primary Unresectable Tumor.; Recurrent and Second Primary Squamous Cell Carcinoma of the Larynx in the Previously Irradiated Territory in Case of Primary Unresectable Tumor. **Intervention:** Radiation: [18F]FDG-PET-voxel intensity-based IMRT
4	Recruiting	**Evaluation of Hypoxia by PET With F-Miso in Radiation Therapy of Prostate Cancer** **Condition:** Prostate Adenocarcinoma **Intervention:** Drug: 18-F-MISO
5	Recruiting	**FLAME: Investigate the Benefit of a Focal Lesion Ablative Microboost in Prostate Cancer** **Conditions:** Prostate Cancer; Radiotherapy; MRI **Interventions:** Radiation: FLAME boost; Radiation: standard arm
6	Recruiting	**BIOPROP20: Biologically Optimised IMRT for Prostate Radiotherapy Hypofractionated Radiotherapy With Intra-prostatic Boosts to Tumour Nodules in Men With Intermediate and High Risk Prostate Cancer** **Condition:** Prostate Cancer **Intervention:** Radiation: Hypofractionated IMRT boost Radiotherapy
7	Recruiting	**Biological Image Guided Antalgic Stereotactic Body Radiotherapy of Bone Metastases** **Condition:** Bone Metastases **Interventions:** Radiation: Conventional Radiotherapy; Radiation: Biological image-guided radiotherapy with conventional dose.; Radiation: Biological image-guided SBRT with dose-escalation.
8	Not yet recruiting	**Do Selective Radiation Dose Escalation and Tumour Hypoxia Status Impact the Locoregional Tumour Control After Radiochemotherapy of Head & Neck Tumours?** **Condition:** Locally Advanced Head and Neck Cancer **Intervention:** Radiation: Radiotherapy with linear accelerators
9	Recruiting	**Comparison of Acute Toxicity and Cost Between Whole Breast Irradiation With Sequential Boost and Simultaneous Integrated Boost After Breast Conserving Surgery.**

Dose Painting relies on a number of essential factors



Biology



Imaging physics / resolution

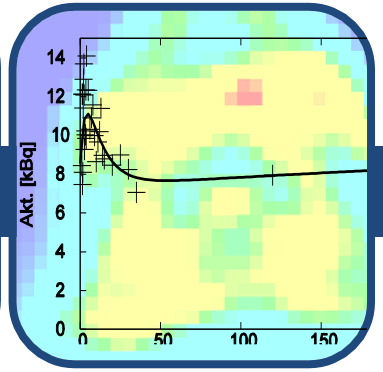
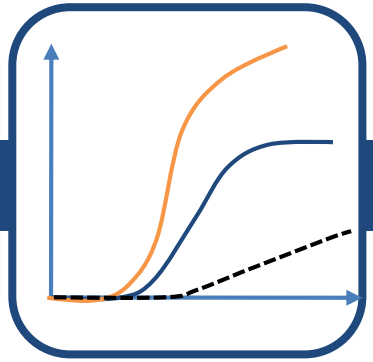
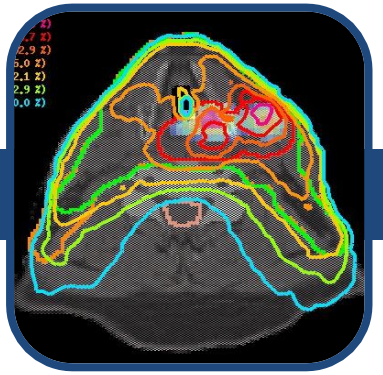


Image analysis / parameter interpretation



Prescription / Calibration function



Technical feasibility

Functional Imaging with MRI and PET

Cell density, microanatomy

DWI, DTI, $[^{18}F]FDG$

Perfusion, permeability of microvasculature

DSC-MRI, DCE-MRI, $[^{18}F]$Galacto RGD, $[^{15}O]H_2O$

Cell membrane synthesis

MRSI (choline), $[^{11}C]$Choline, $[^{18}F]$Choline

Metabolism

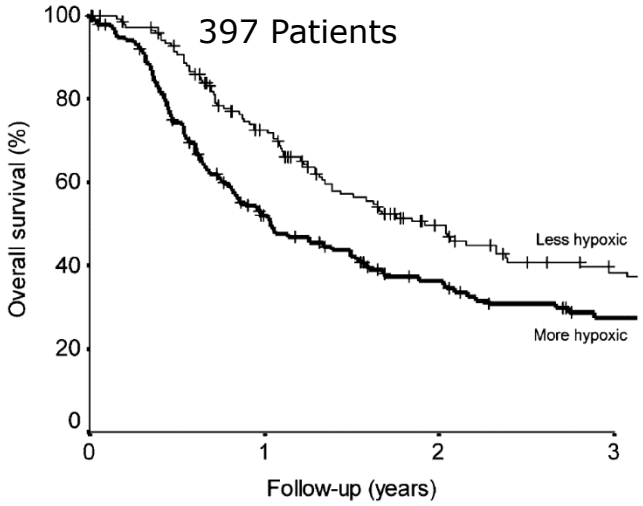
^{31}P-MRSI $[^{18}F]FDG$

Hypoxia

R2* (BOLD), MRSI (lactate) $[^{18}F]$FMISO, $[^{18}F]$FAZA, $[^{18}F]$HX4

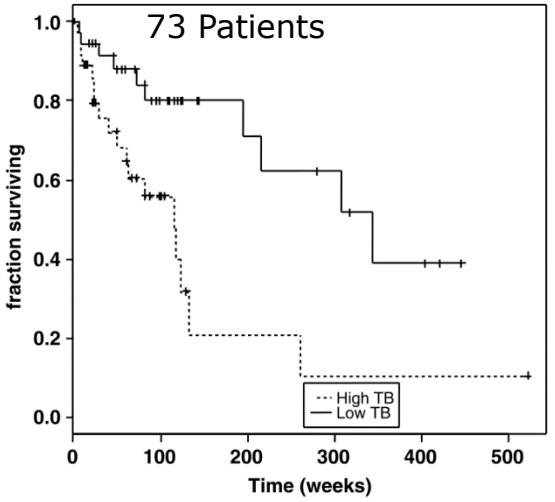
Biology: Tumor hypoxia is a major cause of treatment resistance

Eppendorf measurements



Nordsmark *et al*., Radiother Oncol (2005)

PET using [^{18}F]-fluoromisonidazole (FMISO)

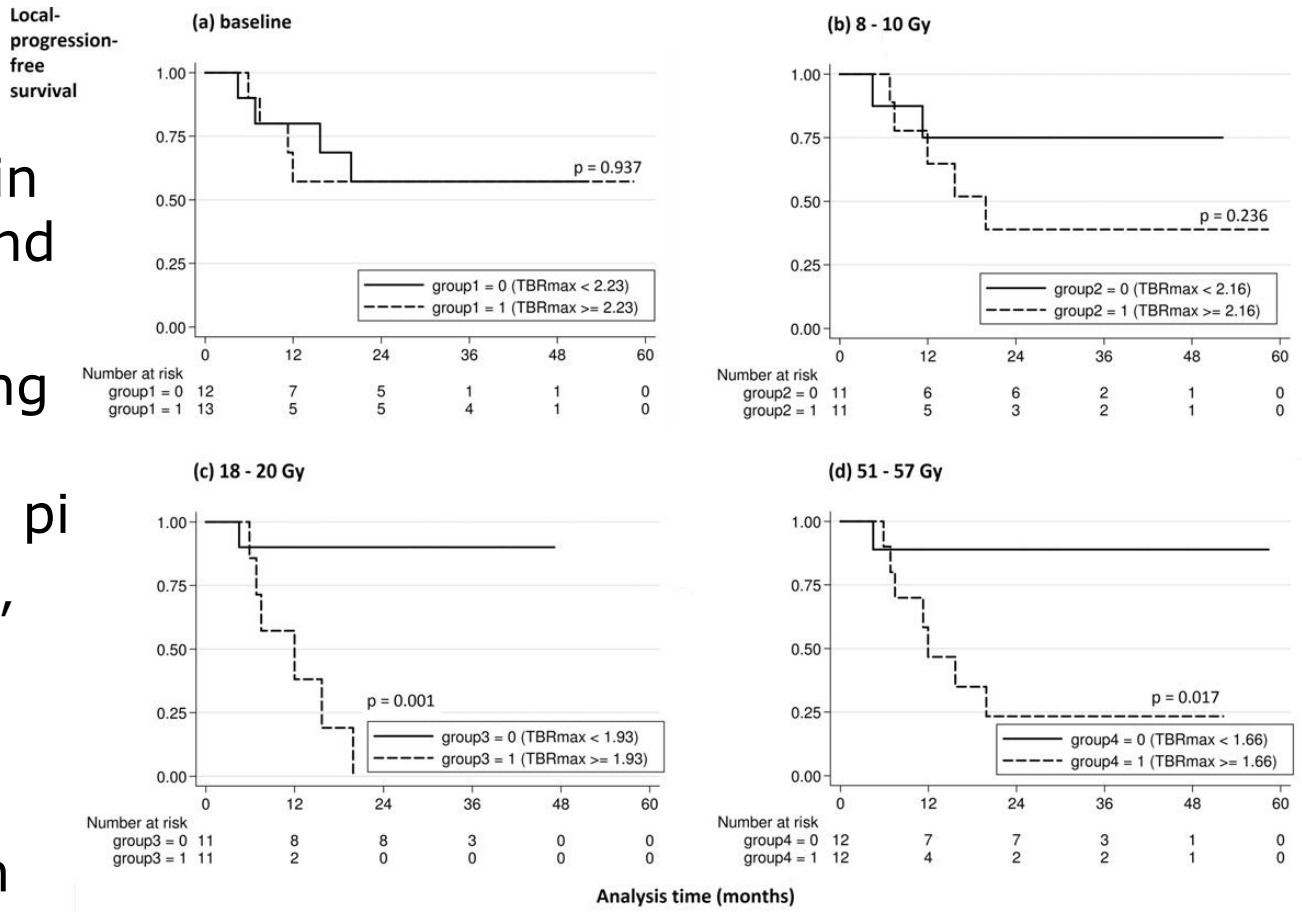


Rajendran *et al*., Clin Cancer Res (2006)

Hypoxia PET Imaging with [^{18}F]-FMISO

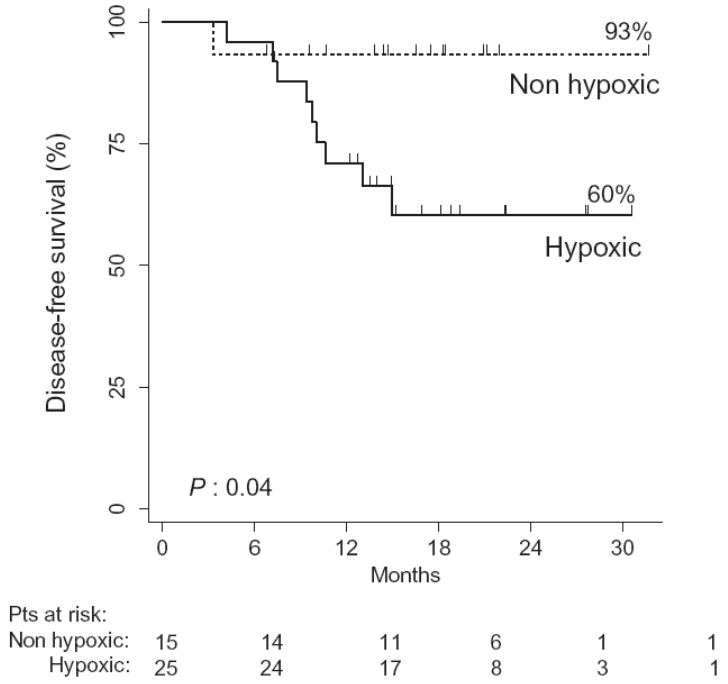
Zips D et al. Radiother Oncol 2012;105(1):21-8.

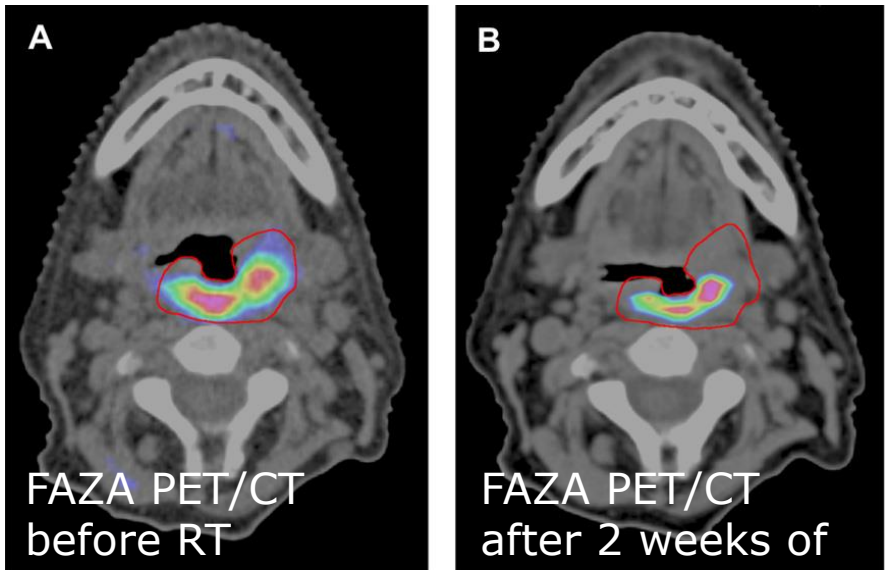
- N=25 HNC patients
- FMISO PET/CT in week 0, 1, 2, and 5
- Different imaging parameters evaluated @ 4h pi
  - HV (T/Bg: 1.4, 1.6, 1.8, 2.0)
  - TBR_{max}
  - SUV_{max}
- Correlation with LPFS in week 2



Hypoxia PET Imaging with [^{18}F]-FAZA

Mortensen LS et al. Radiother Oncol 2012;105(1):14-20.



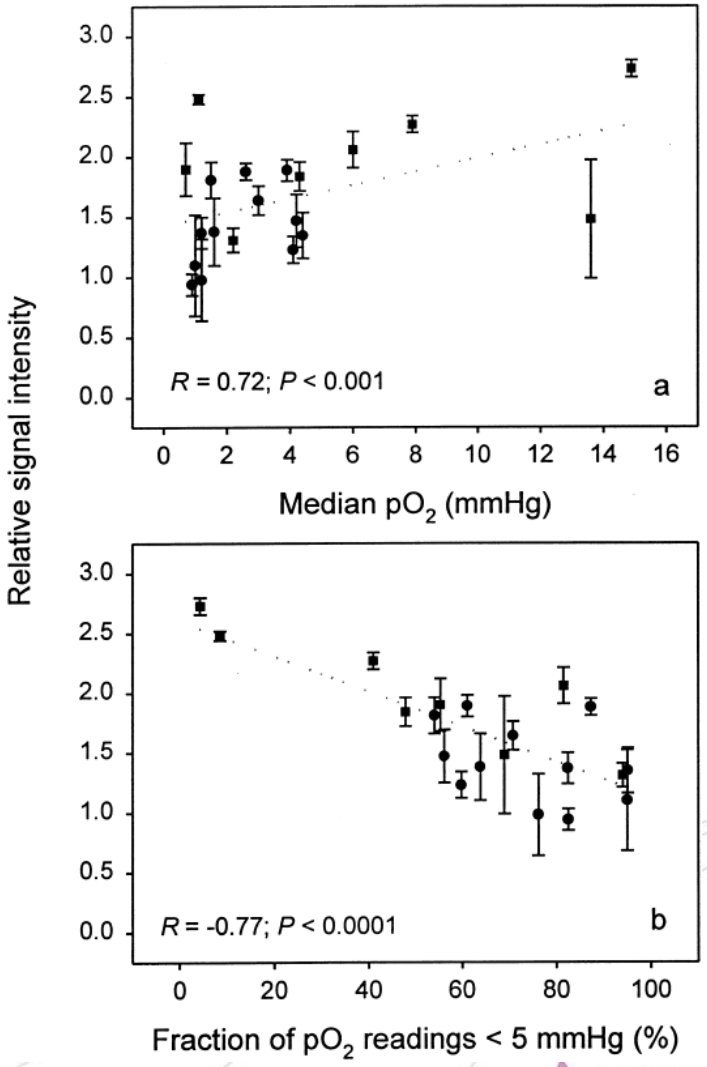


- N=40 HNC
- FAZA PET/CT in week 0 and 2
- $HV_{TMR1.4}$ evaluated @ 2h pi
- Prognostic potential for detection of hypoxia in HNSCC

Correlation between imaging and biological property: Oxygenation vs. perfusion

Lyng H et al. JMRI 2001; 14: 750.

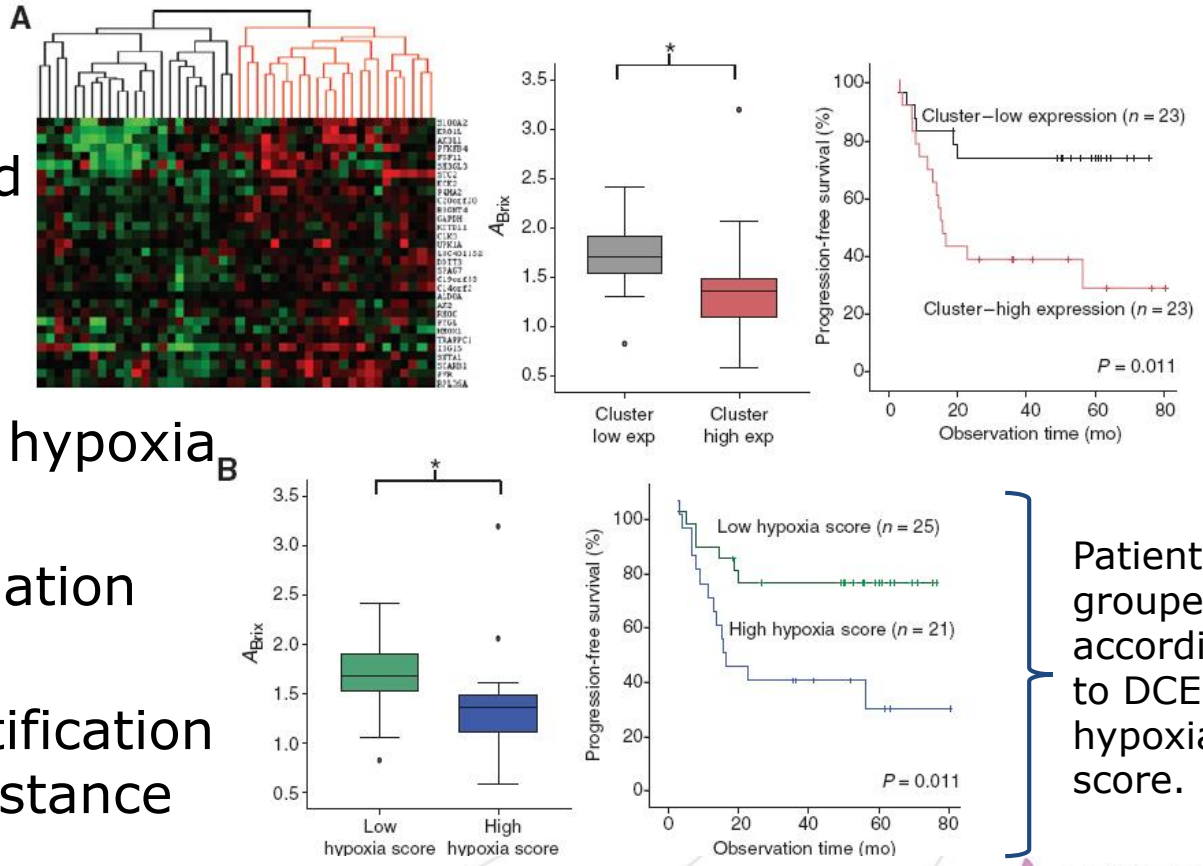
- Comparison DCE-MRI, Eppendorf pO_2 measurements and pathology from biopsies
- Maximum Relative Signal Enhancement (RSI) correlates with pO_2.
- pO_2 correlated to cell density, vascular density was of minor importance



Hypoxia Imaging with DCE-MRI vs. gene expression

Halle C et al. Cancer Res 2012;72(20):5285-95.

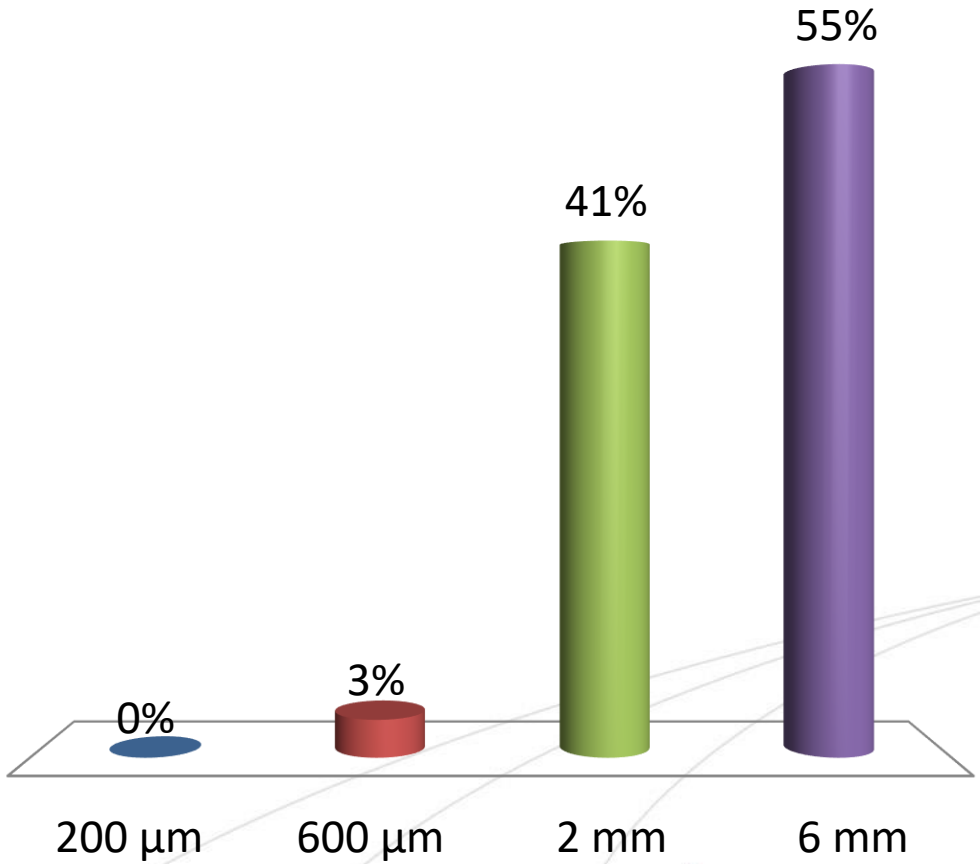
- N=78 cervix patients
- Analysis of gene expression set and DCE-MRI
- Significant correlation between A_{Brix} and hypoxia gene sets
- Independent validation (n=109)
- DCE-MRI for identification of chemoradioresistance



Patients grouped according to DCE-MRI hypoxia score.

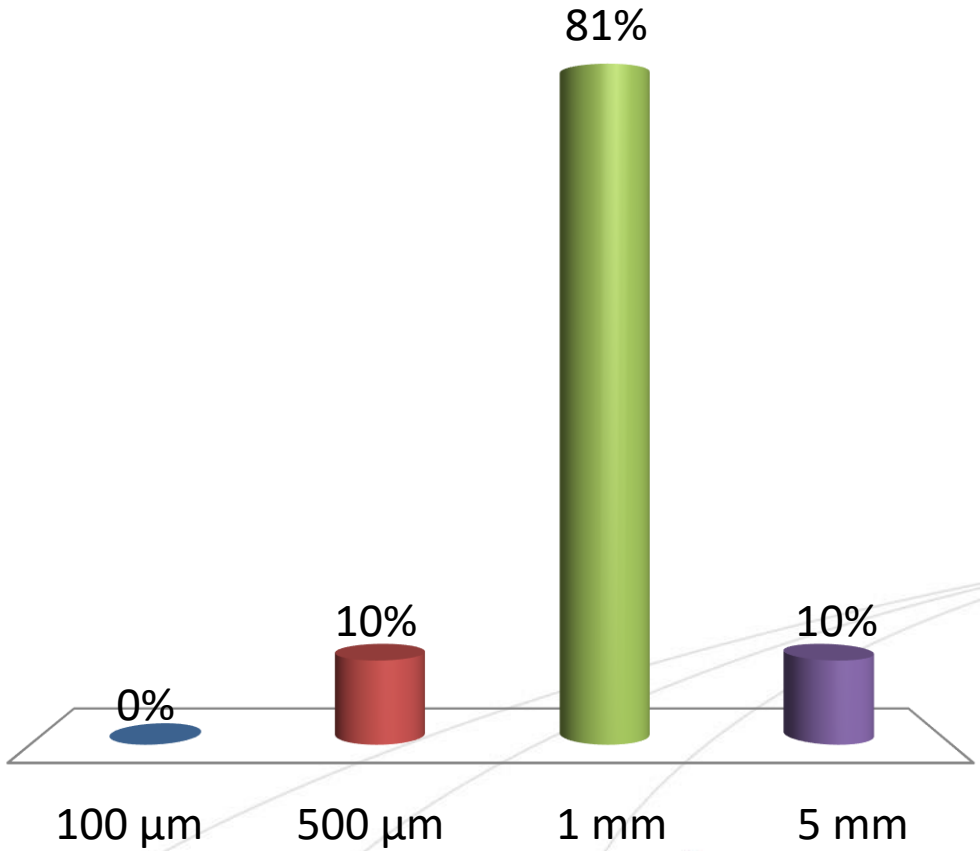
What is the spatial resolution of a PET image?

A. 200 µm
B. 600 µm
C. 2 mm
✓ D. 6 mm



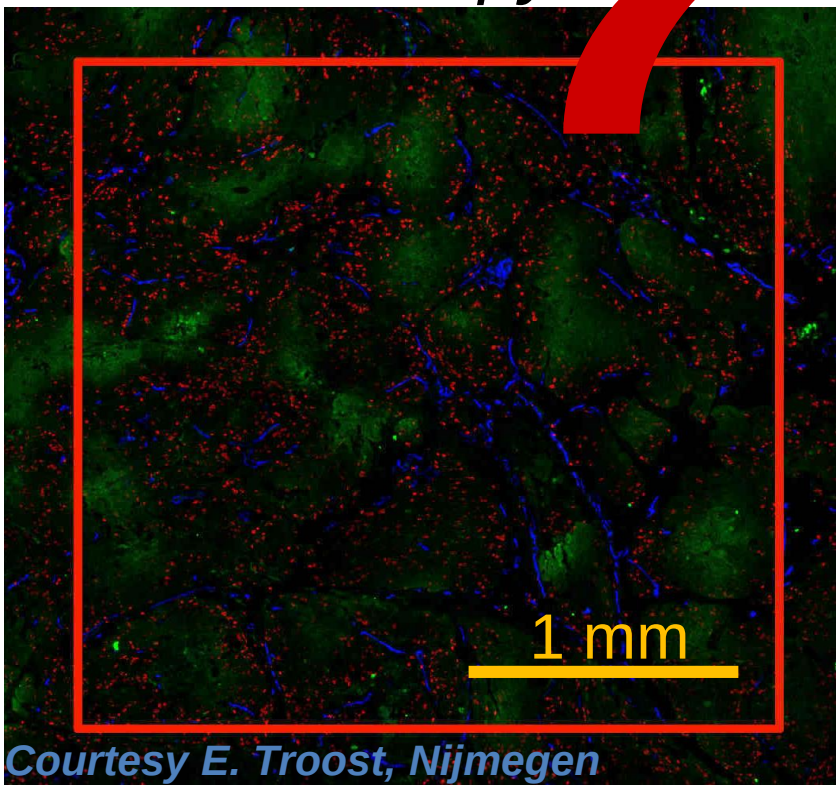
What is the spatial resolution of a MRI?

A. 100 µm
B. 500 µm
✓ C. 1 mm
D. 5 mm



Spatial resolution of functional imaging is challenging

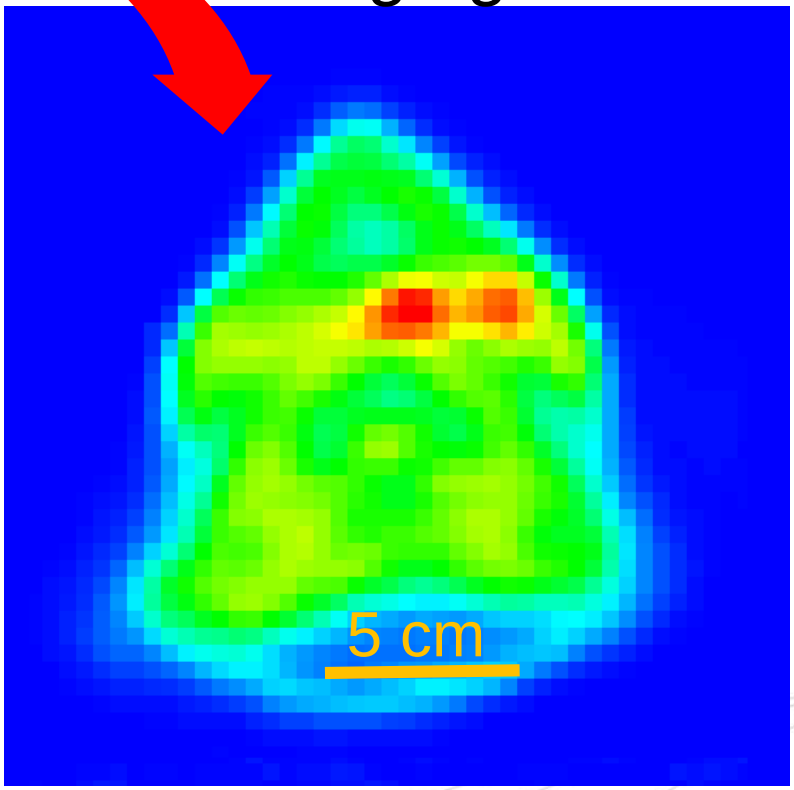
Microscopy



Immunohistochemistry
(vascularization, proliferation, hypoxia)

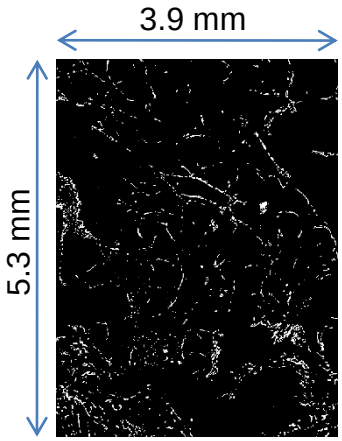
?

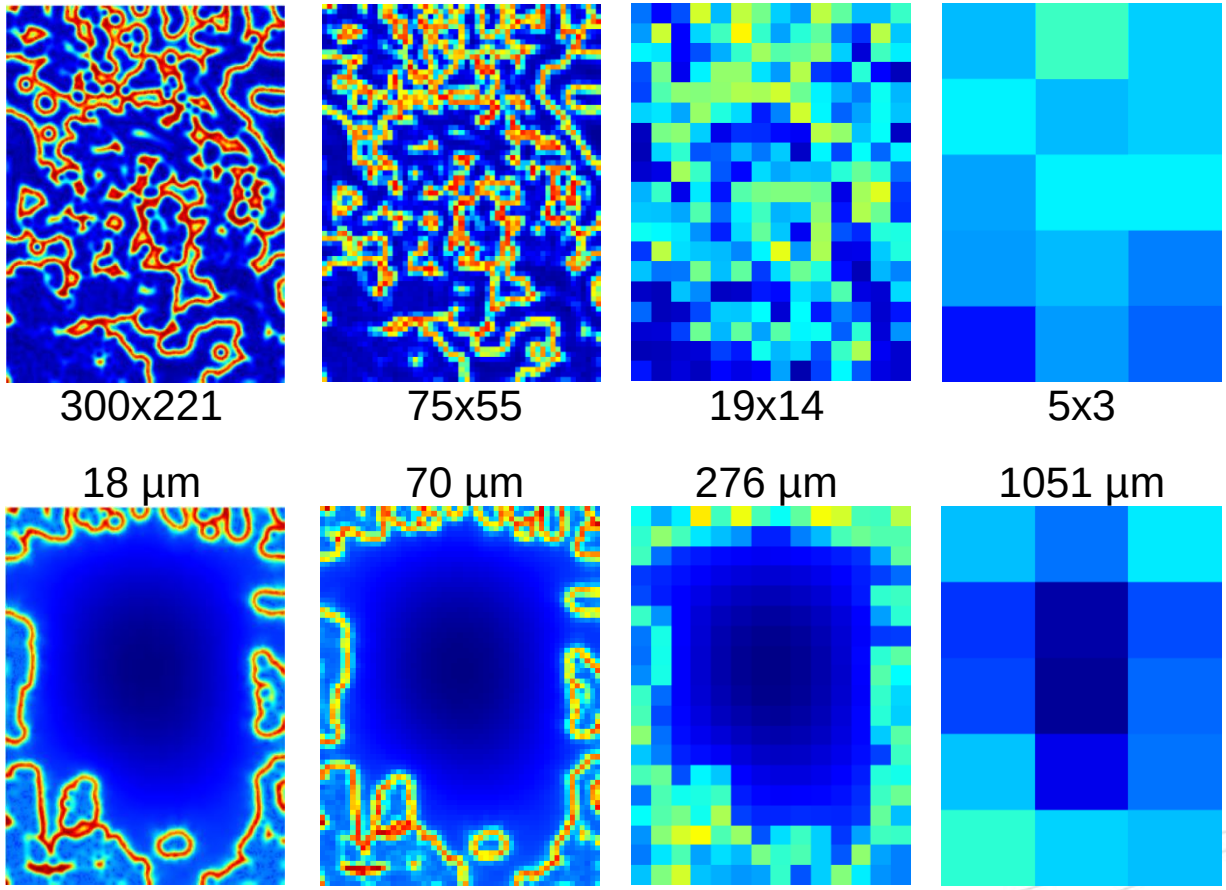
Imaging



Clinical FMISO PET image, 4h pi

PET Image resolution

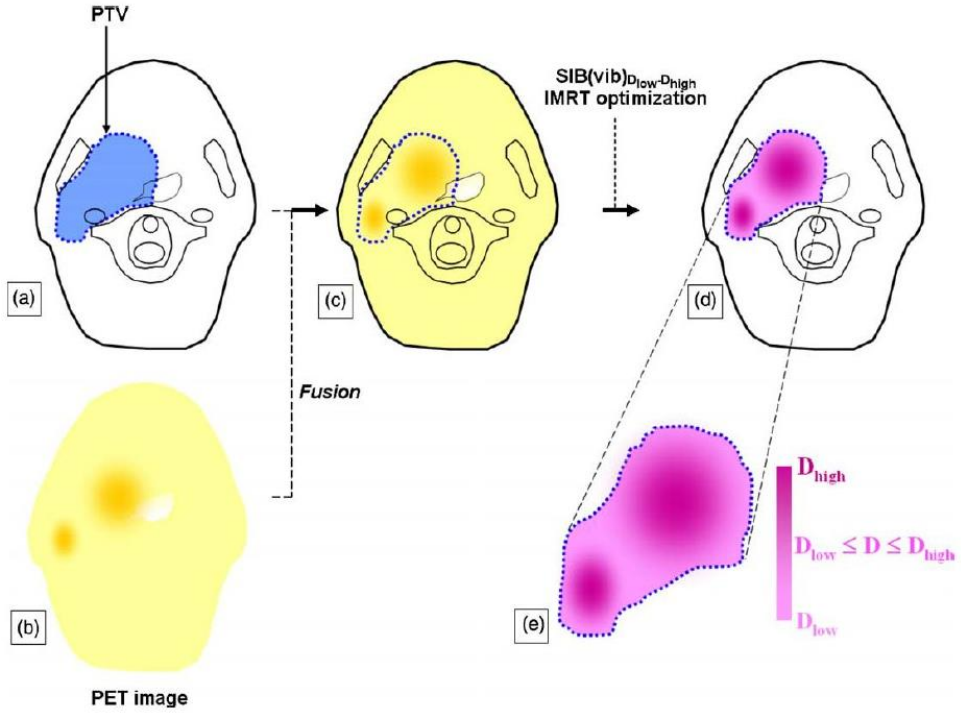


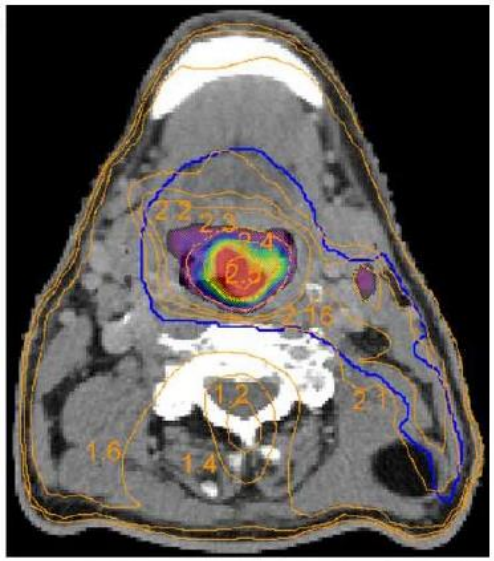


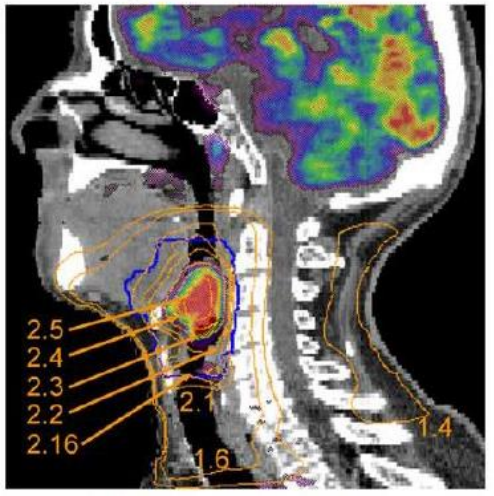
FMISO PET simulation 4 h pi

Assuming a linear relationship between image values and dose prescription is a pragmatic way

Vanderstraeten B et al. Radiother Oncol 2006;79:249-58.



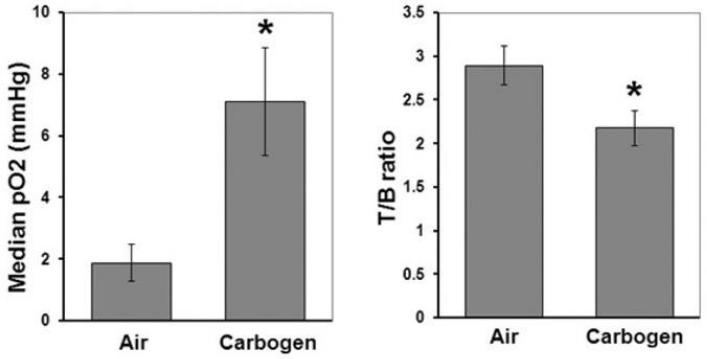


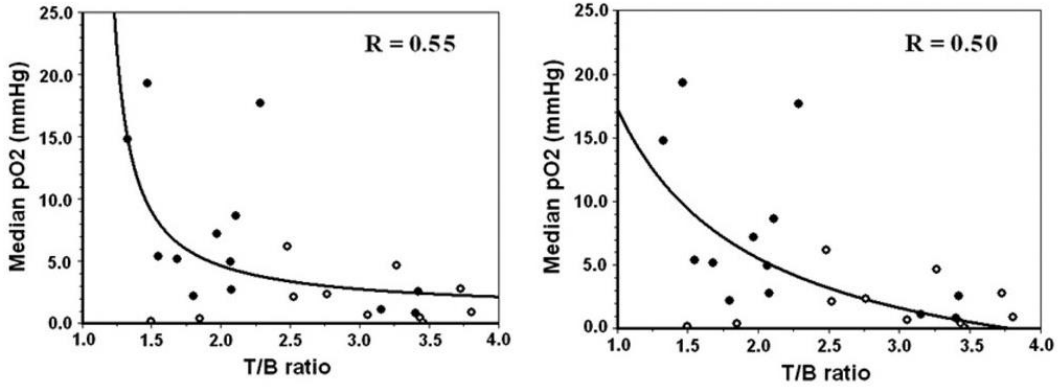


Relating functional imaging information to the underlying biological phenomenon …

Tran LB et al. Radiother Oncol 2012;105(1):29-35.

- Non-linear, hyperbolic function defines the relation between FAZA T/B-ratio and the tissue pO2.
- Fit to data measured in small animal experiments determines the prescription function

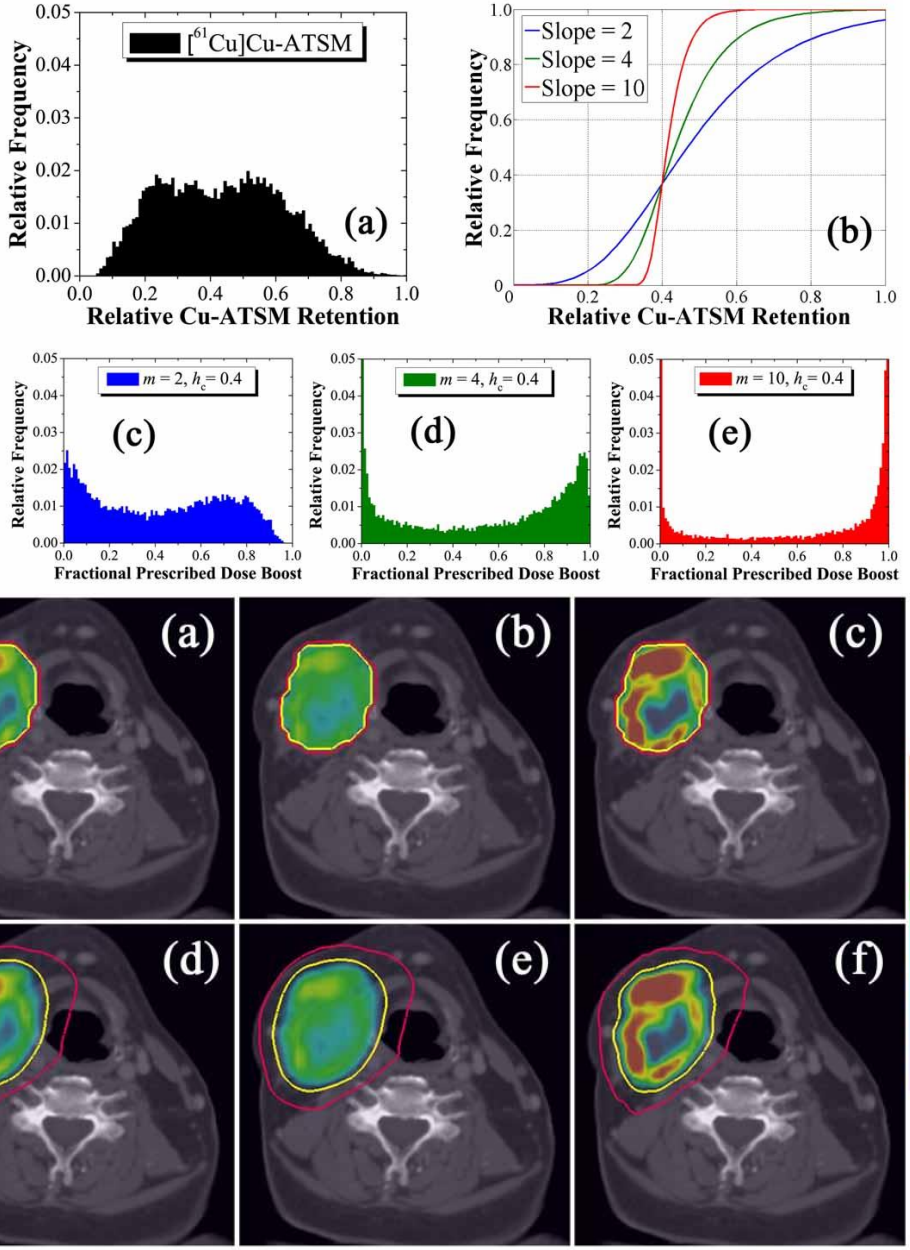




Prescription Function for DPBN

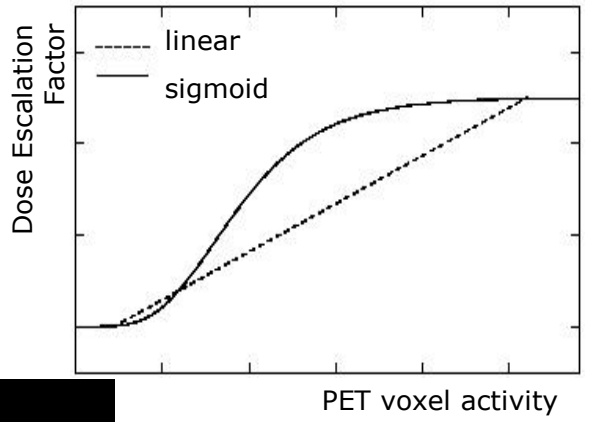
Bowen S et al, PMB 2009

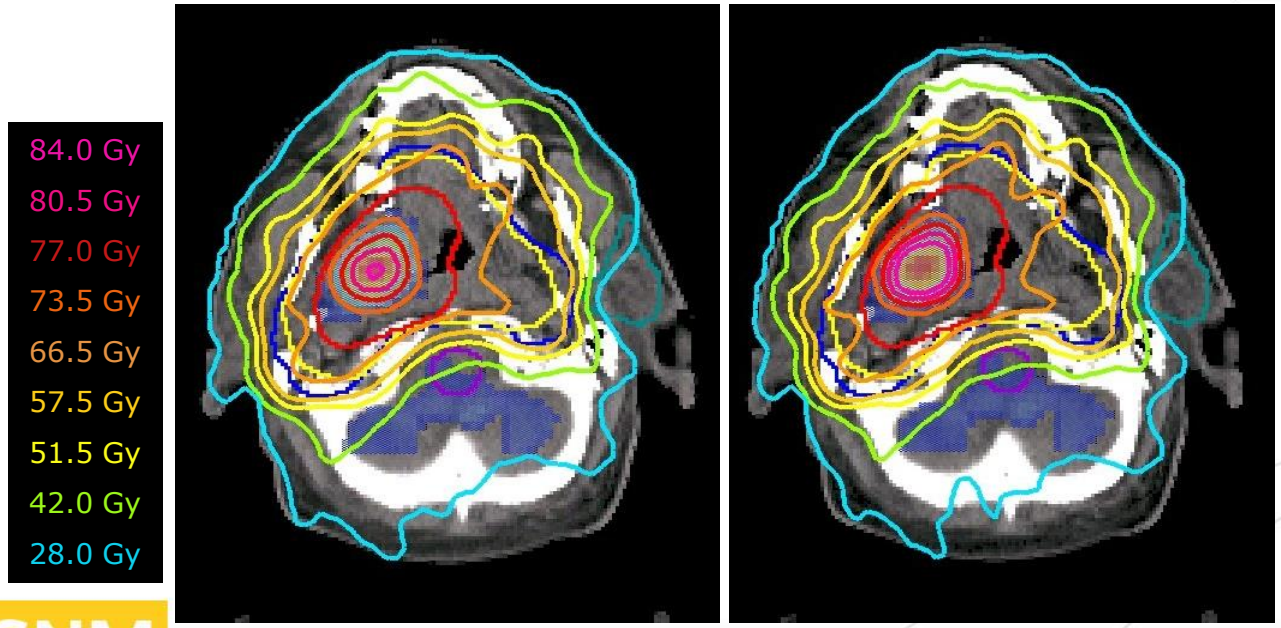
- Function translating image intensities into dose prescriptions is essential
- Enormous impact on planned dose
- Absolute quantification of imaging necessary



Clinical Implementation of DPBN: Prescription function

- Dose prescription is different in each tumor voxel
- Prescription function has to be integrated into the optimisation process during RT-planning





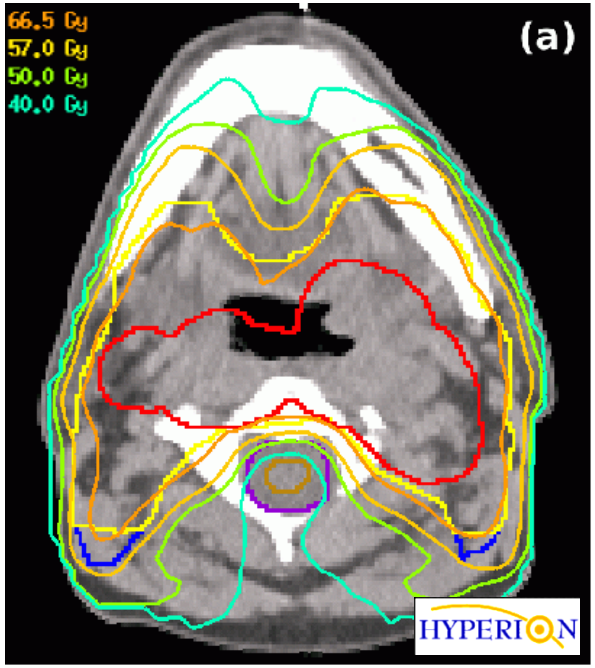
ESNM European School of Nuclear Medicine

ESTRO School

Technical Feasibility of Dose Painting

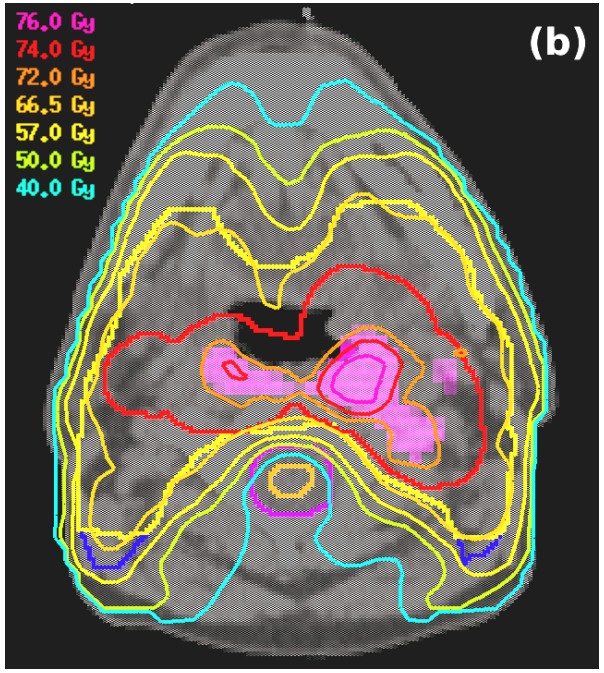
Dose escalation in a functional PTV (*f*-PTV) vs. Hypoxia-guided Dose Painting by Numbers (DPBN) in Head and Neck Cancer.

Thorwarth et al. *IJROBP 2007*



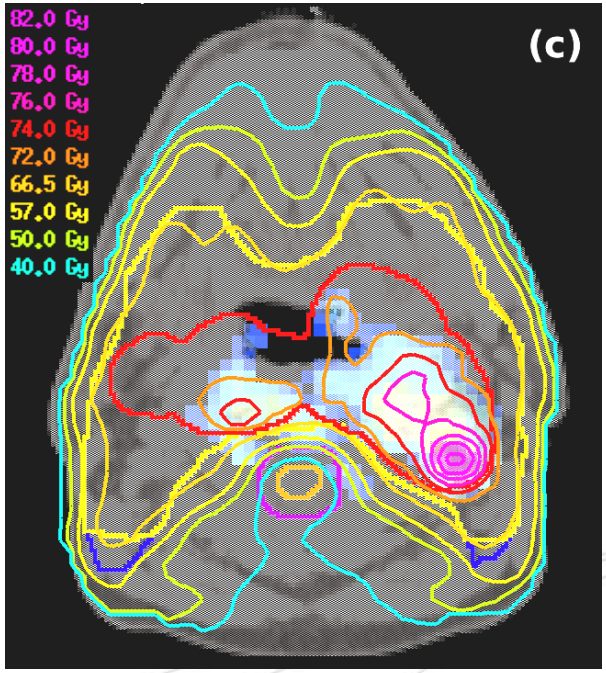
(a) 54/60/70 Gy,

standard IMRT



(b) 54/60/70/77 Gy,

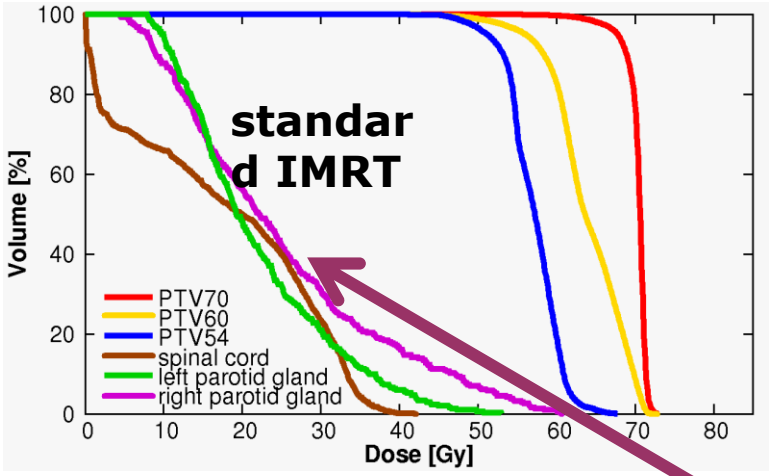
FDG-guided IMRT, *f*-PTV

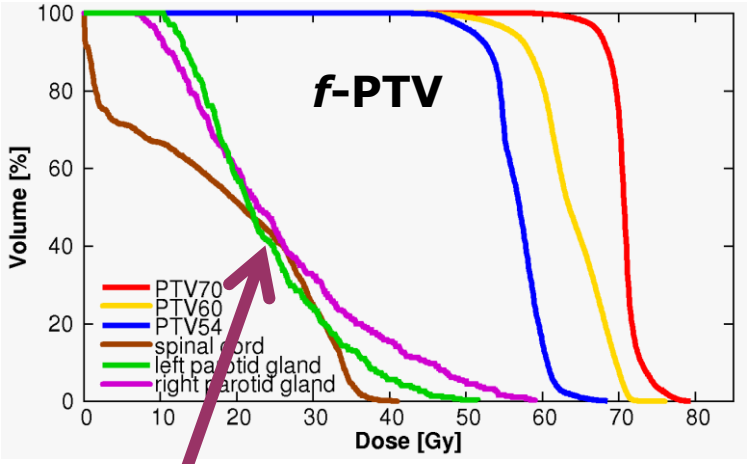


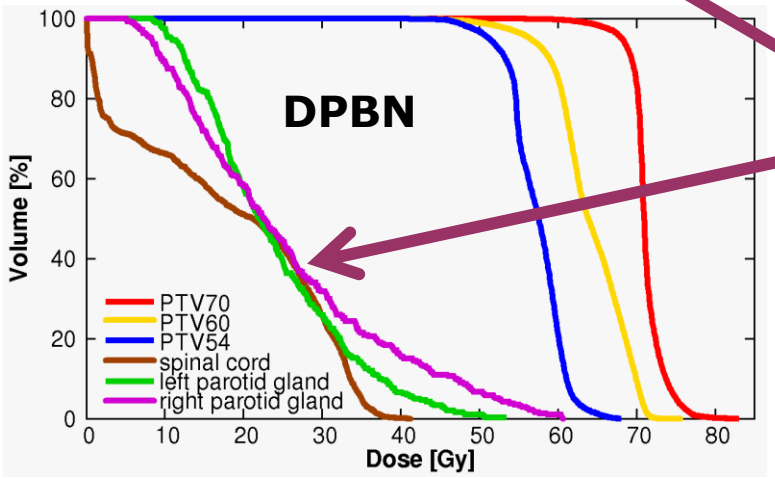
(c) 54/60/70/84 Gy,

FMISO-guided IMRT, DPBN

Technical Feasibility: Isotoxicity



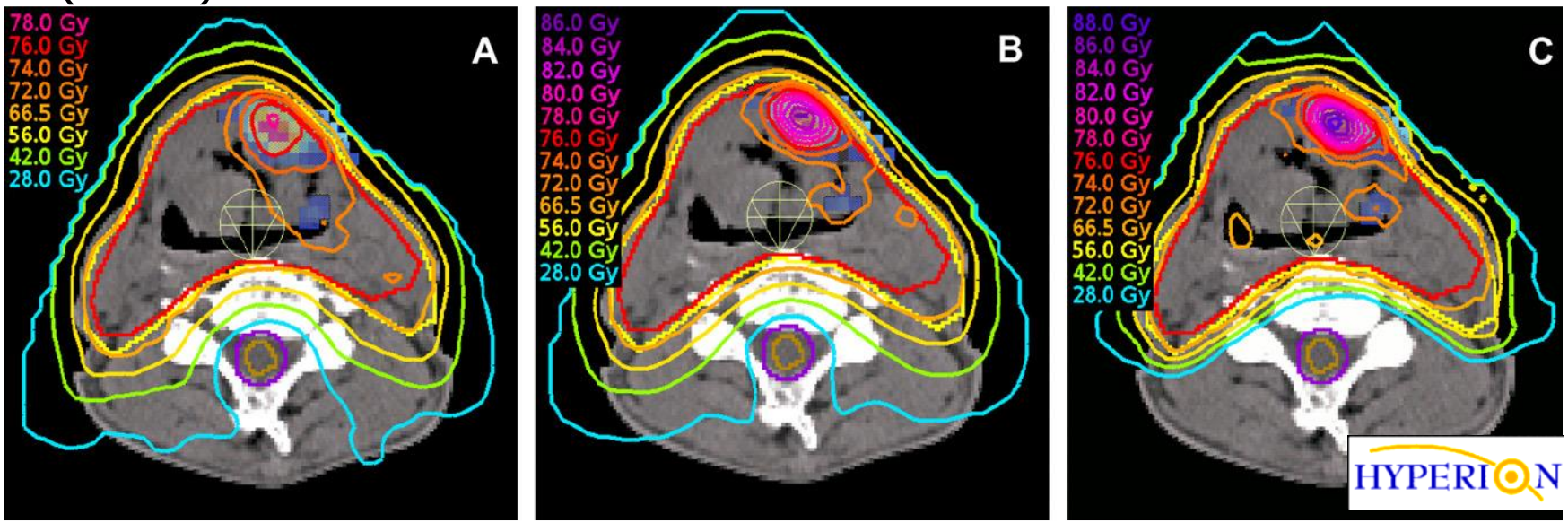




DPBN and dose escalation to a *f*-PTV are feasible with normal tissue constraints comparable to conventional IMRT!

Different Treatment Techniques

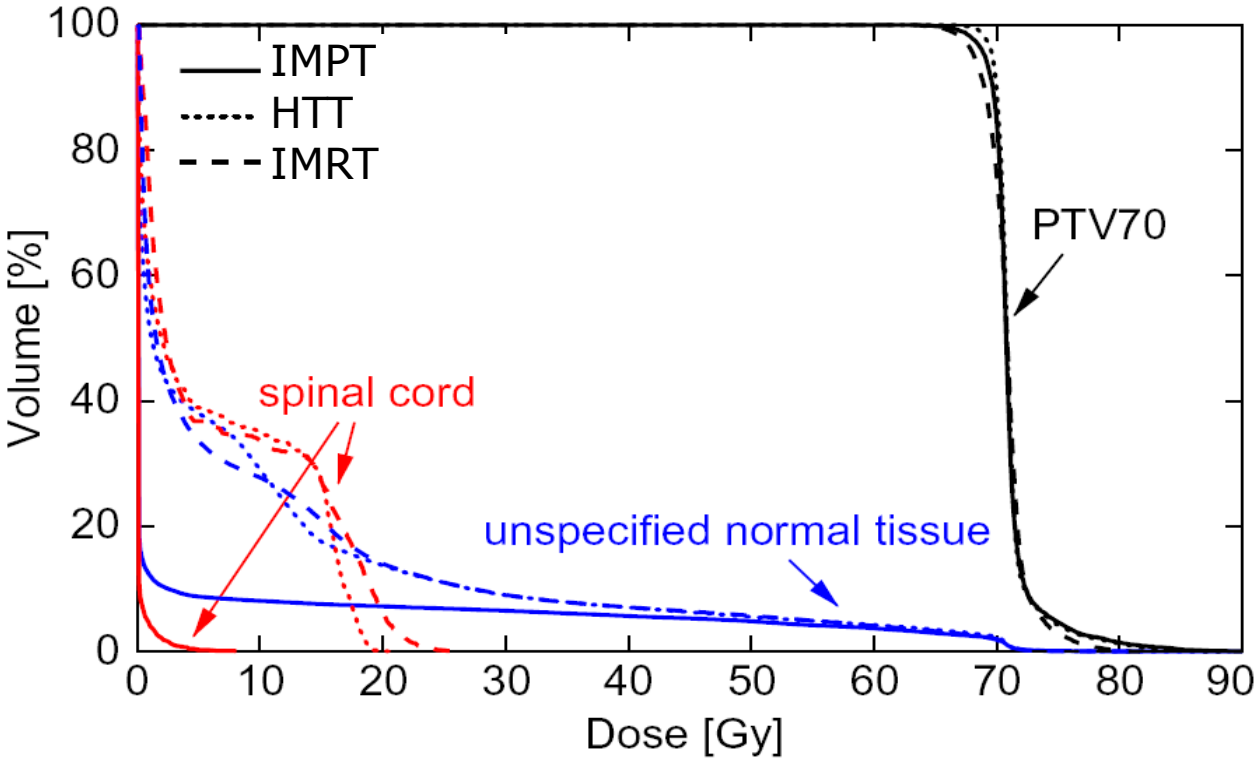
Intensity Modulated Photon Therapy (IMRT) vs. Helical Tomotherapy (HTT) vs. Intensity Modulated Proton Therapy (IMPT).



(A) IMRT (1cm MLC) (B) HTT (C) IMPT

Thorwarth et al. *Radiother. Oncol. 2008*

Different Treatment Techniques



Differences between IMRT, HTT and IMPT appear small compared to the geometrical and biological uncertainties.

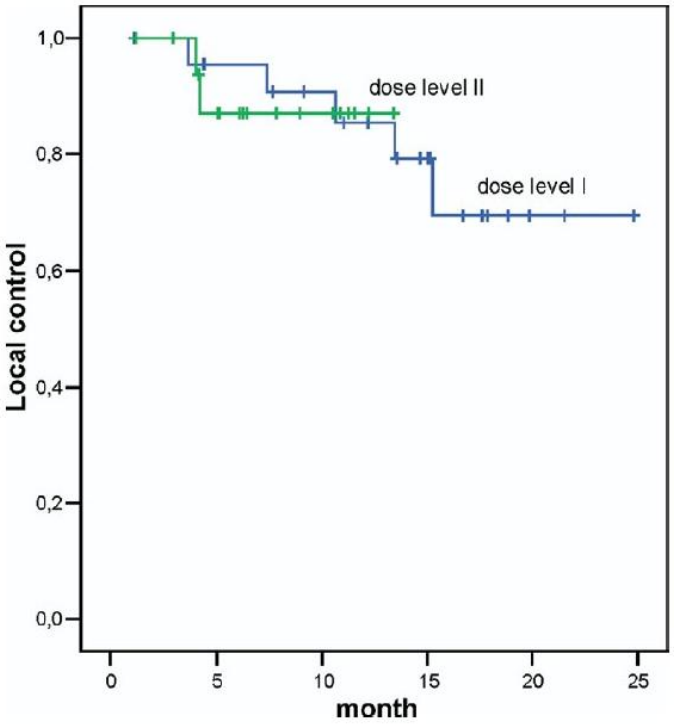
FDG PET/CT guided Dose Painting by Contours in HNC

Madani et al, IJROBP 2007

- n=41 patients
- Phase I study
- 2 different dose levels:
  - Dose level I: 25 Gy (n=23)
  - Dose level II: 30 Gy (n=18)
  - 22 fx à 2.16 Gy

in 10 fx

- 2 cases of dose-limiting toxicity at dose level I
- 1 treatment related death (dose level II)
- Manual GTV_{PET} delineation

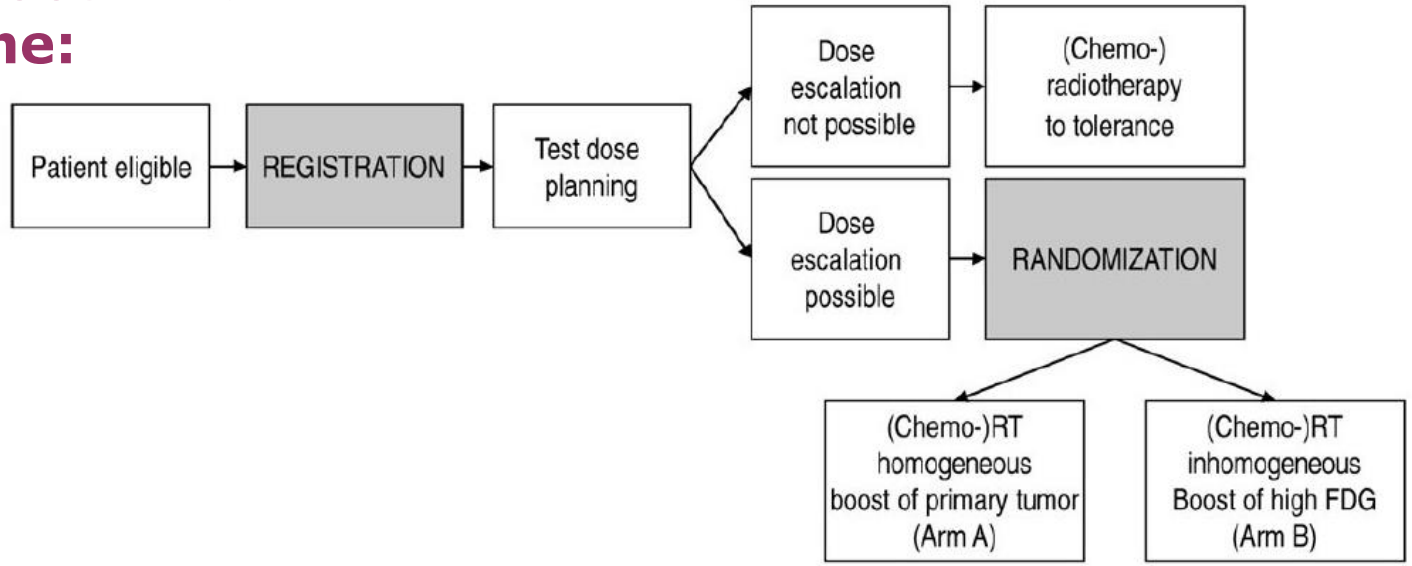


Simultaneous integrated boost based on FDG PET

Van Elmpt W et al. Radiother Oncol 2012;104(1): 67-71.

- PET-boost trial
- Randomizes between escalating the whole primary tumor or the high FDG uptake area (>50% SUV_{max})

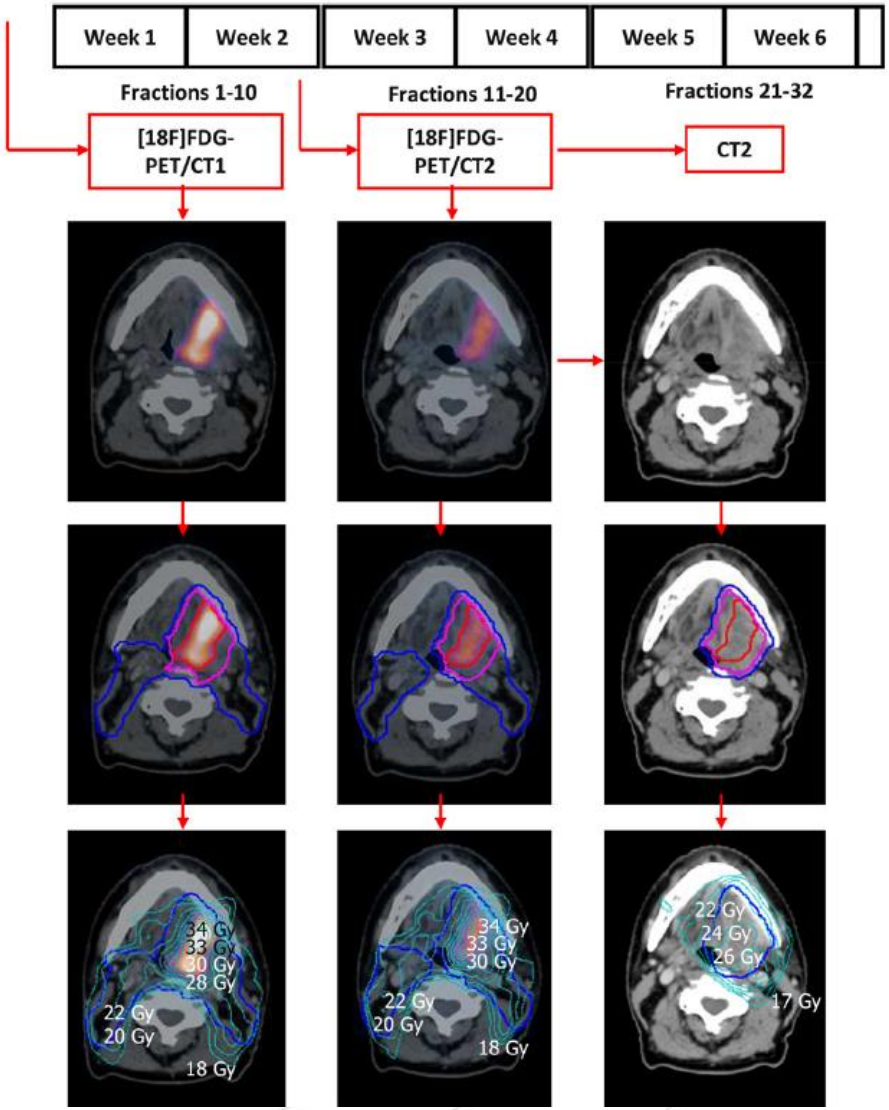
PET-boost trial scheme:



FDG PET/CT guided DP by numbers in HNC

Duprez et al, IJROBP 2011

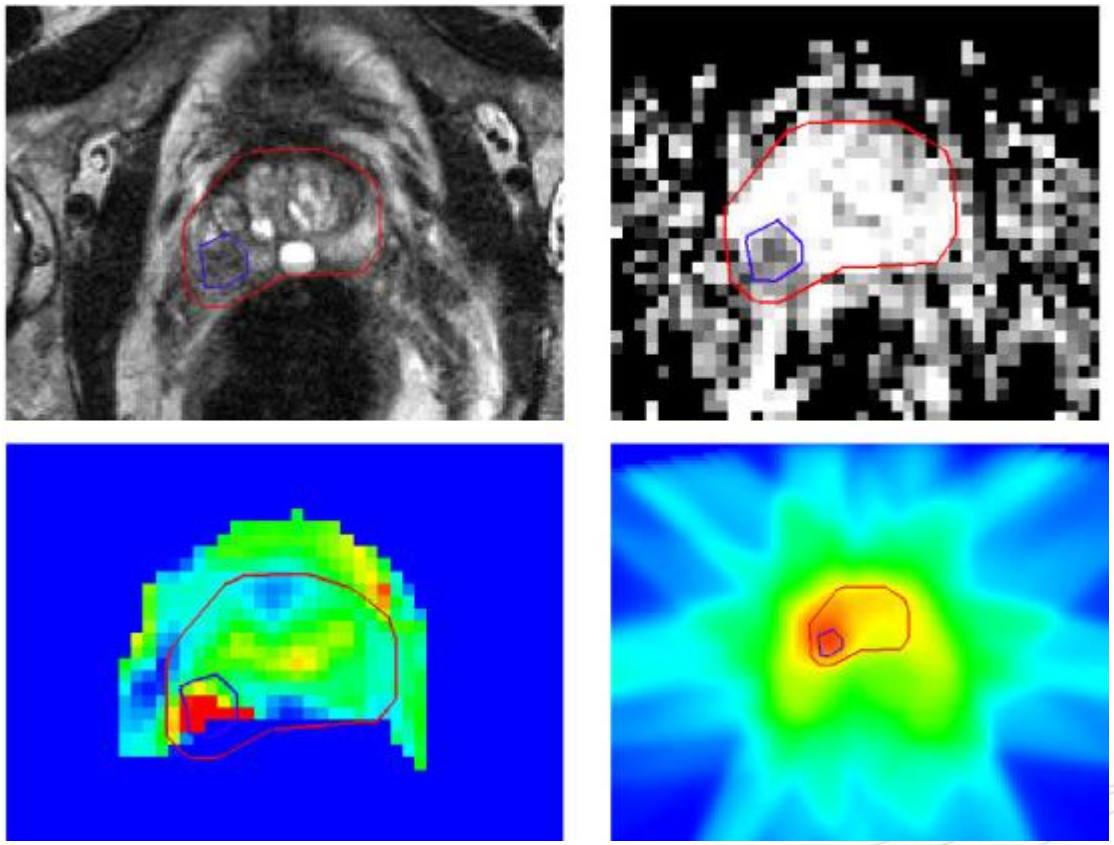
- n=21 patients
- Phase I study
- 3 separate treatment plans for each patient
- 2 different dose levels: median dose of 80.9 Gy to CTV_{high_dose} vs. 85.9 Gy to the GTV
- Prescription function: linear, arbitrary
- DPBN treatment feasible



MRI-based DPBC in prostate cancer

Lips IM et al, Trials 2012.

- Single blind randomized controlled Phase III
- Standard arm: 77 Gy
- Microboost to macro-scopic tumor volume: 95 Gy.
- Delineation according to DCE and DW MRI.



Hypoxia dose painting (HDP) in HNC: A randomized phase II trial in Tübingen

Aims

- Feasibility and toxicity of PET-based HDP
- Prospective validation of a hypoxia TCP model

Imaging

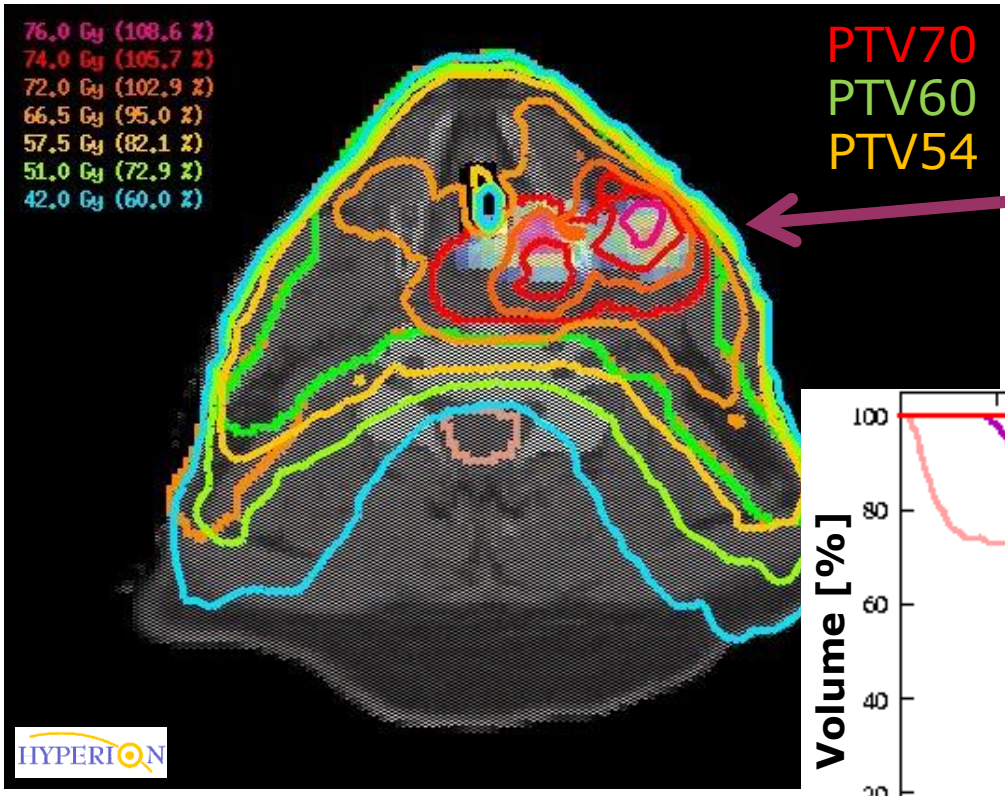
- Planning CT + FDG PET/CT
- Dynamic FMISO PET/CT in treatment position
- Second dyn. FMISO PET/CT after approx. 2 weeks of RT

Therapy

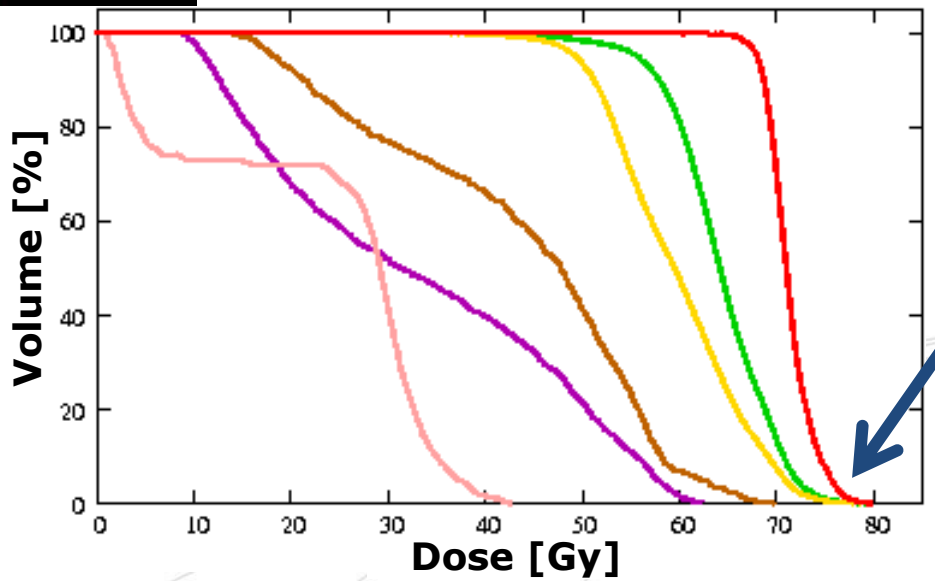
- Randomization of hypoxic patients in 2 arms:
  - **Arm 1: Standard IMRT** - 70 Gy in 35 fx
  - **Arm 2: HDP** - homogeneous dose escalation of 10% in hypoxic tumor areas defined on dynamic FMISO PET/CT data

Welz S et al. Radiother Oncol 2017; accepted.

Hypoxia Dose Painting based on dyn. FMISO PET/CT



Dose Painting to hypoxic Subvolume

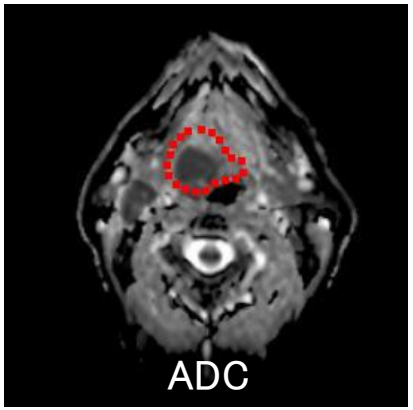


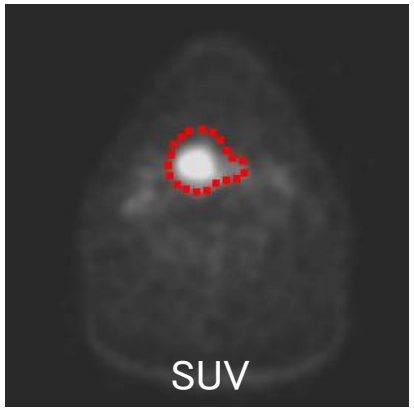
Patient 3: IMRT - Plan 70/77 Gy

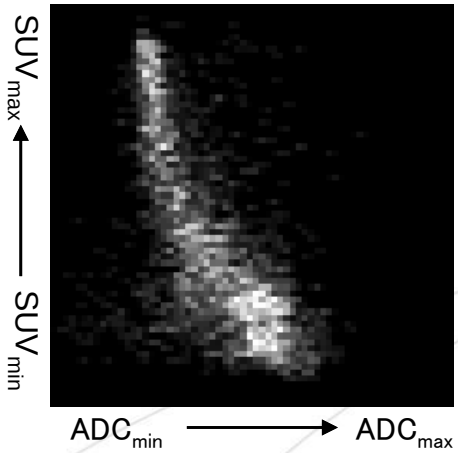
Analysis of tumor heterogeneity

Houweling A et al. Radiother Oncol 2013;106(2):250-4.

- N=18 HNC patients
- Examined with FDG PET and DW-MRI
- Voxel-based correlation of ADC values and FD uptake
- Comparison of ADC- and FDG-based volumes for potential RT dose escalation







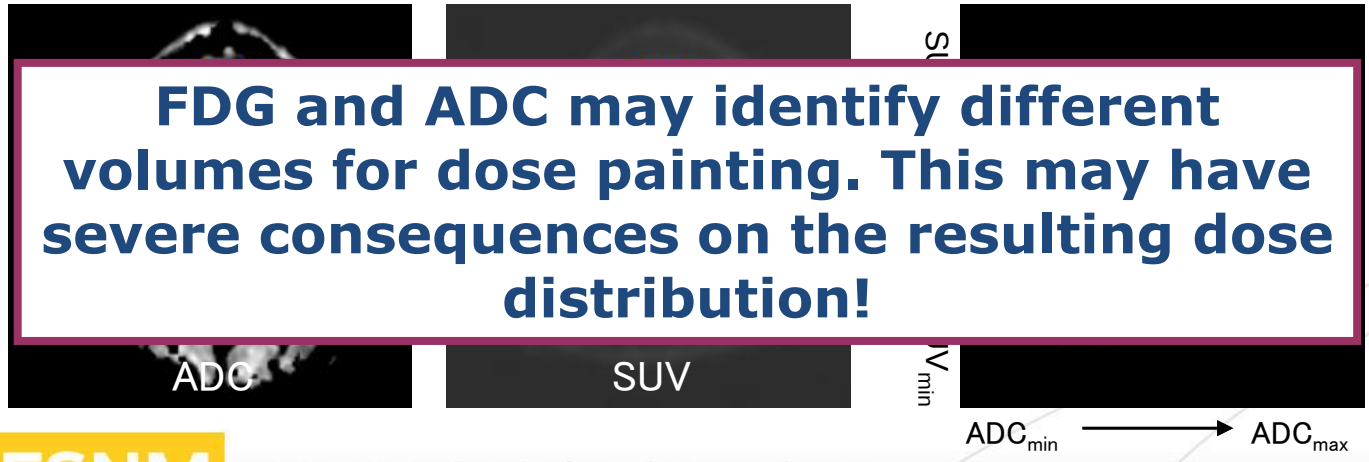
High negative Spearman correlation,

High mutual information

Analysis of tumor heterogeneity

Houweling A et al. Radiother Oncol 2013;106(2):250-4.

- N=18 HNC patients
- Examined with FDG PET and DW-MRI
- Voxel-based correlation of ADC values and FD uptake
- Comparison of ADC- and FDG-based volumes for potential RT dose escalation

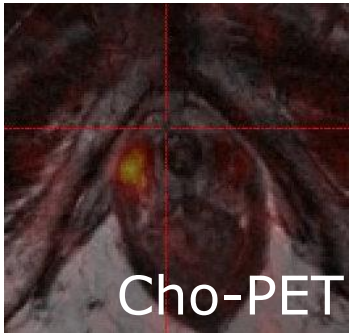


FDG and ADC may identify different volumes for dose painting. This may have severe consequences on the resulting dose distribution!

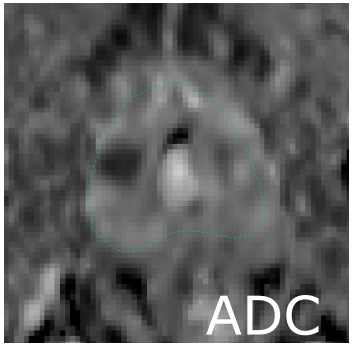
Positive Spearman correlation,

Low mutual information

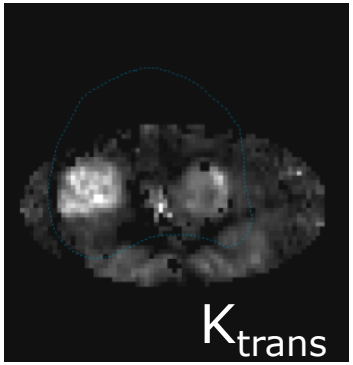
Probabilistic dose prescription according to multi-parametric PET/MR



+

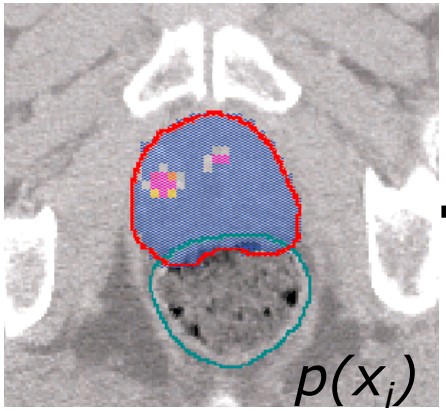


+

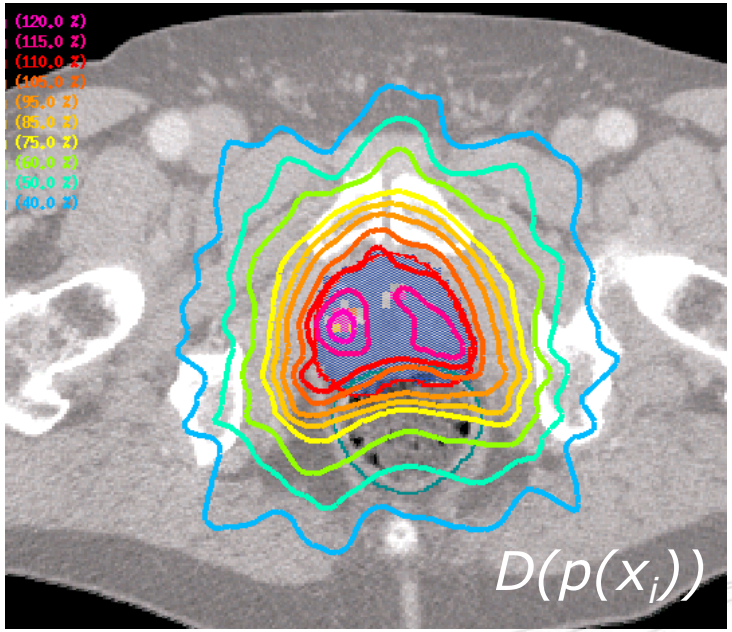


=

$$TCP = \prod_i (p_i TCP_i + (1 - p_i))$$



Probability map ***p(x$_i$)*** for the presence of tumor derived from multi-parametric PET/MR imaging.



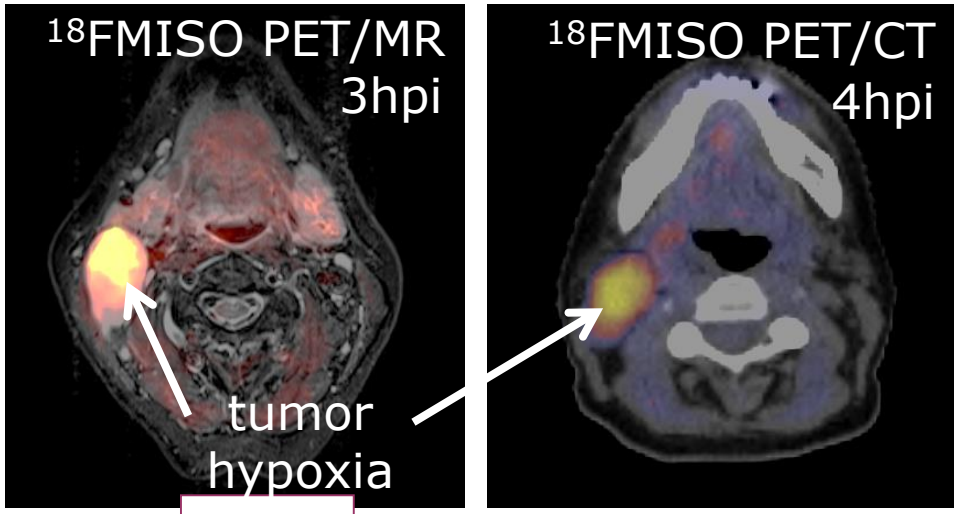
Probability dose painting ***D(p(x$_i$))*** shapes the dose according to the probability map *p(x$_i$)*.

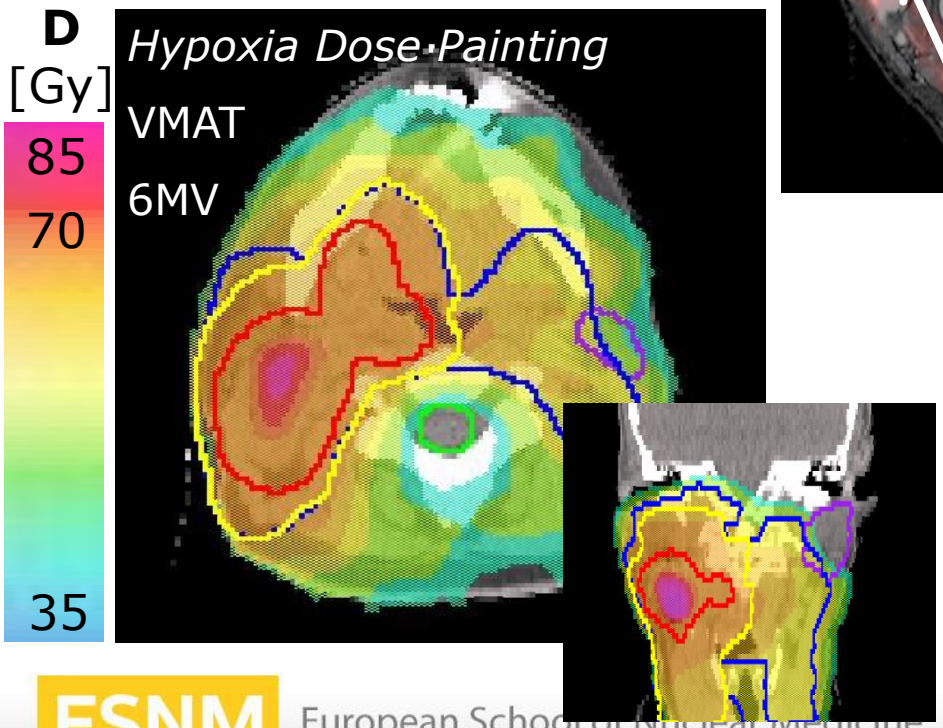
M. Alber, D. Thorwarth.

Radiother Oncol 2014;111:354-9.

Dose painting based on multi-parametric imaging

Multi-parametric characterization of tumor tissue by various **PET** and **MRI** techniques:





bio-iRT

Individualisation of RT dose prescriptions by integration of functional imaging information!

Summary/Conclusion

Functional Imaging

- Can visualize a variety of different biological /functional tumor properties

Key Issues for Dose Painting

- How to translate functional imaging information into dose prescriptions?
  - ? Robustness
  - ? Automation
  - ? Which imaging parameter to use?
  - ? Resolution?
  - ? Prescription Function

Multi-parametric imaging for Dose Painting

- Investigate tumor heterogeneity, in combined imaging studies
- Investigate local response to establish image-based dose-effect relations
- Dose-effect relations based on mp-imaging properties

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The challenge of clinical trials involving imaging based target volume concepts and future perspectives

PET-Plan,
a simple trial testing FDG PET/CT based target volume delineation in locally advanced NSCLC

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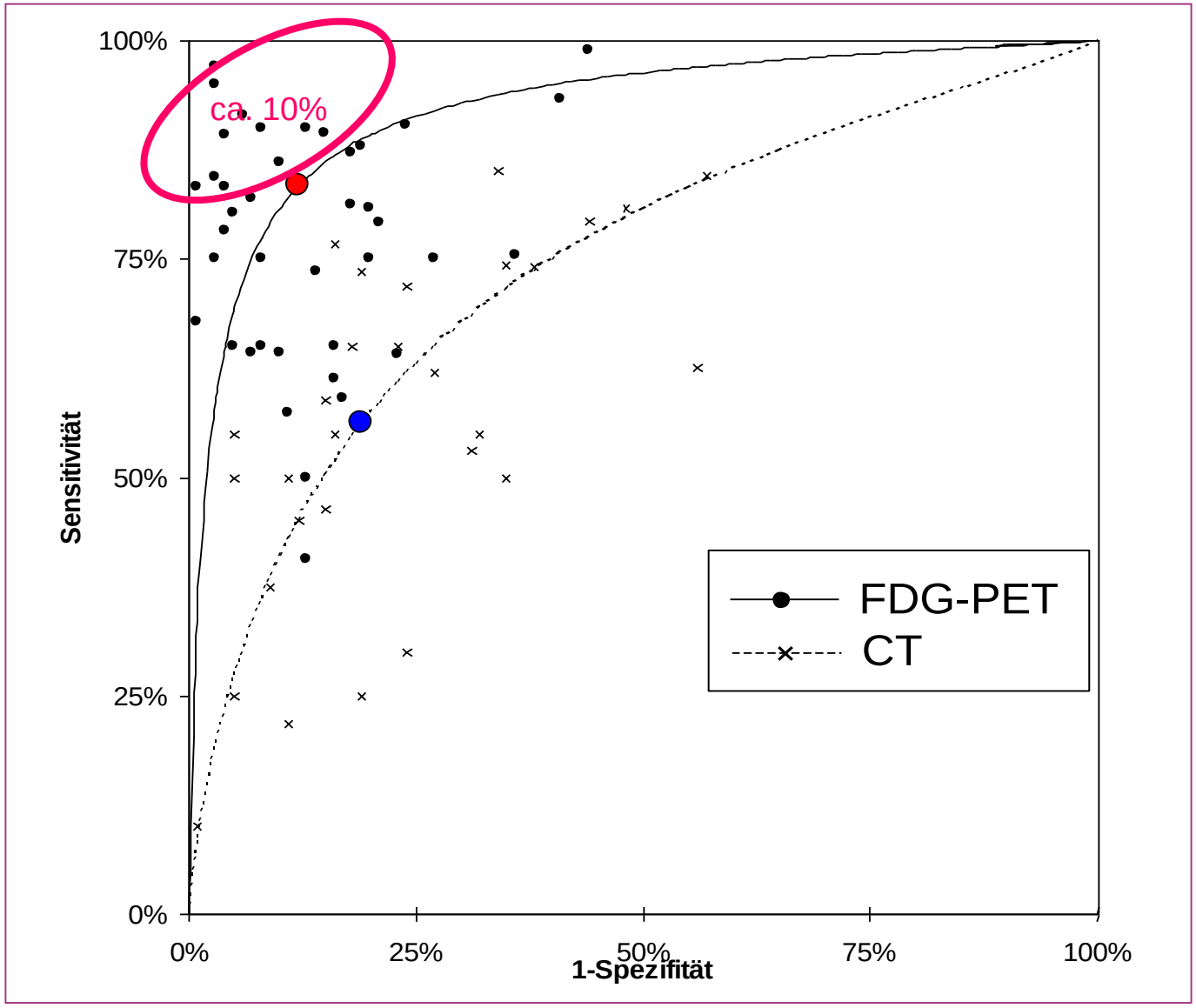
FDG-PET/CT in N-staging of NSCLC



Hellwig 2009: Metaanalysis
21 studies, 691 patients

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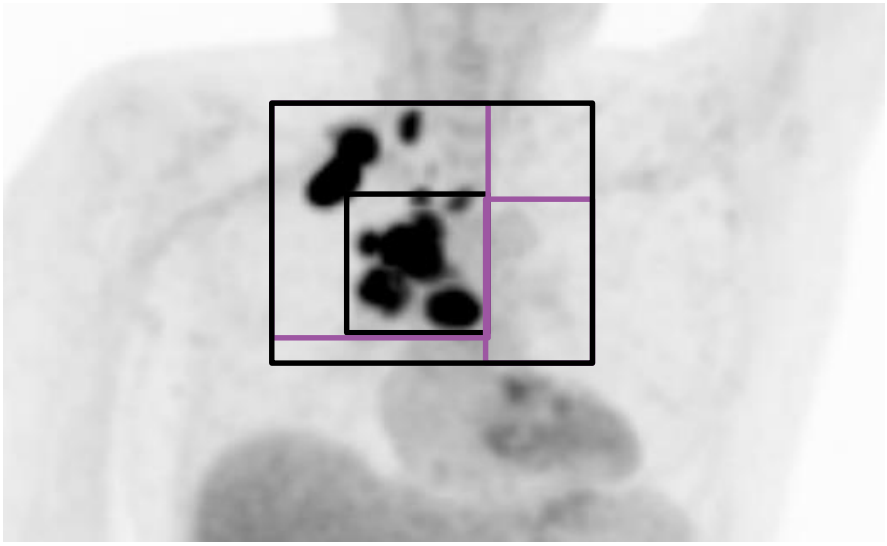
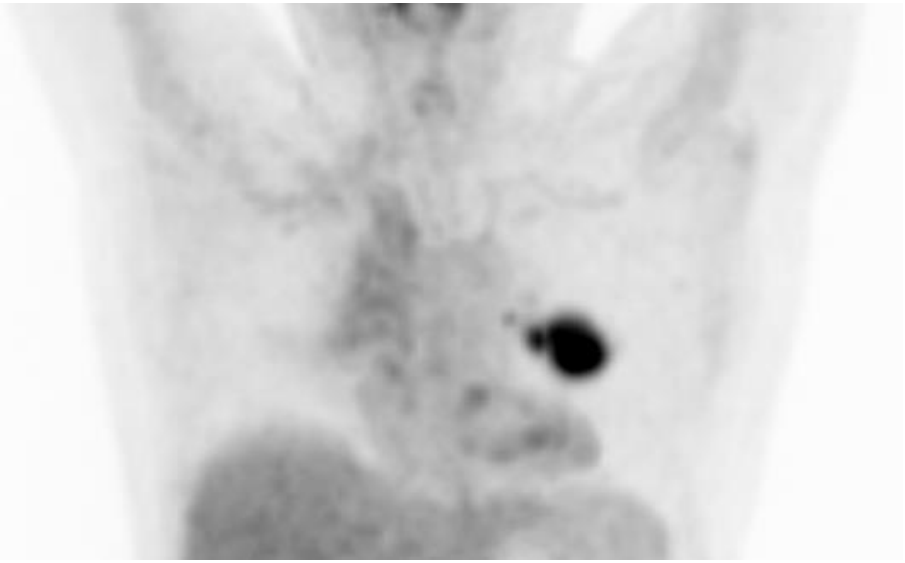
Questions to medical imaging: nodes





diagnostic imaging:

N2

RT treatment planning:

Treat what?

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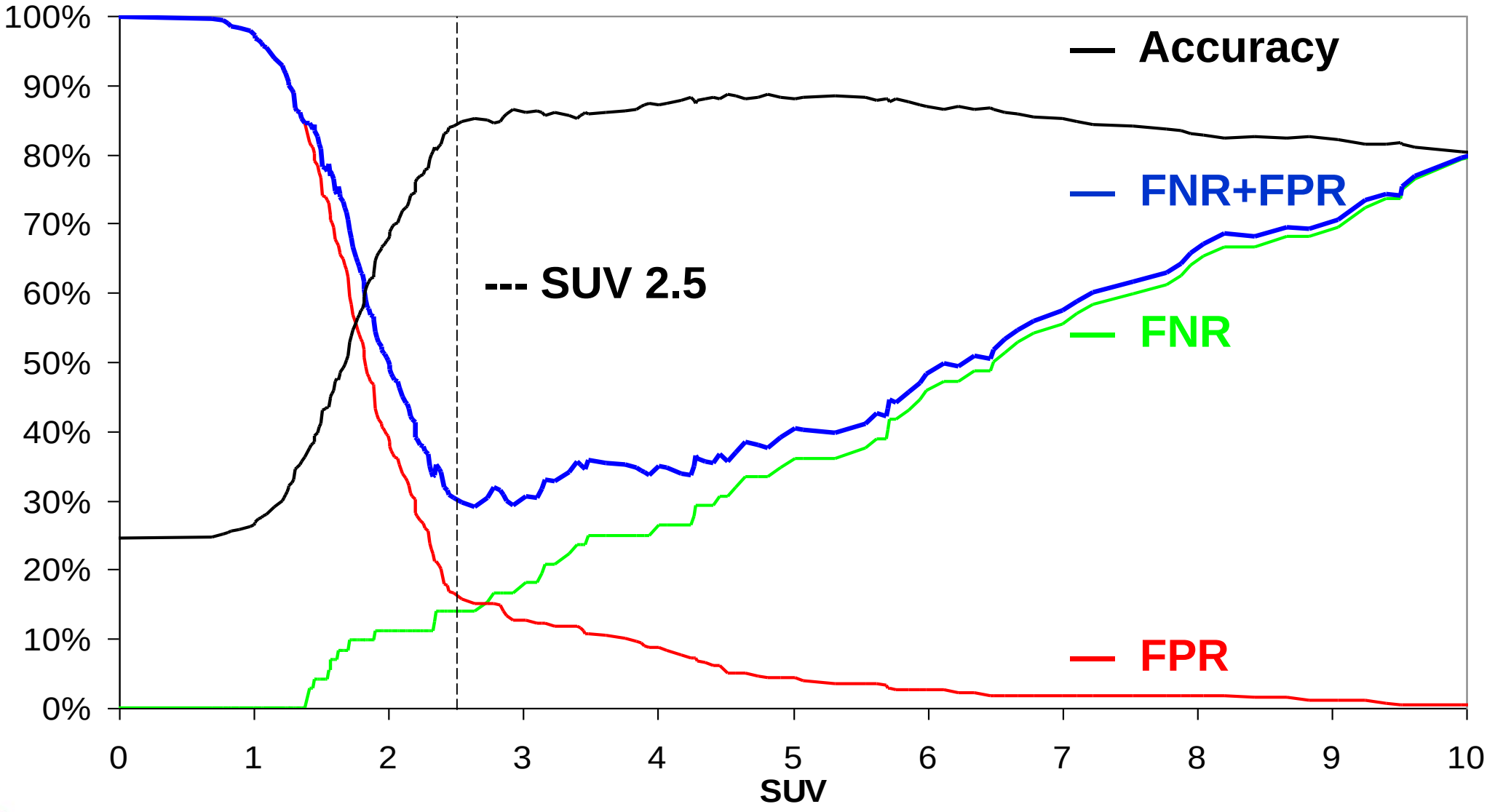
Error rates and accuracy vs SUV threshold



Hellwig J Nucl Med. 2007;48:1761-6.

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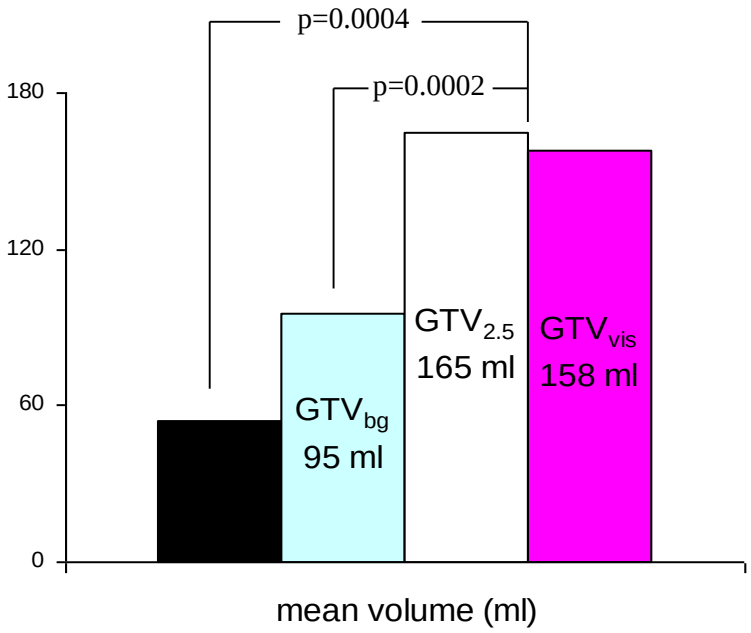
PET based GTV-contouring

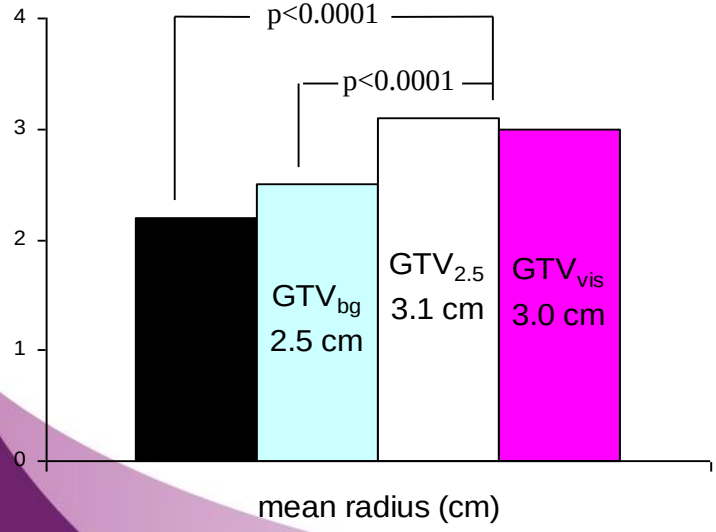


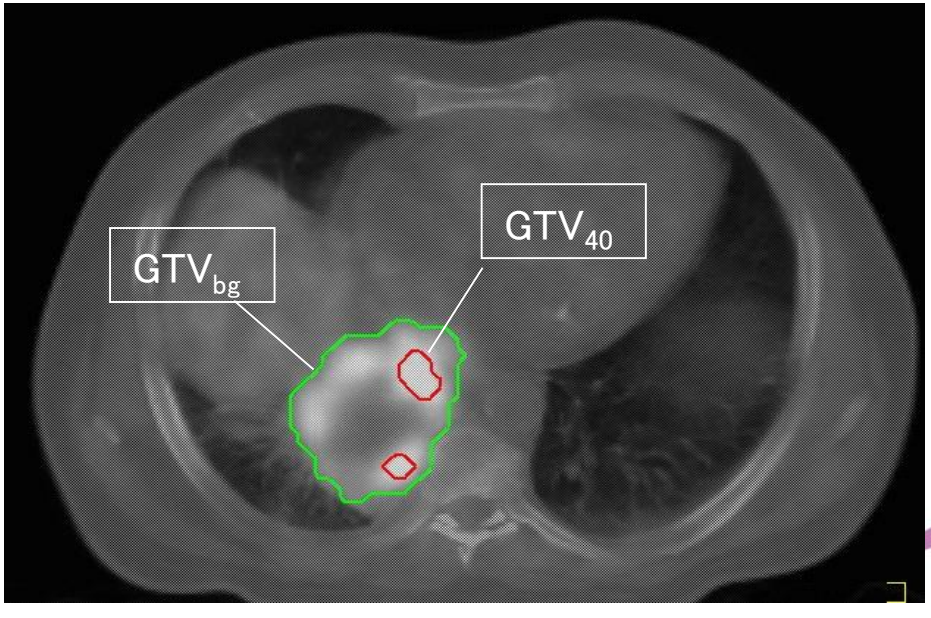
Size: $GTV_{40} < GTV_{bg} < GTV_{2.5} \cong GTV_{vis}$

significant differences,

correlation with
- SUV_{max}
- size of lesion
- FDG-inhomogeneity

mean difference (radius 2.5/40): 0.9 cm





Nestle JNM 200

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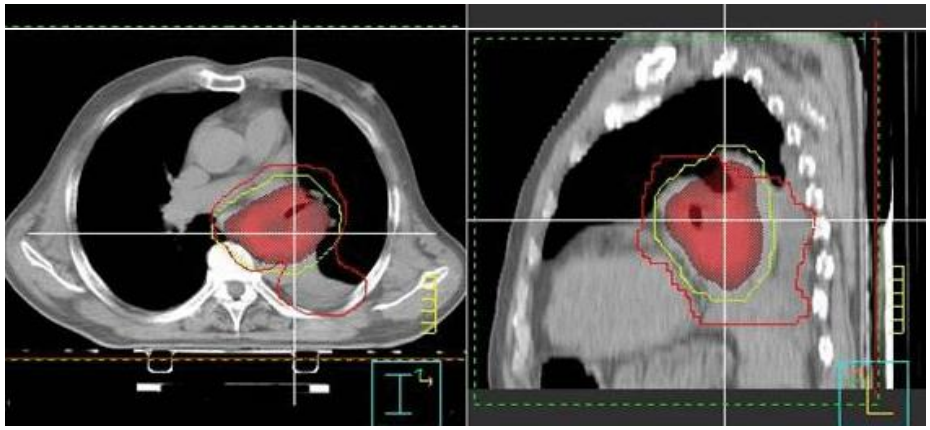
Arbeitsgemeinschaft
„Nuklearmedizin und Strahlentherapie“
der DEGRO und DGN

Arbeitsgemeinschaft
Radiologische Onkologie
der Deutschen Krebsgesellschaft

PET - Plan



Optimierung der Strahlentherapieplanung von Patienten mit inoperablen lokal fortgeschrittenen nicht-kleinzelligen Bronchialkarzinomen mittels F-18-FDG PET

Prospektive randomisierte multizentrische Therapieoptimierungsstudie

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

gefördert
durch die
Deutsche Krebshilfe

PET-Plan: Optimisation of radiotherapy planning for patients with locally advanced NSCLC using FDG-PET

UNIVERSITÄTS KLINIKUM FREIBURG

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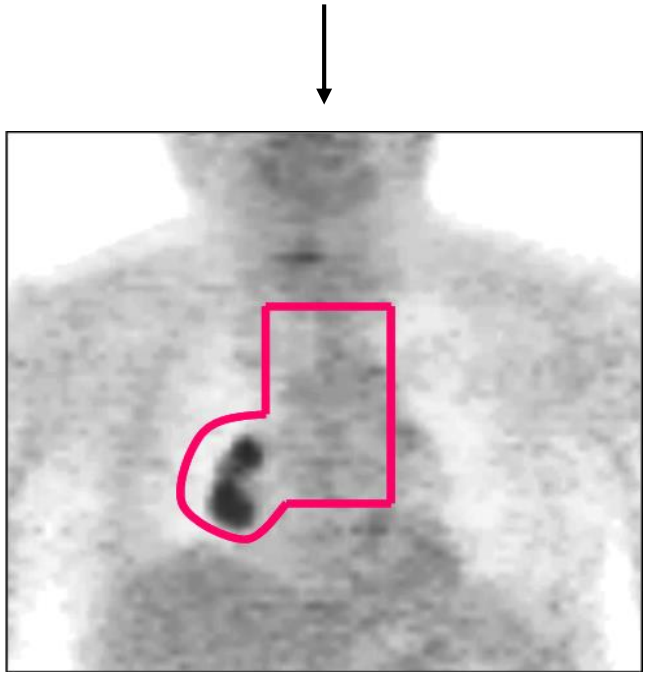
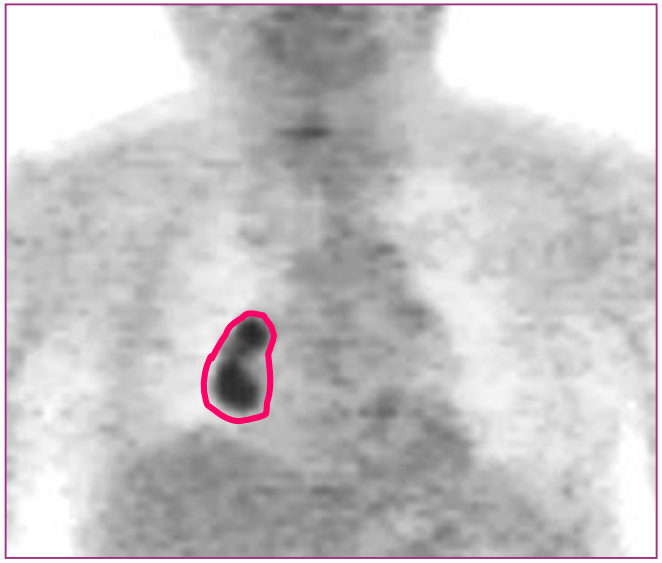
PET-Plan trial: question

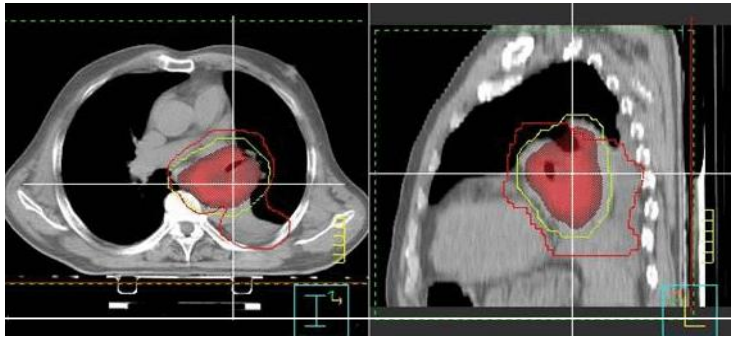


?



ENI

FDG-PET based SNI
with better
dose escalation possibilities?



PET - Plan

gefördert durch die
Deutsche Krebshilfe

equivalence study, hypothesis:

Dose escalated RCT after FDG-PET based RT-planning leads to at least similar outcome concerning local control and toxicity compared to conventional planning

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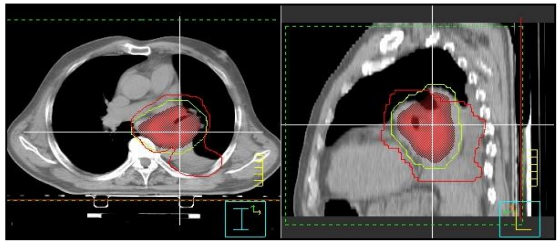
PET-Plan: in/exclusion



Main inclusion criteria:

NSCLC II-III
KPS >60%
inoperable (interdisciplinary consensus)
FeV1 > 1,0 l or > 35%
simultaneous RCT possible

Main exclusion criteria

supraclavicular LN
resection, previous CHT

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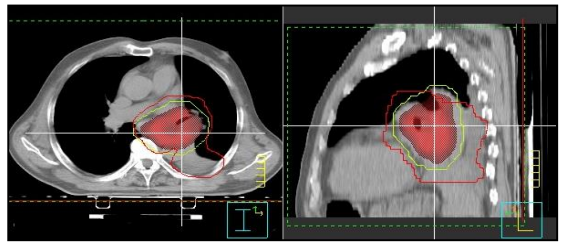
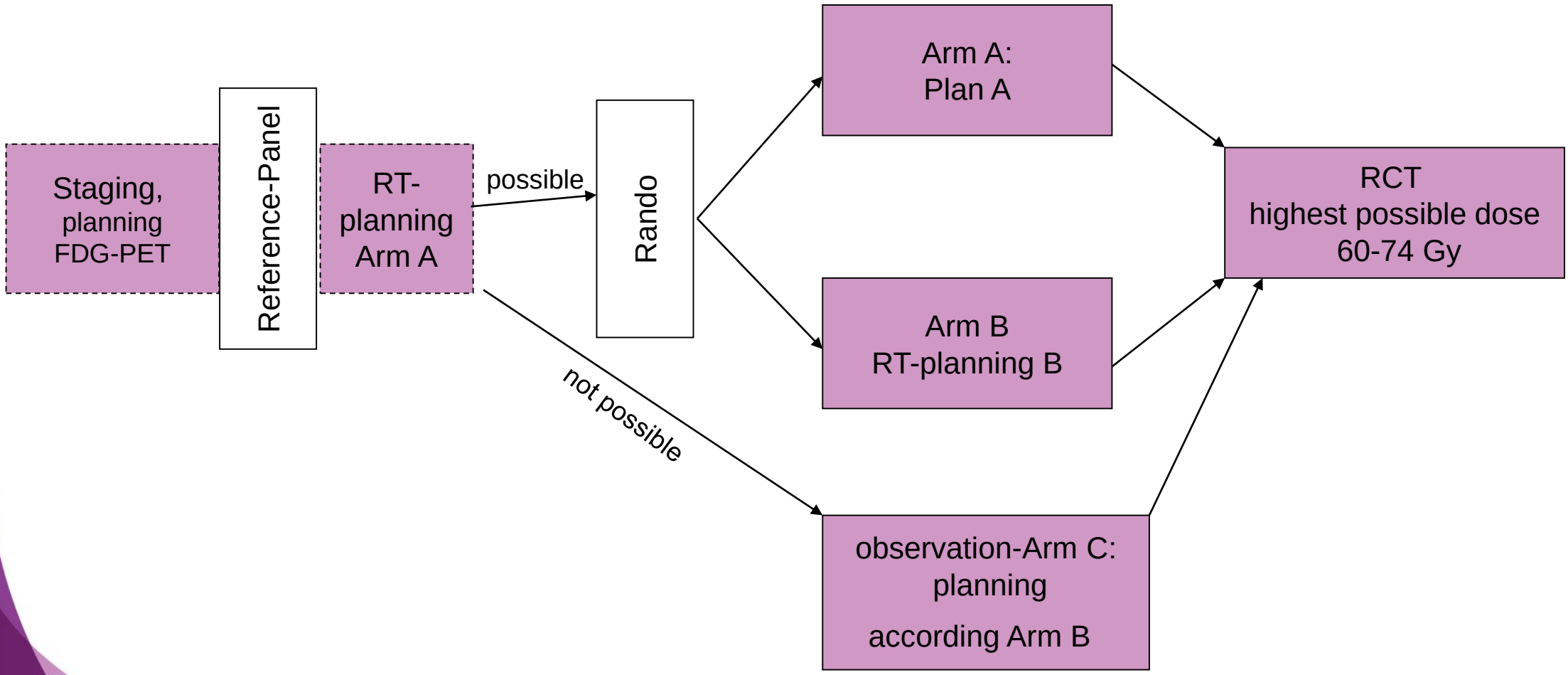
PET-Plan: Flow-Chart





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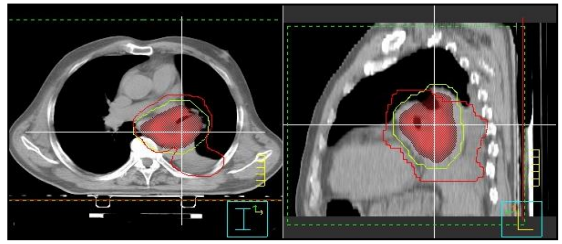
PET-Plan: Endpoints



primary

local progression free survival

secondary

toxicity (CTC; RTOG/EORTC)
doses to PTV reached by escalation

biometry

one-sided test; α=0,025, Power 80%
primary analysis: non-inferiority
secondary analysis: superiority of arm B

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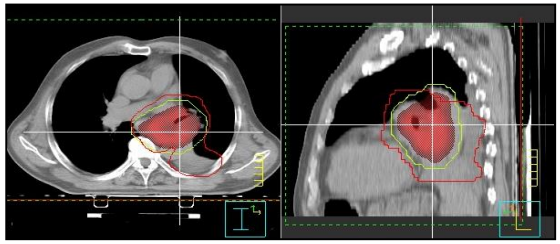
PET-Plan: Treatment



Arm A PET-Volume + atelectasis (3cm) + CT-positive LN:
escalated TD 60 – 74 Gy/ 2 Gy
elective LN (>10% risk) 50 Gy/ 2 Gy

Arm B PET-Volume
escalated TD 60 – 74 Gy/ 2 Gy

Observational arm C

RT-planning according arm A not possible:
RT in analogy to arm B

Dose escalation:

All patients
highest possible dose by NT restrictions

simultaneous chemotherapy

all pts: Platin containing doublet
e.g. Platin-Vinorelbine, Platin-Etoposid

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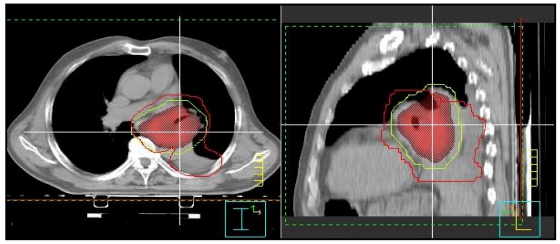
PET-Plan: target volumes



„PET-volume“

primary tumor (PET-GTV + 3 mm + 8-10 mm)

FDG-positive LN-stations (anatomical, Chapet)

elective LN volume

according to table (10% risk) anatomically + 8-10 mm

Lokalisation Primärtumor	zusätzlich zu bestrahlende (bildgebend negative) Lymphknotenstationen				
Oberlappen rechts	1R	2R	4R	7	10/11R
Mittellappen	1R	2R	4R	7	10/11R
Unterlappen rechts		2R	4R	7	10/11R
Rechts zentral	1R	2R	4R	7	10/11R
Oberlappen links	1L	2L	4L	7	10/11L
Unterlappen links			4L	7	10/11L
Links zentral	1L	2L	4L	7	10/11L

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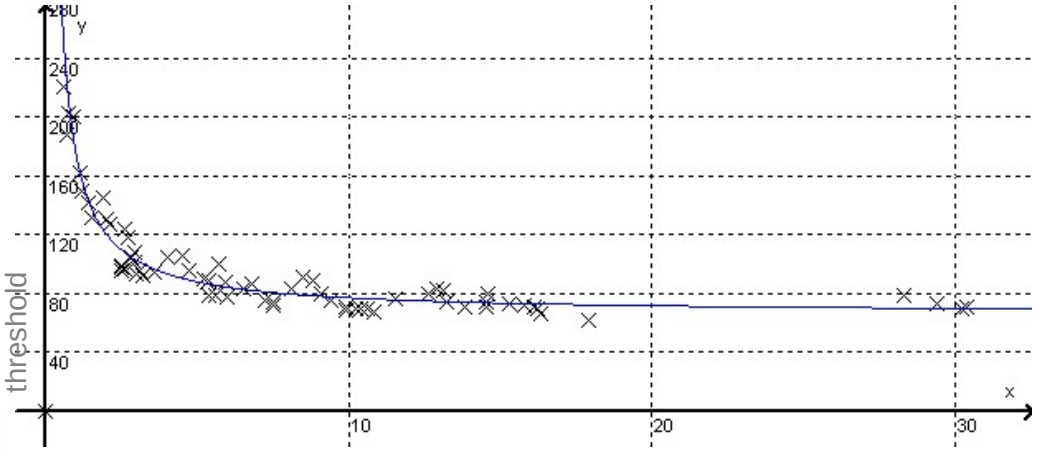
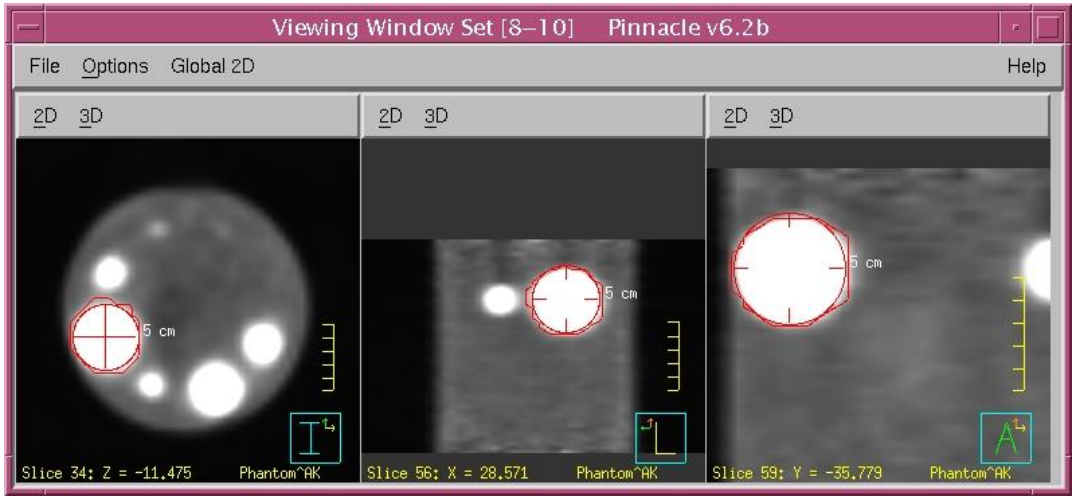
Eur J Nucl Med Mol Imaging (2008) 35:1989–1999
DOI 10.1007/s00259-008-0875-1

ORIGINAL ARTICLE

A contrast-oriented algorithm for FDG-PET-based delineation of tumour volumes for the radiotherapy of lung cancer: derivation from phantom measurements and validation in patient data

Andrea Schaefer · Stephanie Kremp · Dirk Hellwig · Christian Rübe · Carl-Martin Kirsch · Ursula Nestle





source / background – algorithm:

$I_{threshold} = (x * I_{lesion}) + (y * I_{background})$

… some QA

although a special software is available, the contrast oriented automatic contouring tool used for the trial needs scanner calibration leading to

- 24 pages of instructions for phantom measurements
- all centers doing measurements before being allowed to use semiautomatic PET contouring
- central evaluation of measurement results
- results of 11 centers evaluated and published

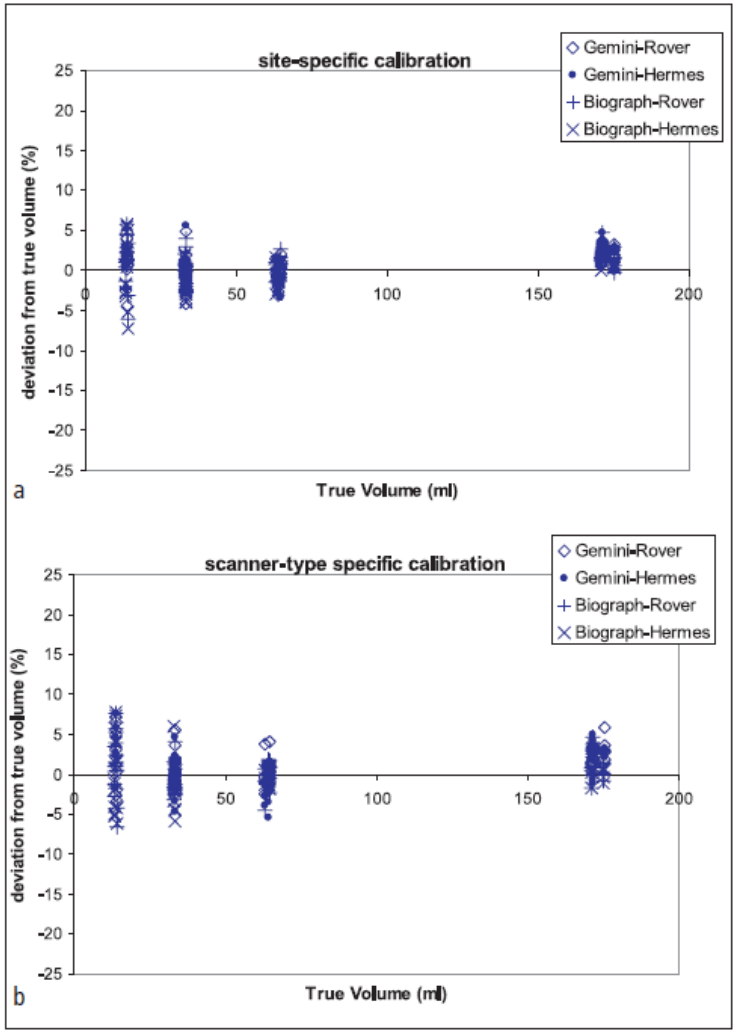
Multi-centre calibration of an adaptive thresholding method for PET-based delineation of tumour volumes in radiotherapy planning of lung cancer

A. Schaefer[1]; U. Nestle[3]; S. Kremp[2]; D. Hellwig[1]; A. Grgic[1]; H. G. Buchholz[4]; W. Mischke[5]; C. Gromoll[6]; P. Dennert[7]; M. Plotkin[8]; S. Senftleben[9]; D. Thorwarth[10]; M. Tosch[11]; A. Wahl[12]; H. Wengenmair[13]; C. Rübe[2]; C.-M. Kirsch[1]

Nuklearmedizin 2012; 51: 101–110
doi:10.3413/Nukmed-0452-11-12

Conclusion

After multi-centre calibration SUV-thresholds calculated by use of the contrast-oriented algorithm at different sites to auto-contour volumes do not differ significantly if compliance in imaging protocols including the evaluation software is guaranteed. Whenever this prerequisite is fulfil-



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… more QA

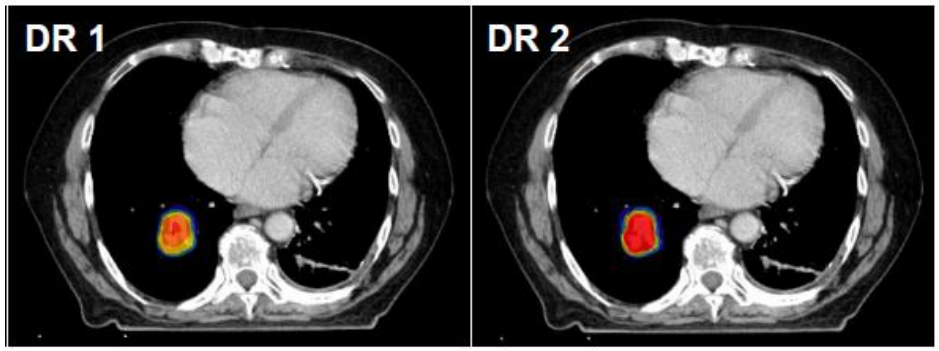
the study protocol contains detailed instructions for imaging based target volume delineation, randomisation is by target volume, dose escalation is mandatory. Therefore, QA is necessary

- for PET based GTV delineation
- for anatomic delineation of LN-stations
- for normal tissue delineation
- for RT-planning

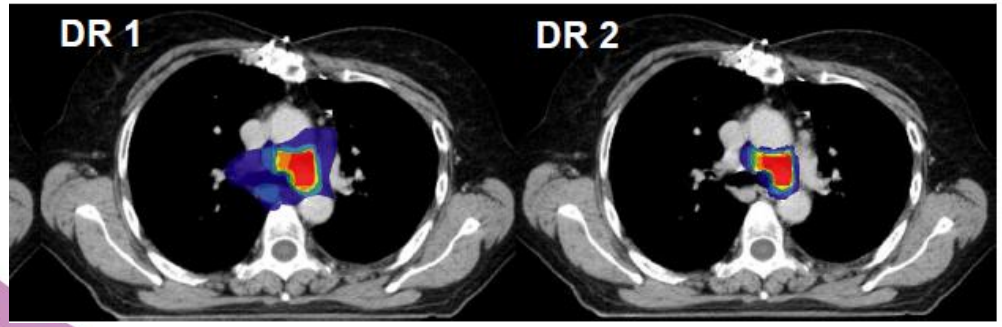
A teaching intervention in a contouring dummy run for a multicentre clinical study improved target volume delineation in locally advanced non-small cell lung cancer.

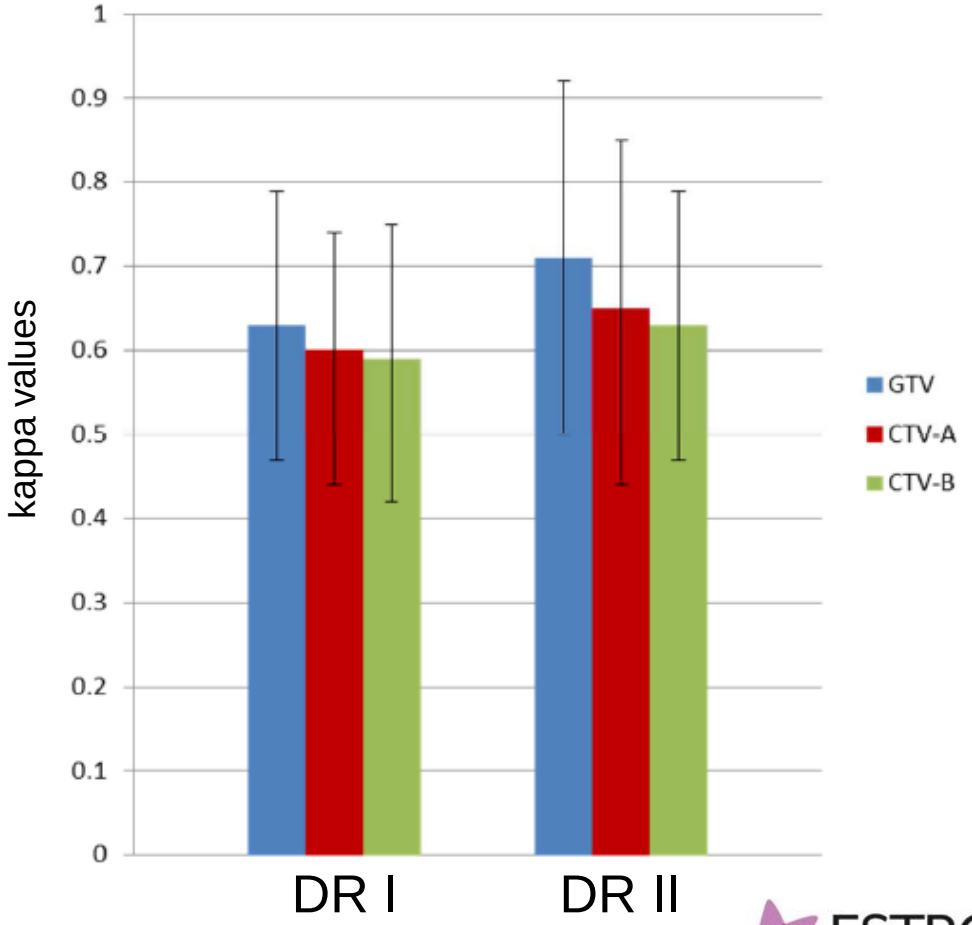
T. Schimek-Jasch[1], E.G.C. Troost[2], G. Rücker[3], V. Prokic[1], M. Avlar[1], V. Duncker-Rohr[4], M. Mix[5], C. Doll[1], A.-L. Grosu[1], U. Nestle[1]

Strahlentherapie Onkologie 2015



GTV)





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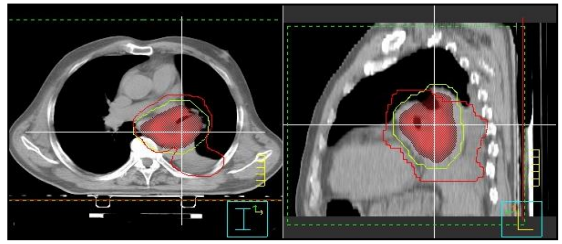
PET-Plan: NT-restrictions



lung

V20 <35% total lung (minus GTV)
and MLD ≤ 20 Gy

esophagus

V55 < 30%
or mean dose 34 Gy

spinal cord

maximum point dose 48 Gy

heart

as low as possible, V40 ≤ 50

liver

V35 <33 % whole organ

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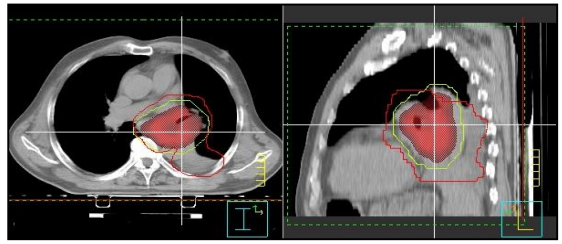
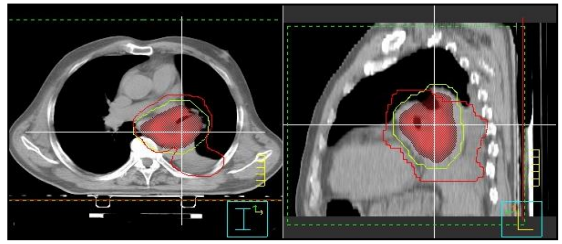
PET-Plan: TV specifications



# eCRF	Parameter	Protokollgemäß	Minor deviation	Major deviation
1	***GTV (Primärtumor)***			
1a	**GTV (Primärtumor) Arm A:** PET-GTV+ Atelektase bis 3 cm	überall FDG-positiver Tumor eingeschlossen	Irgendwo > 5-10mm Abweichung	Irgendwo > 10 mm Abweichung
1b	**GTV (Primärtumor) Arm B:** PET-GTV	überall FDG-positiver Tumor eingeschlossen	Irgendwo > 5-10mm Abweichung	Irgendwo > 10 mm Abweichung
2	***CTV Lymphknoten***			
2a	**CTV** **Eskaliertes LK-Volumen Arm A:** Anatomie	Eingeschlossen nach Panel-Empfehlung, anatomisch* ok	Kleinere anatomische Abweichungen, plausibel begründete Abweichung von Panel-Empfehlung	Massive anatomische Abweichungen, unplausible / nicht begründete Abweichung von Panel-Empfehlung
2b	**CTV** **Eskaliertes LK-Volumen Arm A:** Geometrie	Jeweils überall: anatomisch* konturierte LK-Stationen inclusive PET-Anreicherungen	Irgendwo > 5-10mm Abweichung	Irgendwo > 10 mm Abweichung
	CTV		Kleinere anatomische	Massive anatomische Abweichungen

# eCRF	Parameter	Protokollgemäß	Minor deviation	Major deviation
4	***Physikalische Planung***			
4a	**Dosisberechnung**	Erweiterte Berücksichtigung von Sekundärelektronen (z.B. „collapsed cone“)	-	Keine erweiterte Berücksichtigung von Sekundärelektronen
4b	**Dosisspezifikation** (D_R= Referenzdosis)	ICRU, ≥ 90% des PTV erhalten ≥ 95% der D_R **und** ≥ 97% des GTV erhalten ≥ 95% der D_R **und** Maximum im PTV <110%	Nicht protokollgemäß, aber ≥ 80 % des PTV erhalten≥ 95% der D_R **und** 90 % des GTV erhalten ≥ 95% der D_R **und** Maximum im PTV <118%	≤ 80 % des PTV erhalten ≥ 95% der D_R **oder** ≤ 90 % des GTV erhalten ≥ 95% der D_R **oder** Maximum im PTV ≥ 118 %
6.	***Dosiseskalation*** *(Ausreizen der Normalgewebstoleranzen)*			
6a	**Verordnete Referenzdosis** ($D_{R,v}$)	$D_{R,v}$ 74 Gy **oder** mindestens ein Normalgewebe > 90% der Restriktion belastet	$D_{R,v}$ > 70 Gy **oder** mindestens ein Normalgewebe >80% der Restriktion belastet	$D_{R,v}$ ≤ 70 Gy **und** kein Normalgewebe bis mind. 80% der Restriktion belastet

PET-Plan: RT specifications



RT technique

3D-CRT or IMRT

Dose calculation

Type B algorithms

Dose to PTV

60-74 Gy/2 Gy, compensation of breaks

prescription

ICRU 62 (95-107%)

QA

individual QA of RT-dose datasets, pre-defined specifications

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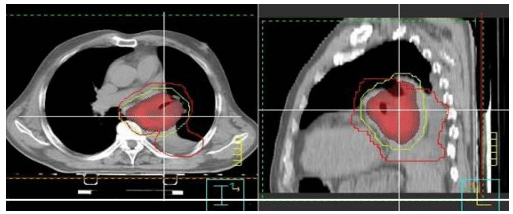


PET - Plan

gefördert durch die
Deutsche Krebshilfe

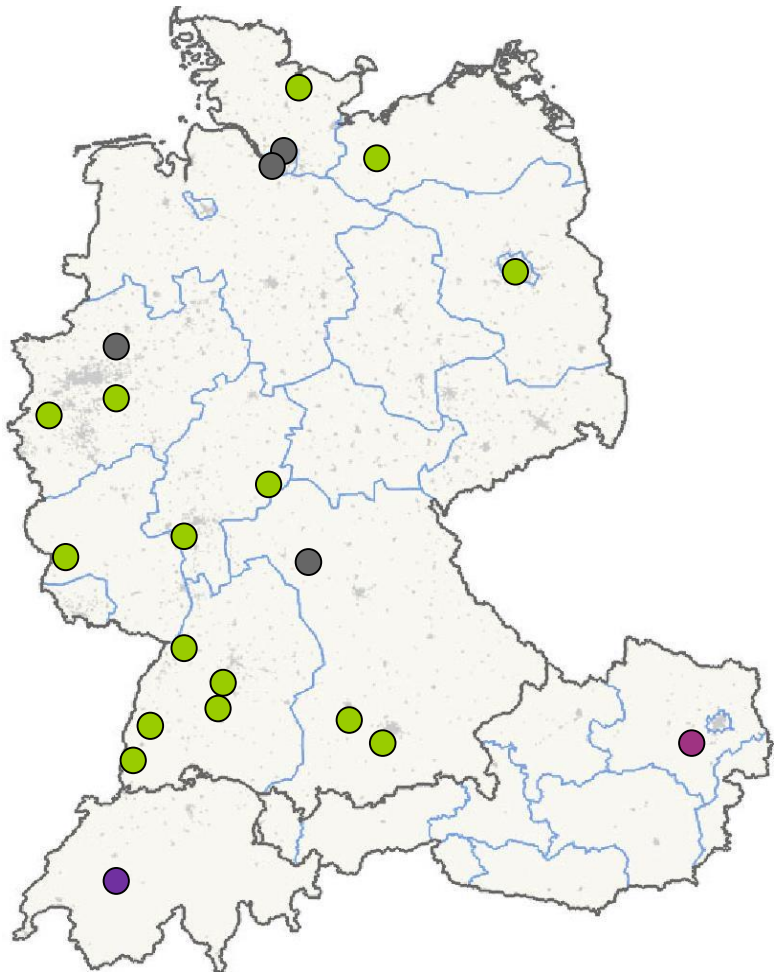
randomized treatment optimisation trial

23 centers in D, CH, A

200 randomised pts with
inoperable NSCLC
+ max. 197 pts in observation arm

funded by deutsche Krebshilfe

pt. recruitment since May 2009



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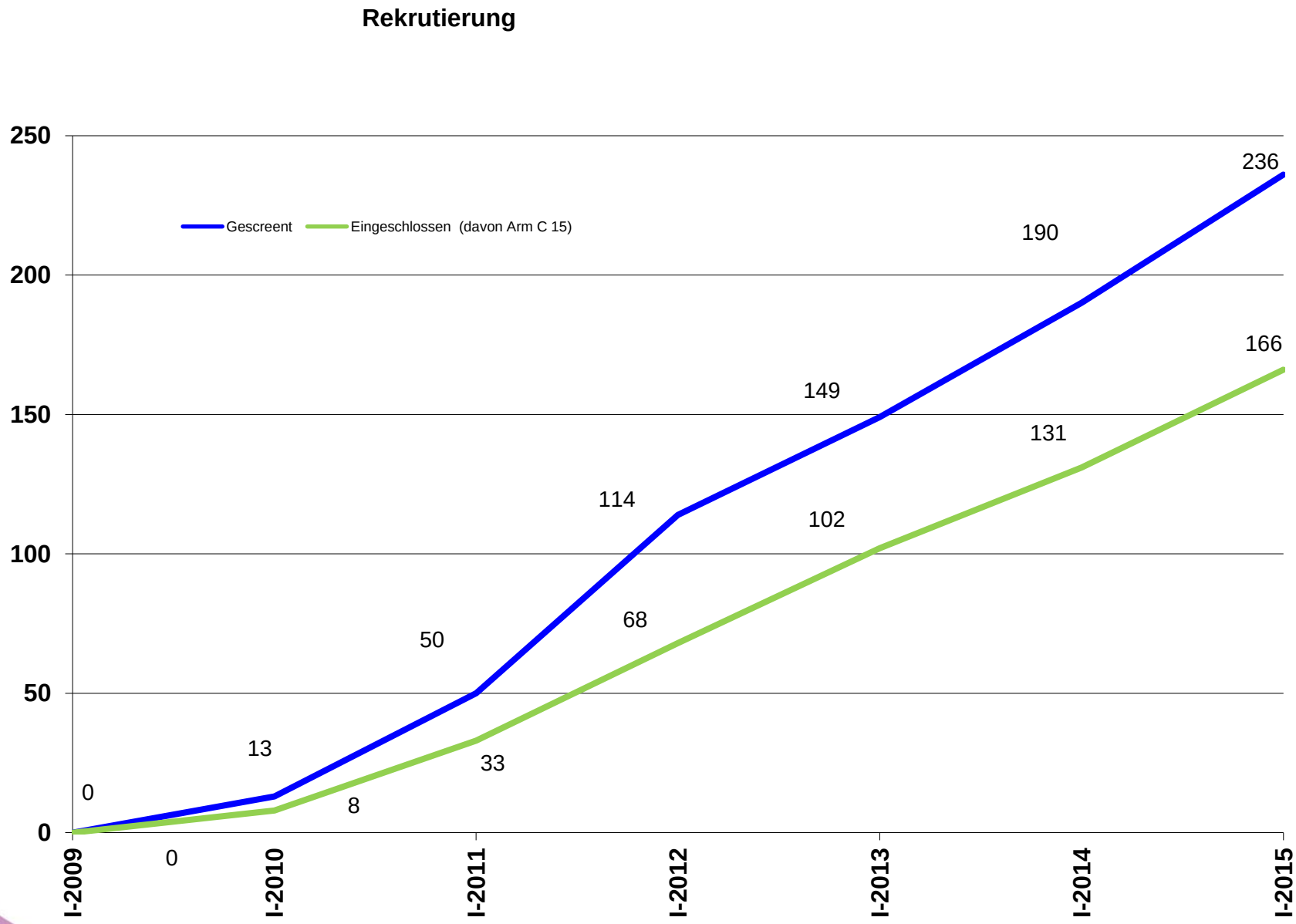
PET-Plan Enrollment 23.02.2015



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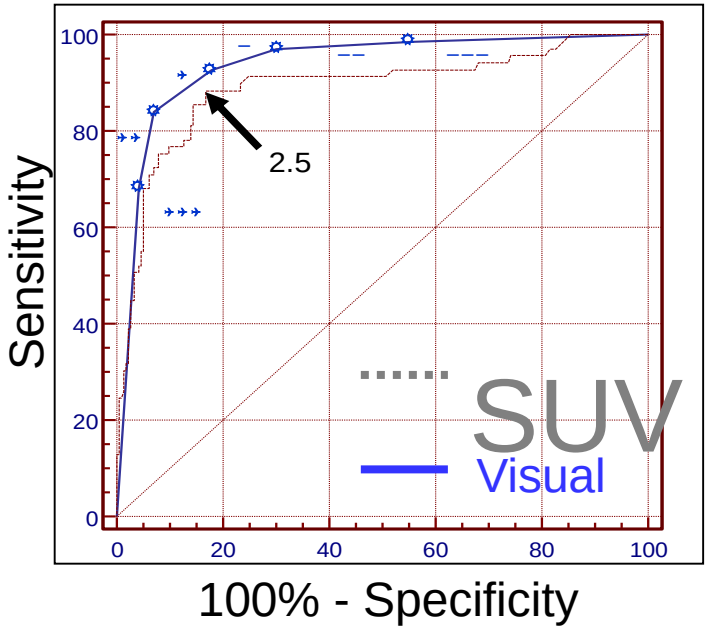
PET-Plan diagnostic Panel

- Expert PET/CT review of all cases included in study
- Safeguarding study centers
  for volume definition when omitting ENI
- Online organised
- 10 experts available



- criterion for PET positivity: visual
- criterion for CT positivity: 1 cm short axis

- reporting by AJCC LN-stations in CT and PET
  (diagnostic literature, common dictionary guiding target volumes,
  planned analysis of recurrence topography)

- 2 blinded reviews, 1 unblinded if necessary

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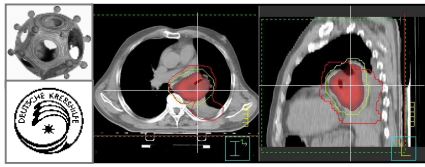
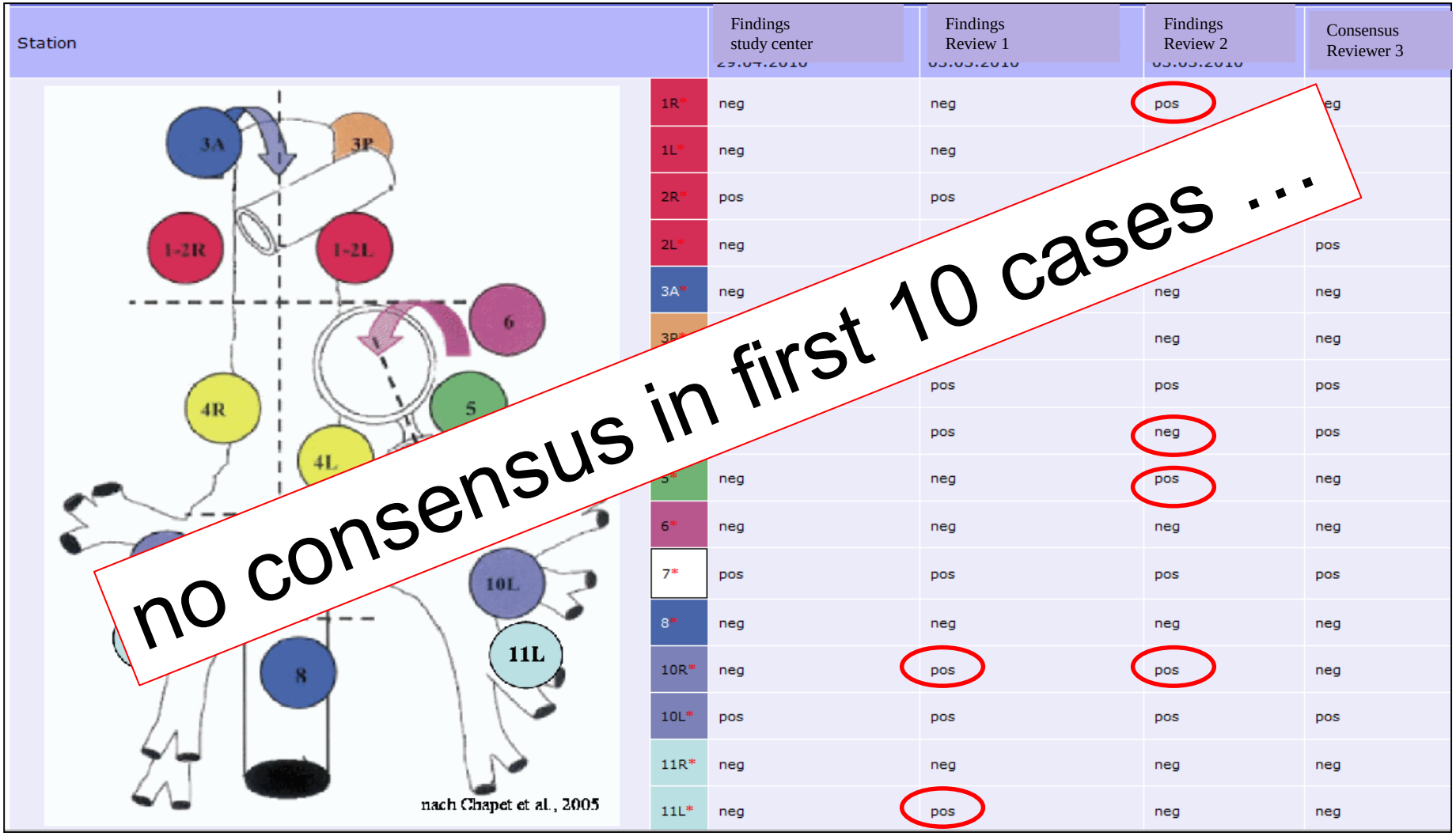
PET-Plan Study: diagnostic expert-panel





Station	Findings study center	Findings Review 1	Findings Review 2	Consensus Reviewer 3
1R*	neg	neg	pos	neg
1L*	neg	neg		
2R*	pos	pos		
2L*	neg			pos
3A*	neg		neg	neg
3P*			neg	neg
		pos	pos	pos
		pos	neg	pos
5*	neg	neg	pos	neg
6*	neg	neg	neg	neg
7*	pos	pos	pos	pos
8*	neg	neg	neg	neg
10R*	neg	pos	pos	neg
10L*	pos	pos	pos	pos
11R*	neg	neg	neg	neg
11L*	neg	pos	neg	neg

no consensus in first 10 cases …

32 LN-reports for PET (16) and CT (16) to be entered at each review step

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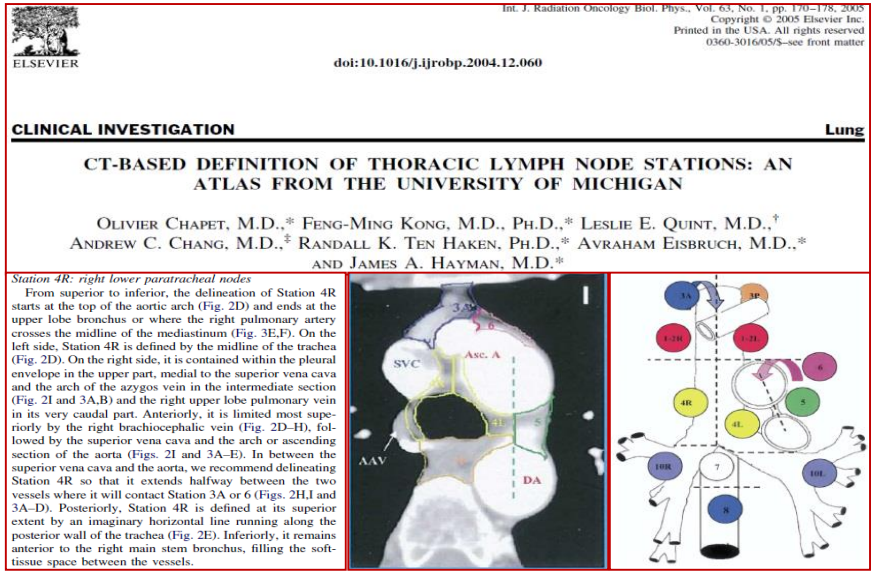
What now?

positivity
PET: visual
CT: 1 cm short axis

reporting by LN-station according to atlas



Int. J. Radiation Oncology Biol. Phys., Vol. 63, No. 1, pp. 170–178, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.12.060

CLINICAL INVESTIGATION **Lung**

CT-BASED DEFINITION OF THORACIC LYMPH NODE STATIONS: AN ATLAS FROM THE UNIVERSITY OF MICHIGAN

OLIVIER CHAPET, M.D.,* FENG-MING KONG, M.D., PH.D.,* LESLIE E. QUINT, M.D.,† ANDREW C. CHANG, M.D.,‡ RANDALL K. TEN HAKEN, PH.D.,* AVRAHAM EISBRUCH, M.D.,* AND JAMES A. HAYMAN, M.D.*

Station 4R: right lower paratracheal nodes

From superior to inferior, the delineation of Station 4R starts at the top of the aortic arch (Fig. 2D) and ends at the upper lobe bronchus or where the right pulmonary artery crosses the midline of the mediastinum (Fig. 3E,F). On the left side, Station 4R is defined by the midline of the trachea (Fig. 2D). On the right side, it is contained within the pleural envelope in the upper part, medial to the superior vena cava and the arch of the azygos vein in the intermediate section (Fig. 2I and 3A,B) and the right upper lobe pulmonary vein in its very caudal part. Anteriorly, it is limited most superiorly by the right brachiocephalic vein (Fig. 2D–H), followed by the superior vena cava and the arch or ascending section of the aorta (Figs. 2I and 3A–E). In between the superior vena cava and the aorta, we recommend delineating Station 4R so that it extends halfway between the two vessels where it will contact Station 3A or 6 (Figs. 2H,I and 3A–D). Posteriorly, Station 4R is defined at its superior extent by an imaginary horizontal line running along the posterior wall of the trachea (Fig. 2E). Inferiorly, it remains anterior to the right main stem bronchus, filling the soft-tissue space between the vessels.

Initiation of harmonisation process:

refinement of reading criteria
validate against biopsy results

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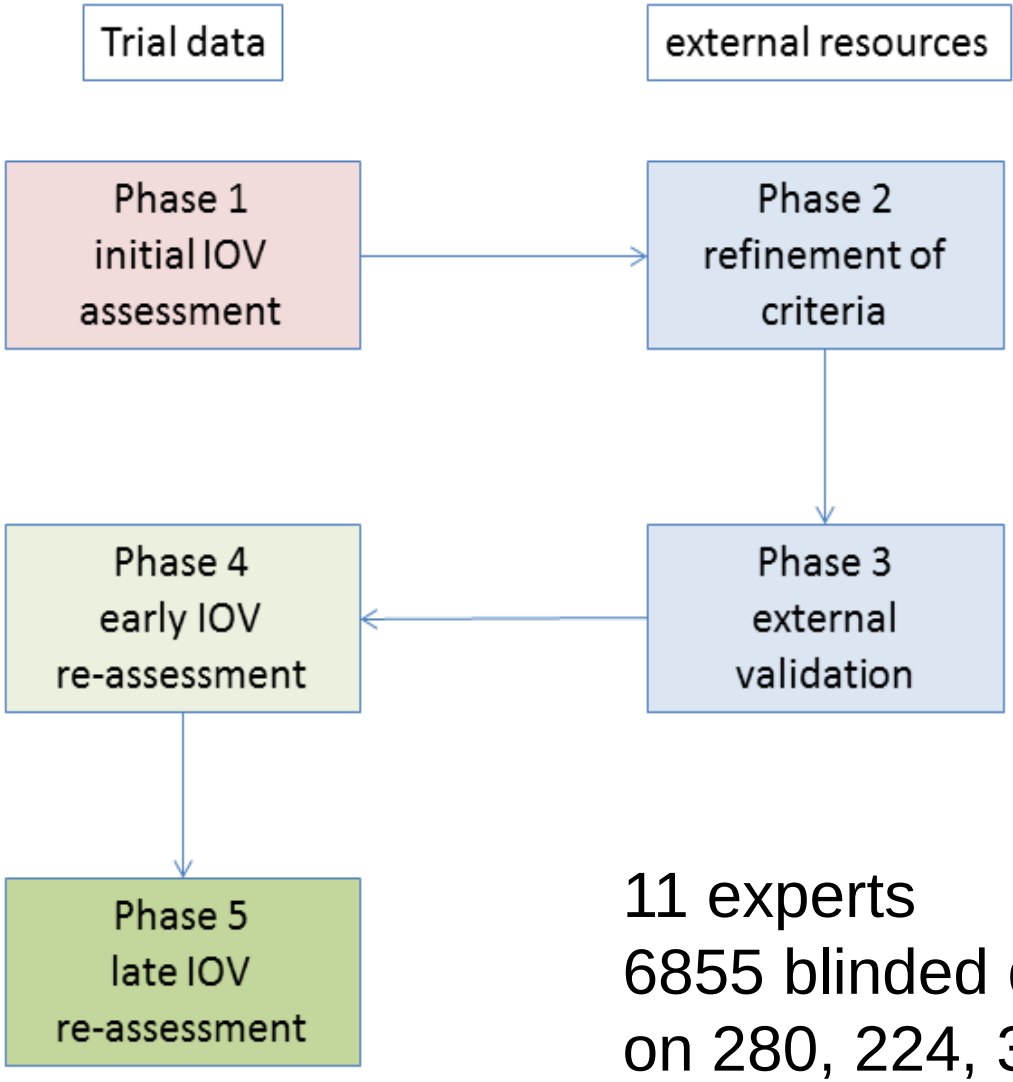
PET-Plan panel harmonisation



11 experts
6855 blinded diagnostic statements
on 280, 224, 336 nodal report items

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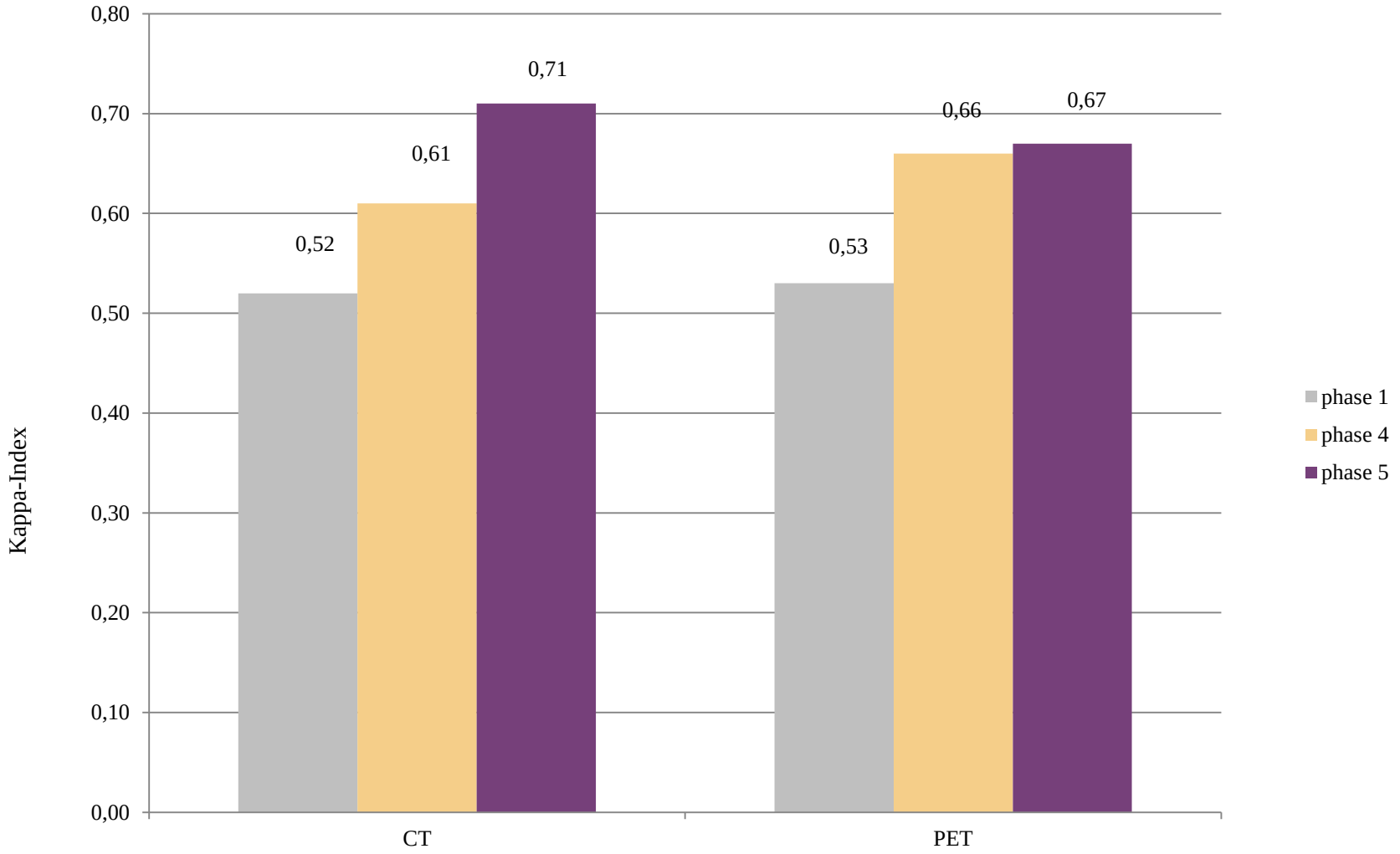
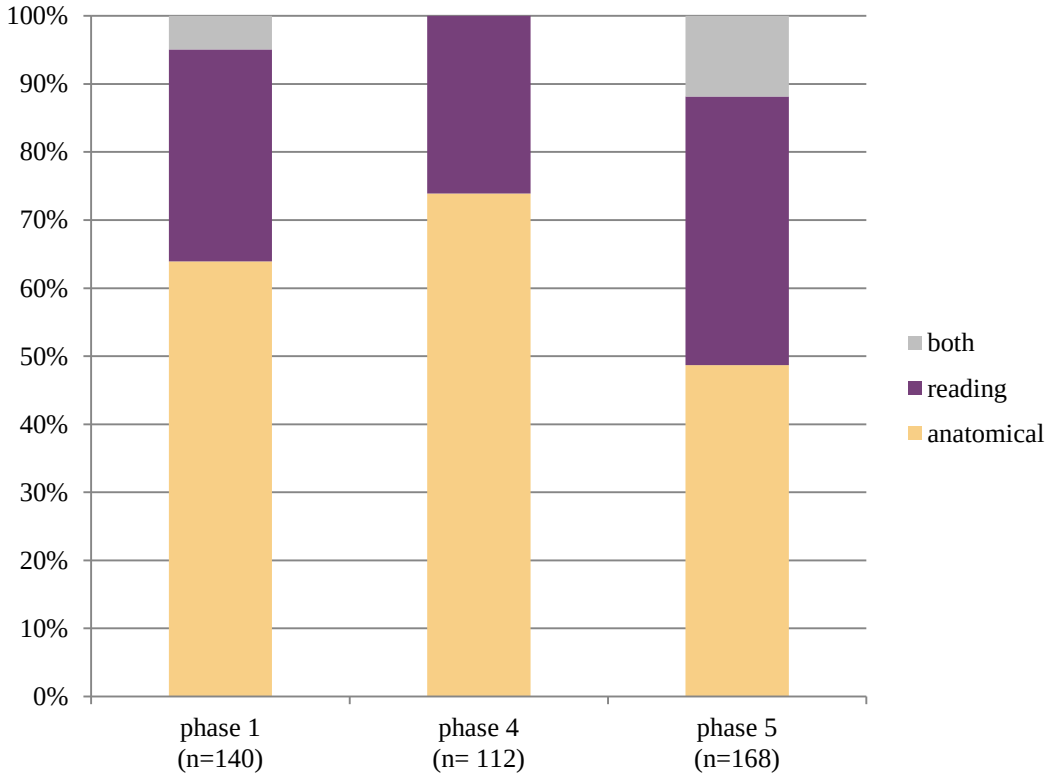
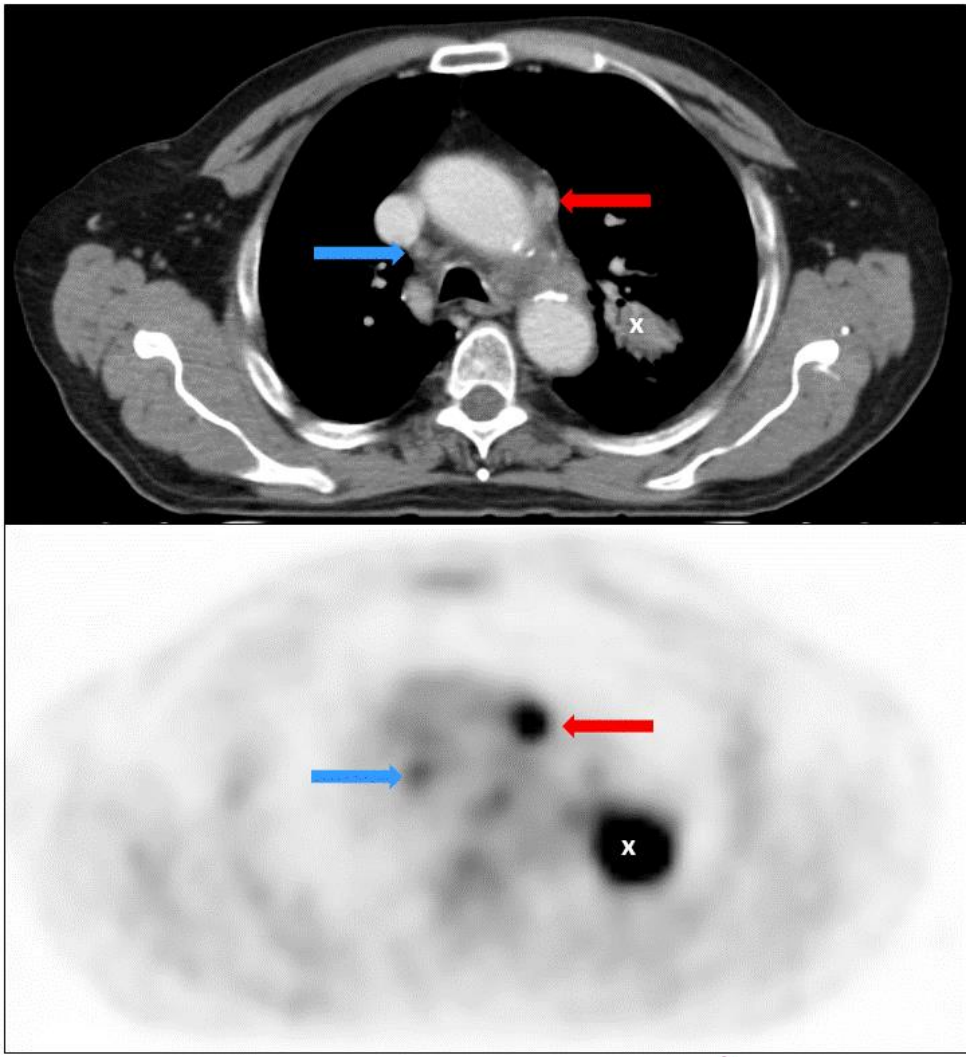
overall observer agreement by phase



Results of the categorization of dominant reasons for reporting disagreements per nodal station





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Anatomy …

Allocation of LNs to AJCC-stations:

- frequent reason for discrepant reporting
- eminently important for MC-communication
- backbone for analysis of recurrence

- in case of unequivocal findings
  less relevant for correct GTV delineation
- Melbourne solution: arrow-marked reports

academic problem?

„forcing chaotic patho-anatomy to artificial cage“?

Post-study: Measurable effect of harmonisation

anatomic

1. **LN station infiltrated by primary**

   → report positively

2. **Anatomical allocation**

   → use atlas!

3. **Bulky disease**

   → report all affected LN stations

diagnostic

1. **Viewing technique**

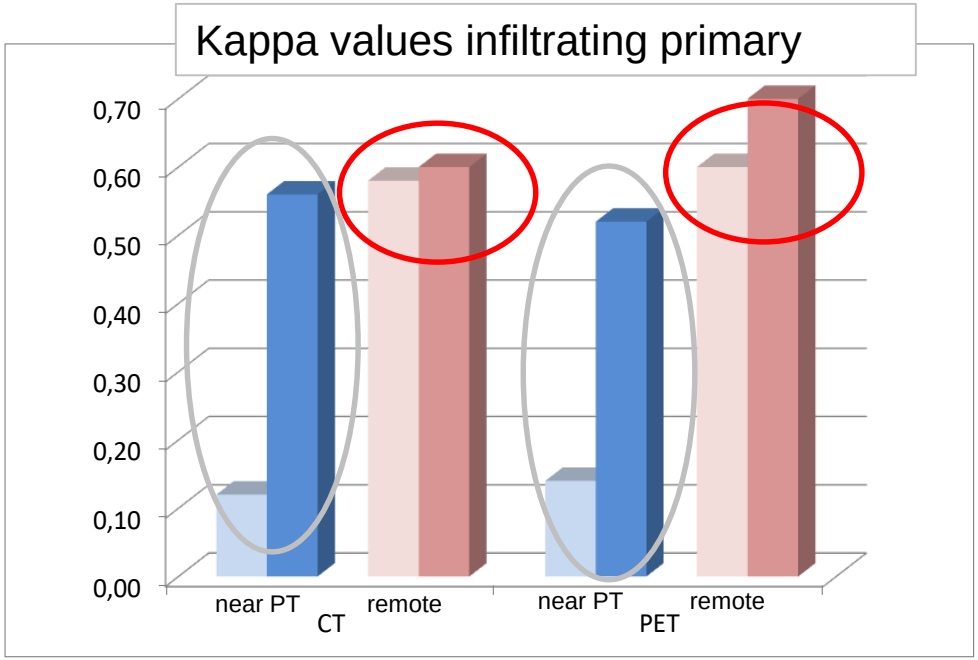
   → PET-MIP (LK?) -> PET volume -> CT

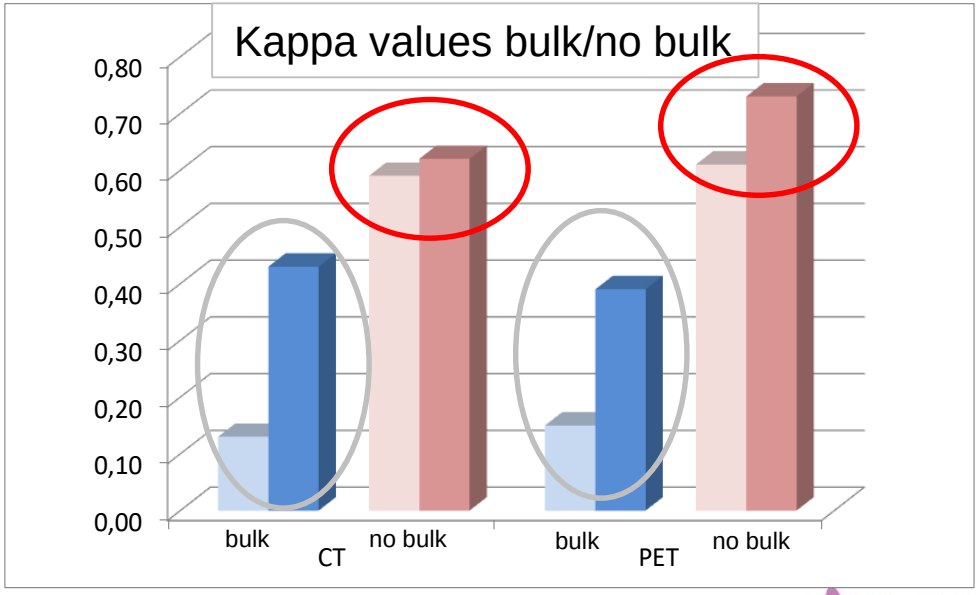
2. **Reading criteria**

   → visibility in the MIP leading

3. **How to deal with equivocal findings**

   → include Prä-Test Probability
   (Giraud et al.)
   in doubt: report positively
   (RT-context!)





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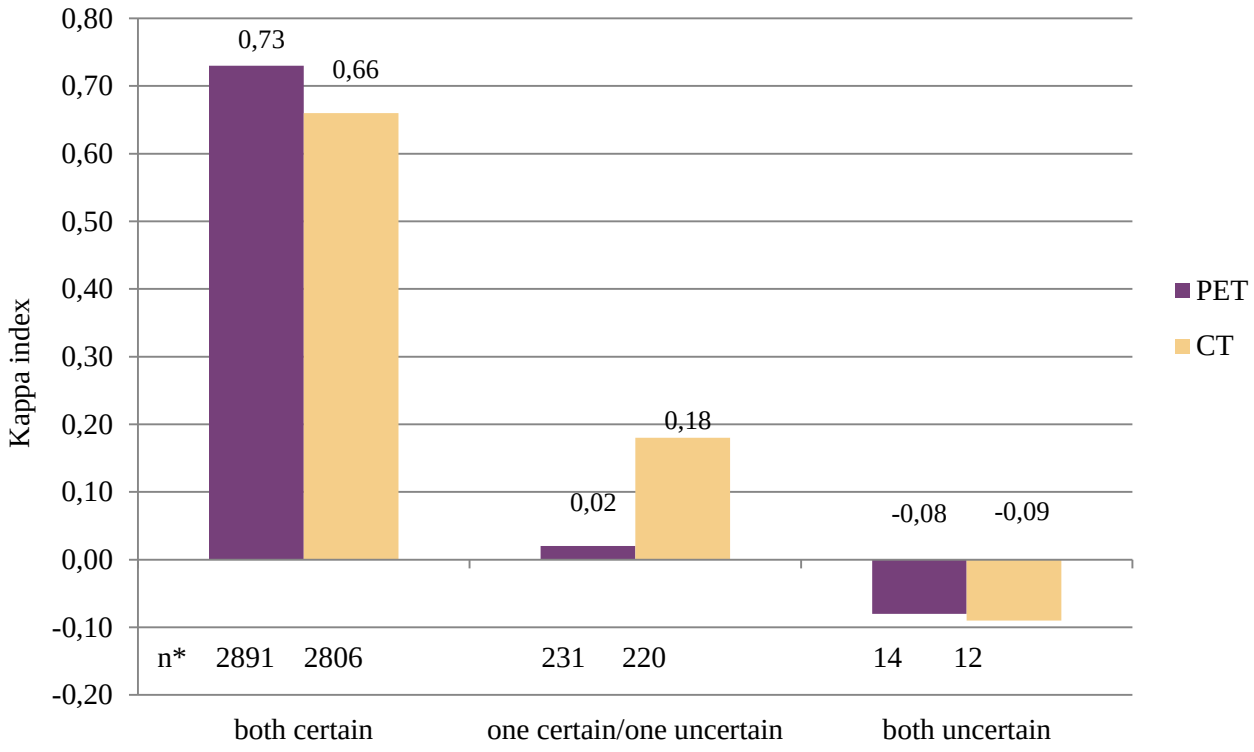
Are you sure about your finding?

Association of subjective certainty of observers with inter observer agreement



* number of statement pairs included in each analysis

Goldstandard-study:

68% (FP) vs. 90% (RP) pos LN-reports

reporting the „sureness“ of findings may ease further treatment decisions

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Summary (Panel)

- **Diagnostic reports differ!**
  There is a significant variability of diagnostic reports, which may be due to diagnostic and/or anatomic reasons.

- **Improvement by discussion and criteria**
  By elaboration of detailed reporting criteria and joint discussion the variability can be reduced.

- **Safety for RT-purposes**
  Using the criteria as adjusted to radiotherapy needs (high sensitivity), a safe basis for target volume reduction can be provided.

- **There is not always „yes“ or „no“**
  Due to the <100% diagnostic accuracy, unclear findings must be expected; communication of diagnostic doubst may ease treatment decisions

- **Timelines**
  Due to the time-consuming process of blinded reviews, after harmonisation we changed the process to 1 unblinded review

Nestle U. et al. EJC 2015

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Published Ahead of Print on November 15, 2010 as 10.1200/JCO.2010.30.3271
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2010.30.3271

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

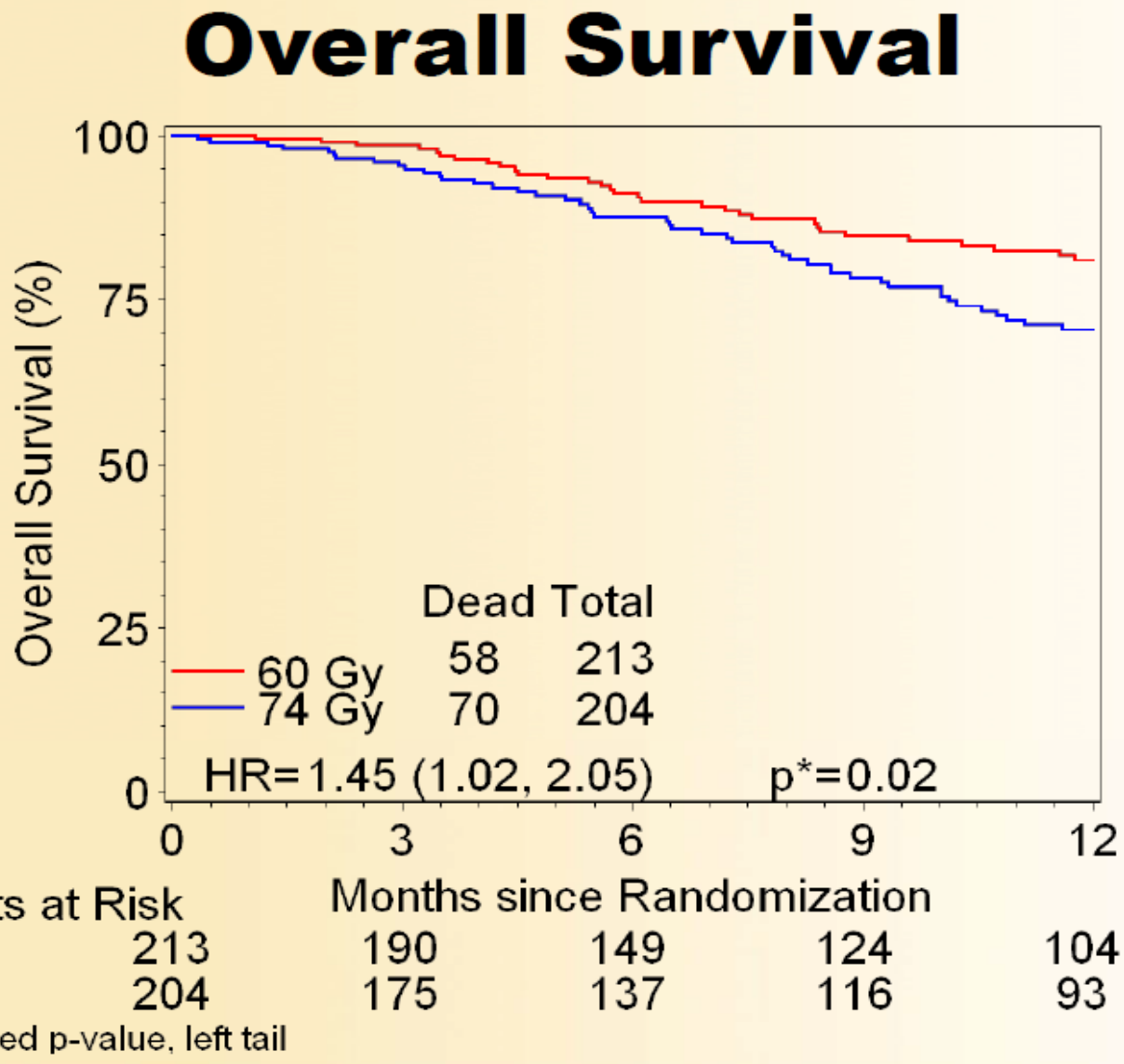
European Organization for Research and Treatment of Cancer Recommendations for Planning and Delivery of High-Dose, High-Precision Radiotherapy for Lung Cancer

Dirk De Ruysscher, Corinne Faivre-Finn, Ursula Nestle, Coen W. Hurkmans, Cécile Le Péchoux, Allan Price, and Suresh Senan

There is no evidence to suggest that elective nodal irradiation is indicated in any patient group that receives curative or radical doses of radiotherapy for inoperable NSCLC.[58] Selective nodal irradiation on the basis of CT or FDG-PET resulted in less than 5% of isolated nodal failures.[59,60]

RTOG 0617: interim results

J Bradley / ASTRO 2011 Plenary



Summary

- the implementation of new imaging methods in treatment need validation by clinical trials
- it my be difficult to ask the right question, being of interest for both the imaging as well as the therapeutic perspective and to get this funded
- the large issue in the multicenter setting of such trials is QA of imaging, treatment and follow up
- you may encounter completely unexpected problems with imaging, calibration, interpretation and the development of your study question over time….

Perspective: PET/MRI

ESTRO Teaching Course on Advanced Molecular Imaging

Bordeaux, April 9-13, 2017

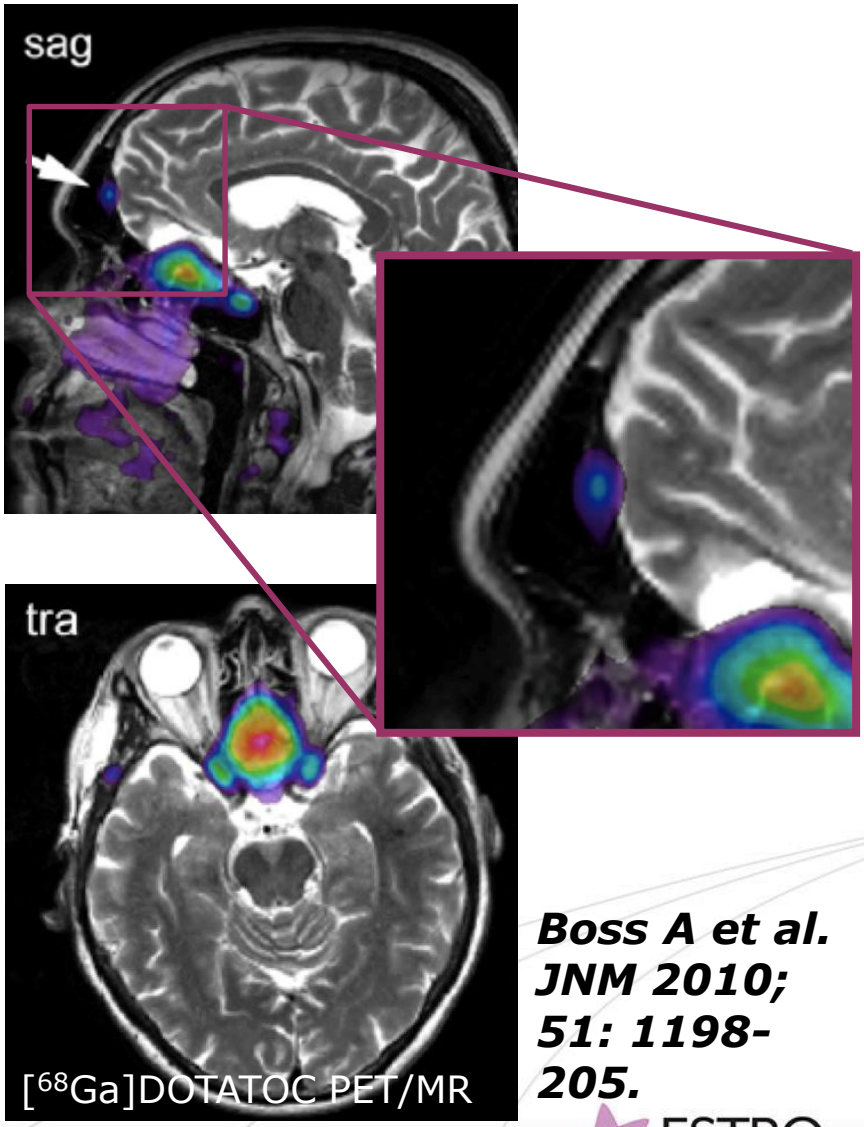
Daniela Thorwarth, Section for Biomedical Physics, University Hospital for Radiation Oncology Tübingen, Germany

Combined PET/MR for Radiation Oncology

Visualization of anatomical, functional and molecular information of tumor tissue

Improved accuracy of target volume delineation based on PET/MR

Multi-parametric functional PET/MR imaging for biologically adapted RT dose prescriptions



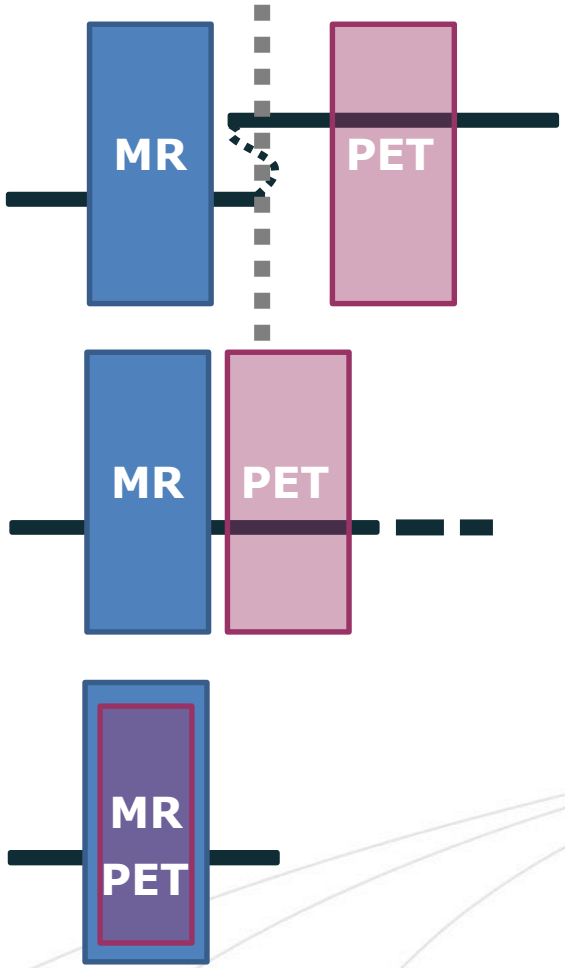
Boss A et al. JNM 2010; 51: 1198-205.

Combined PET/MR: Technical Realization

1. **Separate PET- and MR-systems**
   - Imaging systems in different rooms
   - Patient couch on rails
   - Time delay between PET- and MR image acquisition

2. **Co-planar PET/MR systems**
   - PET and MR back to back
   - Rotating table platform
   - 3T MRI plus TOF PET

3. **Integrated PET/MR**
   - MR-compatible PET detector ring inside clinical 3T-MR scanner



Integrated PET/MR: Technical Realization

- Simultaneous PET and MR acquisition

MR specification:

- 3T static magnetic field
- 60 cm bore size
- Spatial resolution < 1-3 mm

PET detector:

- MR-compatible PET components (APDs instead of PMTs)
- No time-of-flight (TOF) PET possible

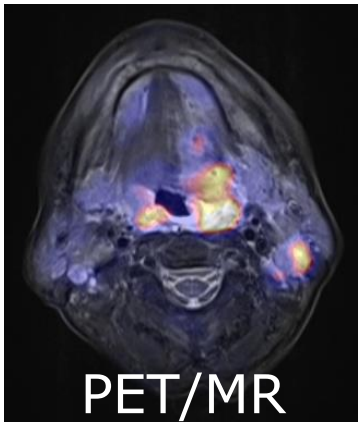
Siemens Biograph mMR

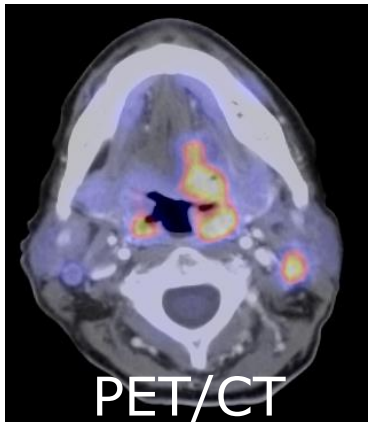
PET/CT vs. PET/MR – PET performance

	PET/MR (mMR)*	PET/CT (mCT)**
Detector material	LSO	LSO
Detector block size (mm)	4 x 4 x 20	4 x 4 x 20
Ring diameter (cm)	65.6	84.2
Axial FOV (cm)	25.8	21.8
Energy window (keV)	430 - 610	435 - 650
Coincidence window (ns)	5.9	4.1
Spatial resolution (mm)	FWHM, 4.3	FWHM, 4.4

** Delso et al. JNM 2011* *** Jakoby et al. PMB 2011*

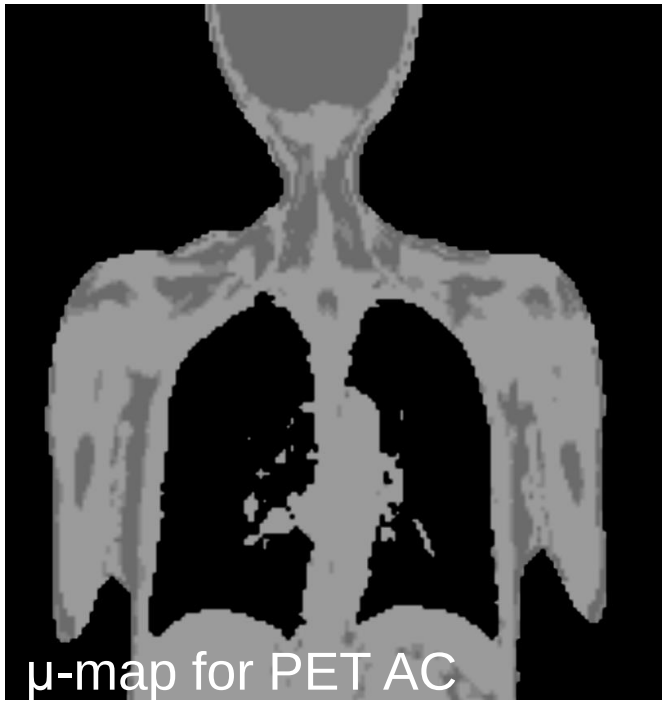
PET/CT vs. PET/MR – practical aspects

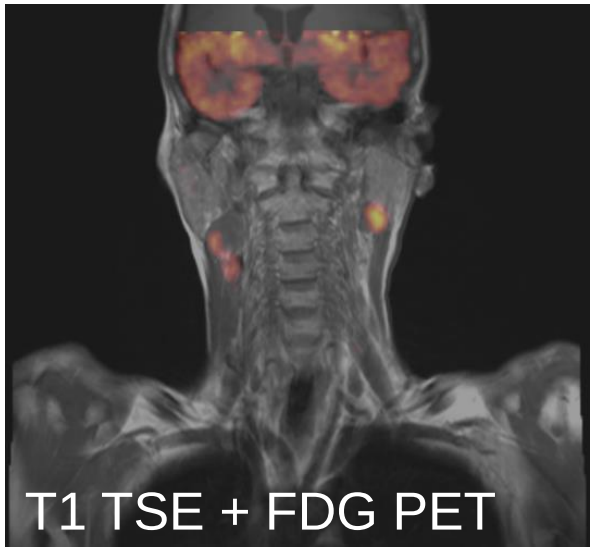




Duration of examination	45 – 60 min	~ 40 min
Image acquisition	simultaneous	sequential
Intrinsic registration	+	+
Radiation exposure	~ 7 mSv	27 - 32 mSv
Attenuation correction	MR-based	CT-based

Technical Challenge for Integrated PET/MR systems: MR-based attenuation correction



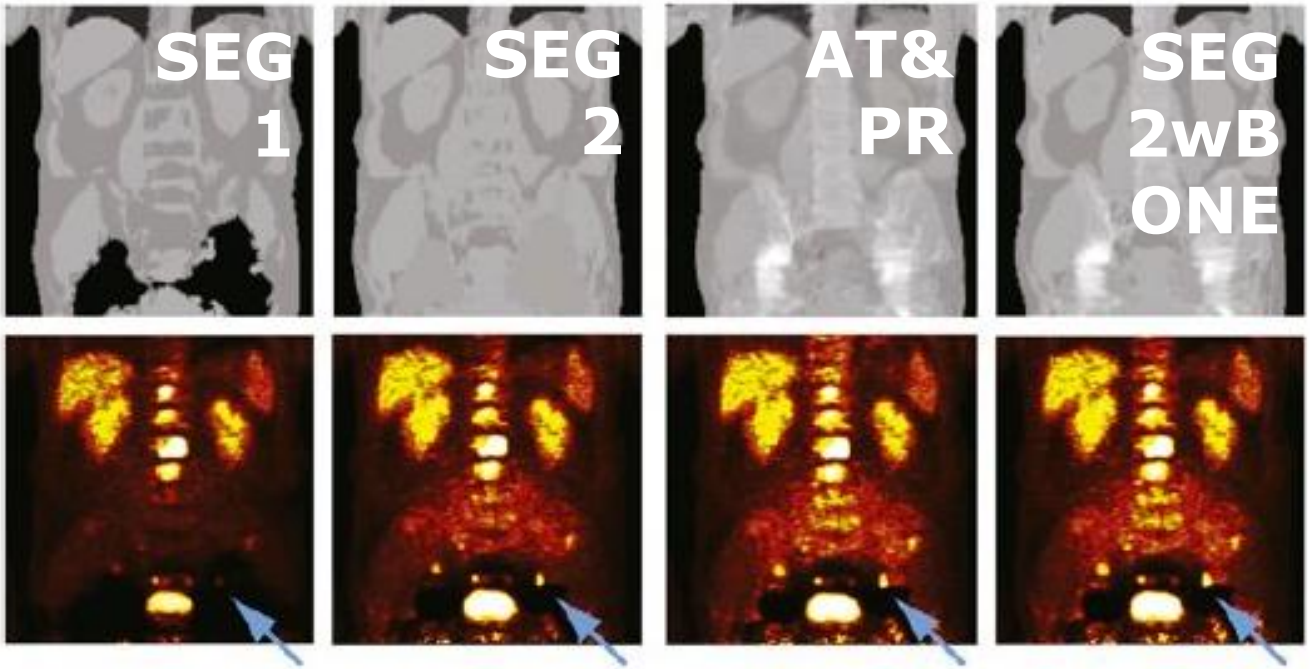


- Segmentation of n=4 tissue compartments using Dixon MR-sequences

- MR-artifacts will effect μ-map and quantitative PET values
- Other techniques for MR-AC have been presented
- Potential to use of segmented μ-map for RT planning?

Comparison of different methods for MR-AC

Bezrukov I et al. J Nucl Med 2013.



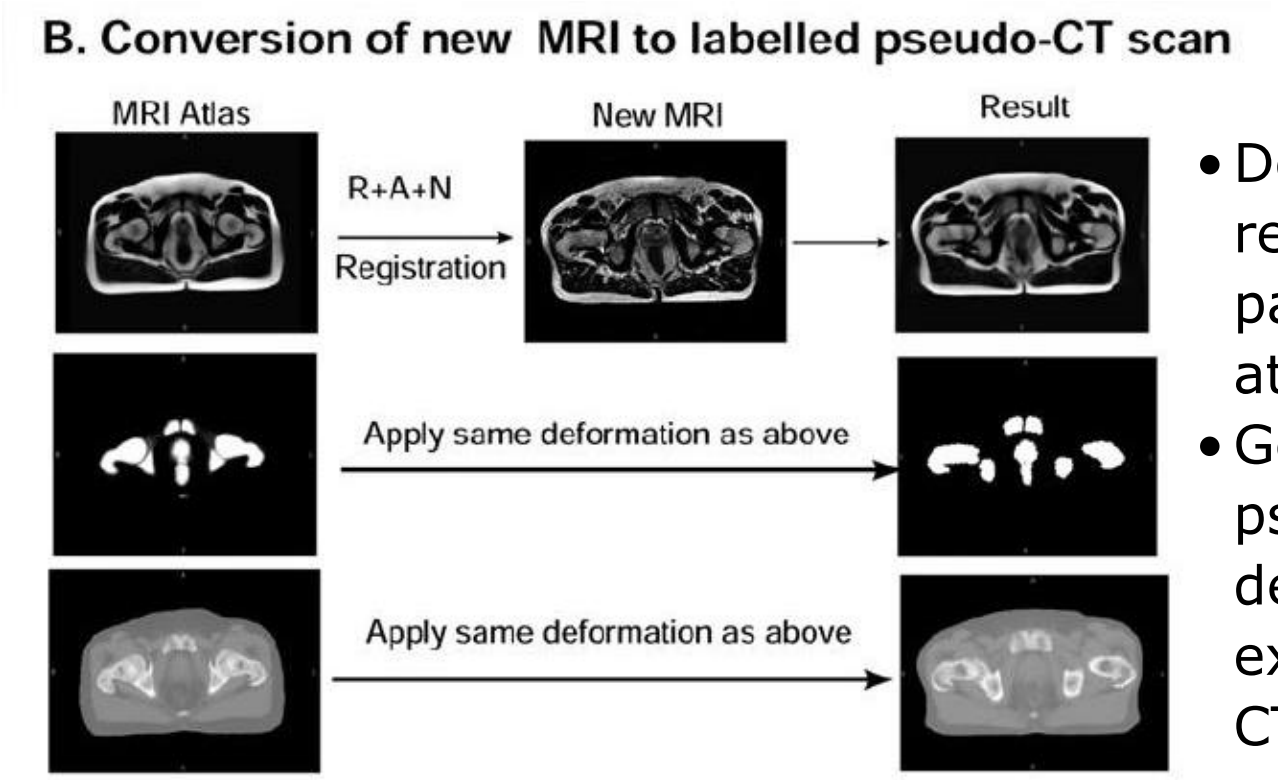
SEG1: basic segmentation

SEG2: refined segmentation

AT&PT: atlas- and pattern recognition based prediction

SEG2wBONE: AT&PT combined with SEG2

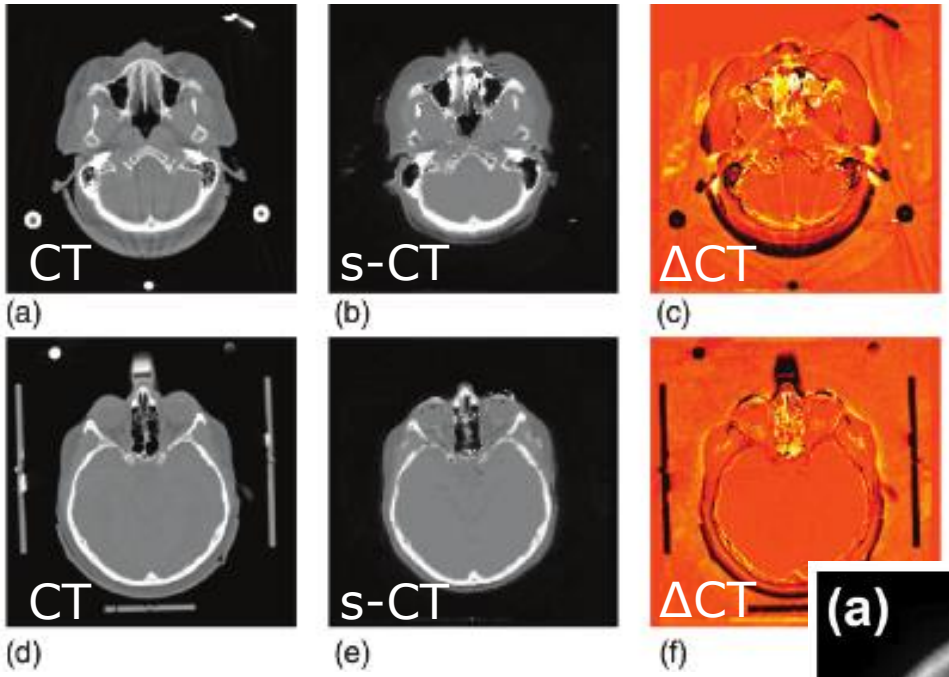
(PET/)MR-only RT: Pseudo-CT generation based on deformable registration



- Deformable registration of patient MR to atlas MR
- Generate pseudo CT by deformation of existing atlas CT

Dowling JA et al. Int J Radiat Oncol Biol Phys 2012; 83: e5-11.

(PET/)MR-only RT: substitute CT generation by transformation of MR-image values

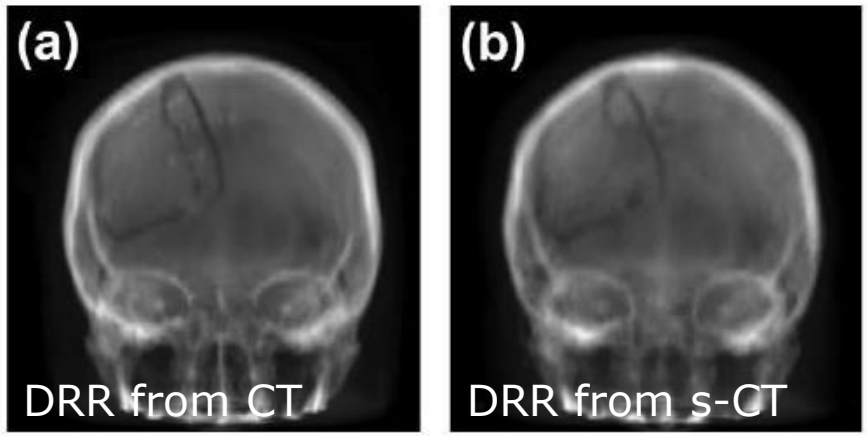


Johansson A et al. Med Phys 2011; 38(5): 2708-14.

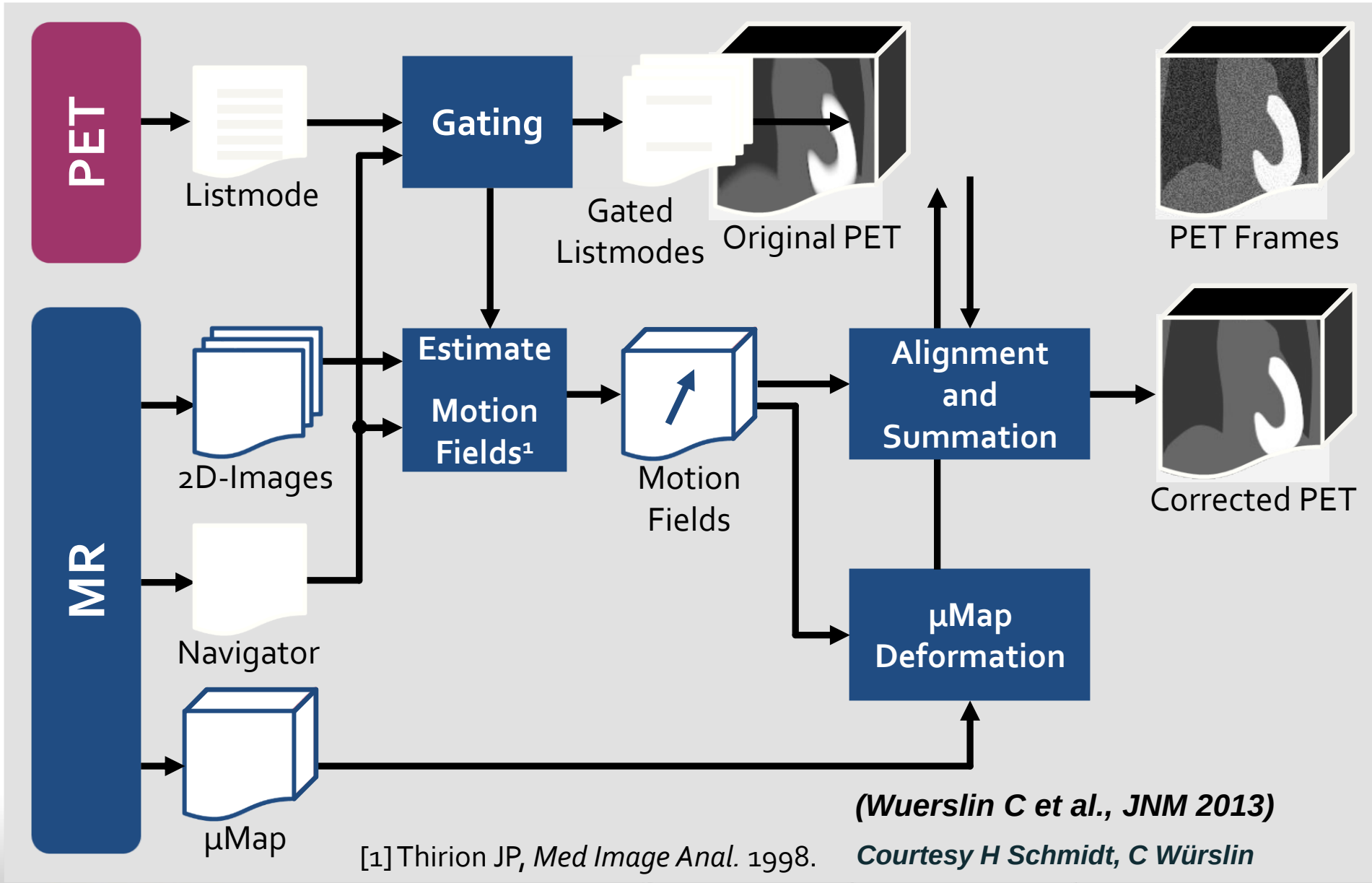
- Generation of substitute CT (s-CT) by applying a Gaussian mixture model to transform the MR image values

- s-CT can be used for RT planning

Jonsson J et al. Radiother Oncol 2013; 108(1): 118-22.



PET/MR motion artifacts

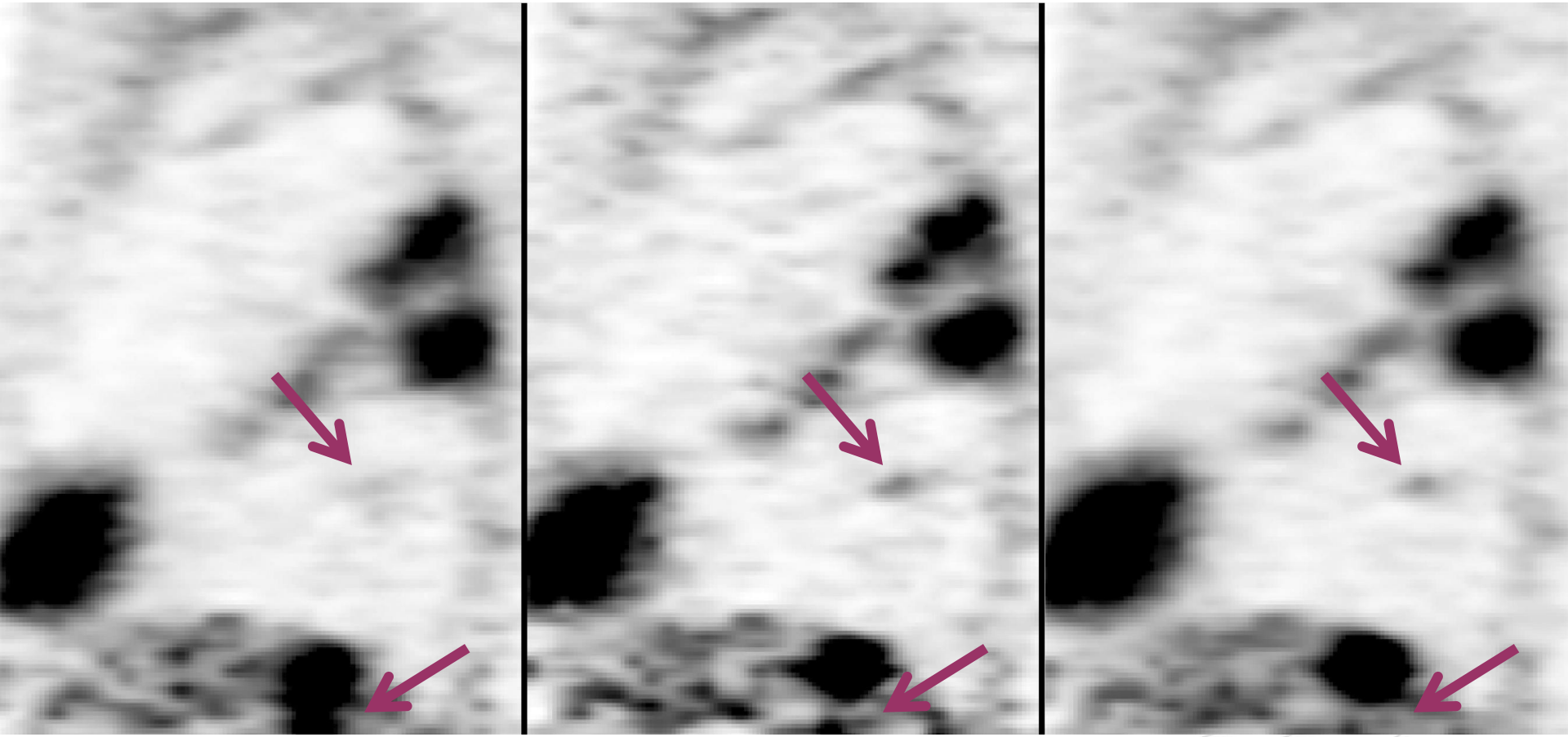


(Wuerslin C et al., JNM 2013)

Courtesy H Schmidt, C Würslin

[1] Thirion JP, *Med Image Anal.* 1998.

MR-based motion correction of PET data



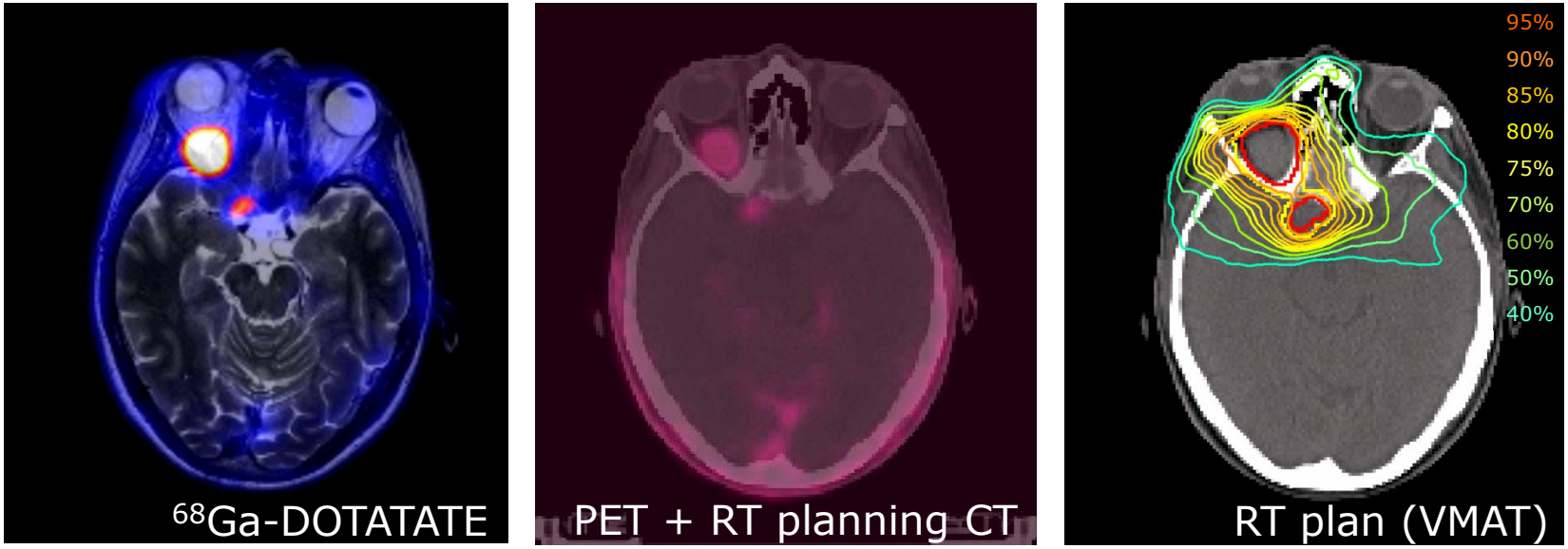
Uncorrected **Standard Gating** **Motion Correction**

Courtesy H Schmidt, C Würslin

Wuerslin et al., JNM 2013

Integration of PET/MR-derived volumes into RTP

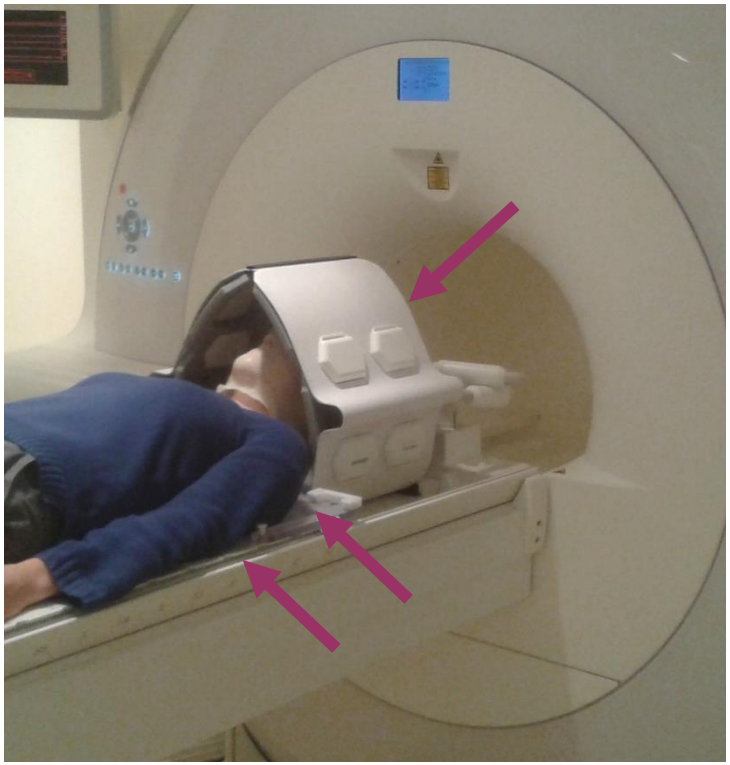
Meningeoma patient (f), 53 y:



Courtesy S. Welz, Tübingen

- Combination of PET and MR (registered) enabled for detection of a small secondary lesion.
- Integration into RT target volume for treatment planning.

Development of a dedicated hardware solution for RT-patient positioning during PET/MR imaging



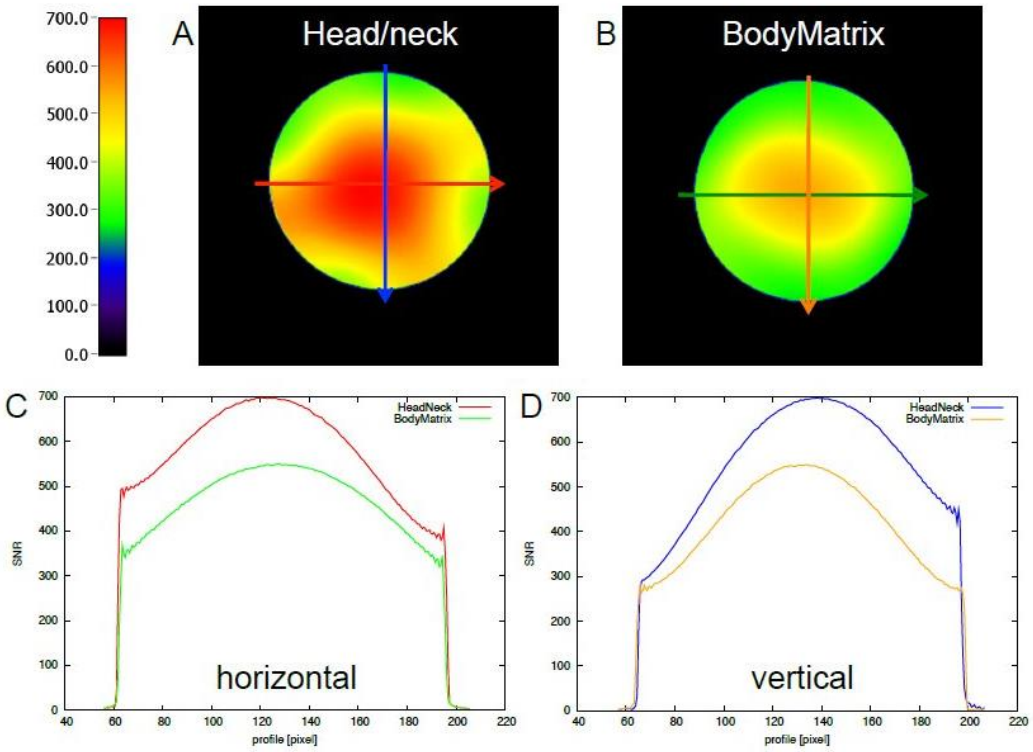
Prototype of table overlay and coil holder for Biograph mMR (Siemens), in cooperation with Q Fix

- **RT table overlay:**
  - Above spine coil
  - RT indexing system
- **RT mask fixation:**
  - Add-on to table overlay
- **RF coil holders (CH):**
  - Fixation for flexible coils (6-channel body matrix)
  - Patient positioning with mask fixation possible

MR compatibility of RT positioning hardware

SNR head/neck RF coil and RT setup using (GE sequence):

Phantom measurements:



- **SNR-reduction:**

  ~ 25%

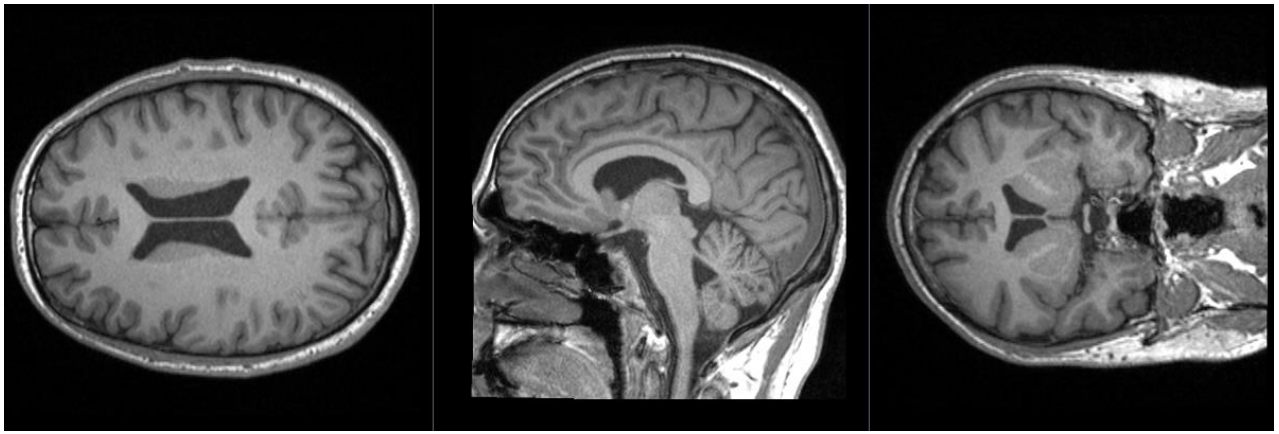
- **Signal homogeneity:**

  comparable

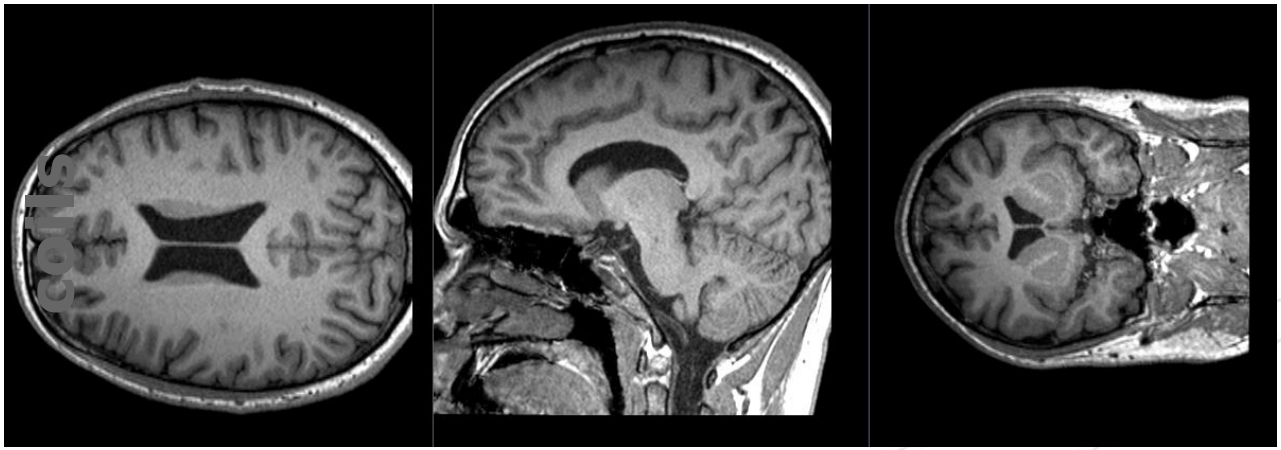
Paulus D et al. Med Phys 2014; 41(7):072505.

MR compatibility of RT positioning hardware

MR scans of a volunteer (MPRAGE):



SNR_{fix} = 109.3

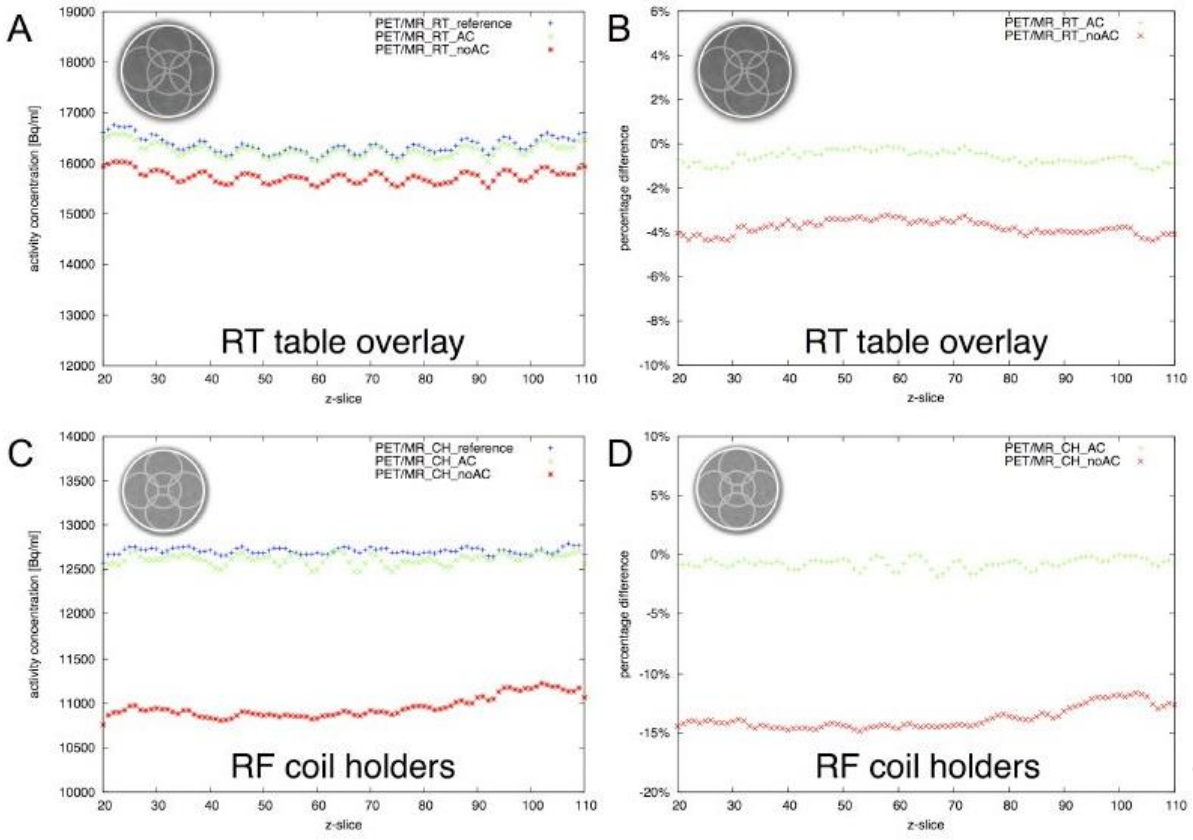


SNR_{flex} = 64.2

R. Winter, Tübingen

PET compatibility

Attenuation of PET signal due to RT positioning hardware tools:



- **Attenuation of table overlay:**

  ~ 3.8 %

- **Attenuation of coil holders:**

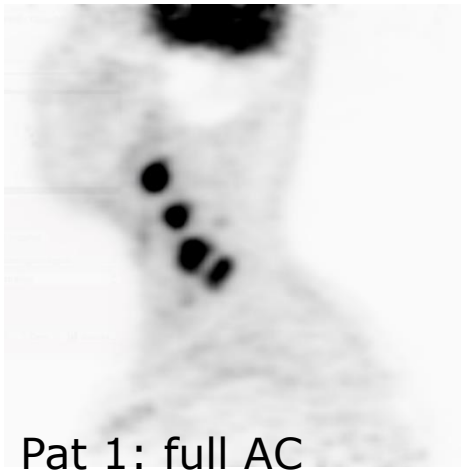
  ~ 13.8 %

Paulus D et al. Med Phys 2014; 41(7):072505.

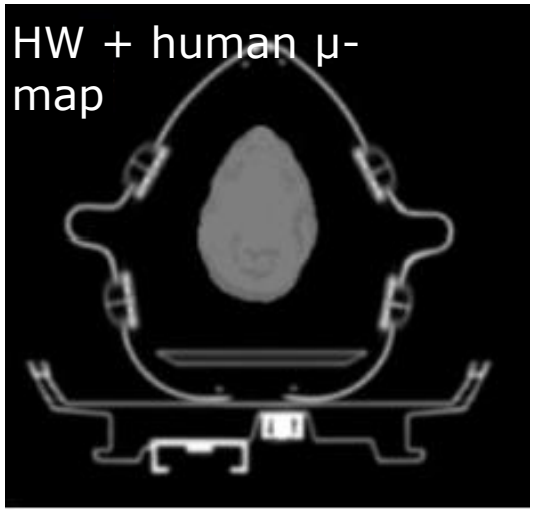
PET hardware attenuation correction: First patients

Comparison of FDG PET activity in n=10 HNC patients:

- Reference scan
- Scan with CH
  - Without AC
  - With AC



Pat 1: full AC

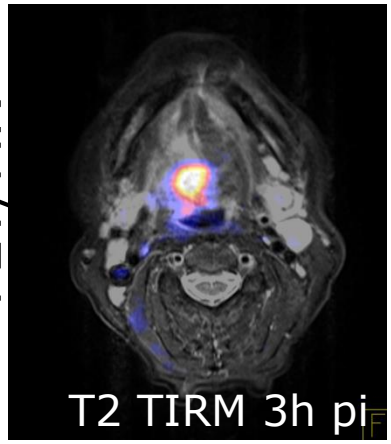


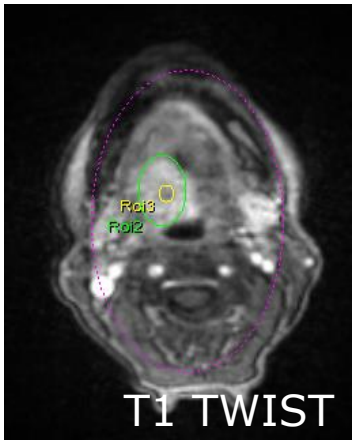
Deviation to reference scan (without CH):

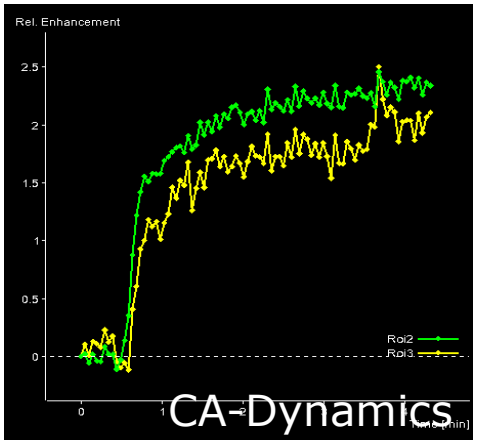
		Full AC of CH + coils	No AC of CH + coils
SUV_{mean}	Tumor	0.6 % (-2.5 – 4.5)	-11.4 % (-14.0 – -6.2)
	Brain	0.7 % (-0.8 – 2.3)	-14.0 % (-15.2 – -12.0)
SUV_{max}	Tumor	0.4 % (-3.6 – 5.8)	-11.8 % (-15.8 – -5.1)
	Brain	-1.4 % (-4.3 – 3.1)	-15.8 % (-19.0 – -10.3)

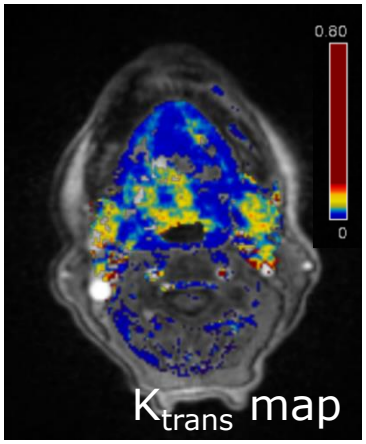
Multiparametric Hypoxia Imaging using Combined PET/MR

FMISO PET/MR

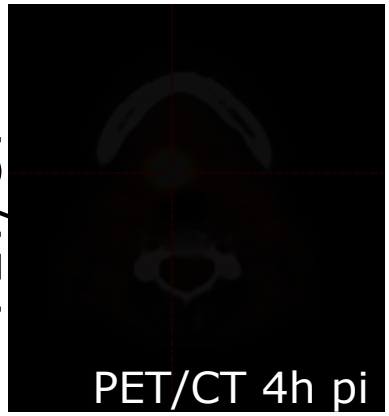








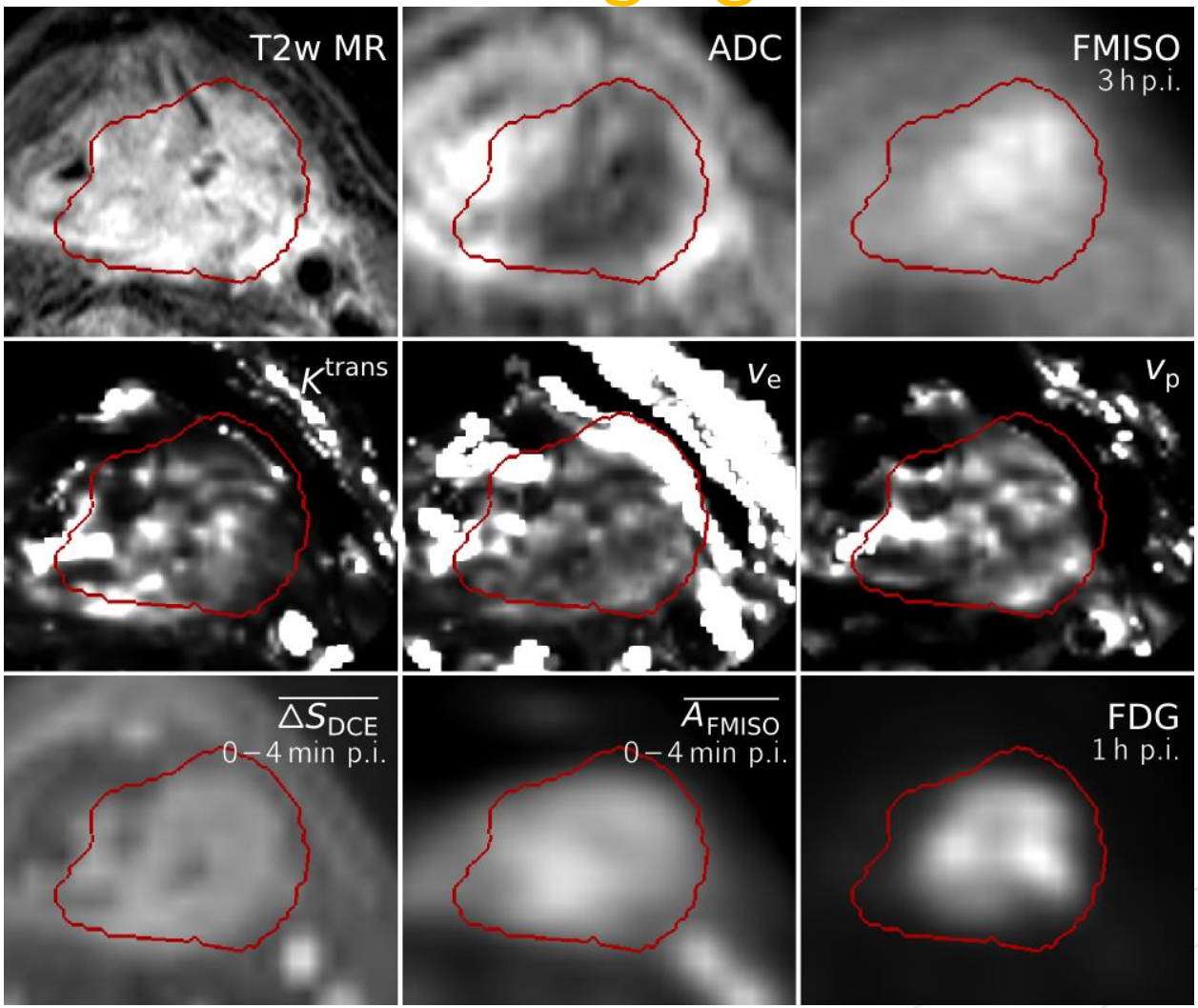
FMISO PET/CT



PET/MR Protocol:

- FMISO PET acquisition for 30 min (ca. 3h pi)
- short diagnostic MR-Protocol
- DCE-MRI
- DW-MRI

Multi-parametric functional PET/MR Imaging in HNC



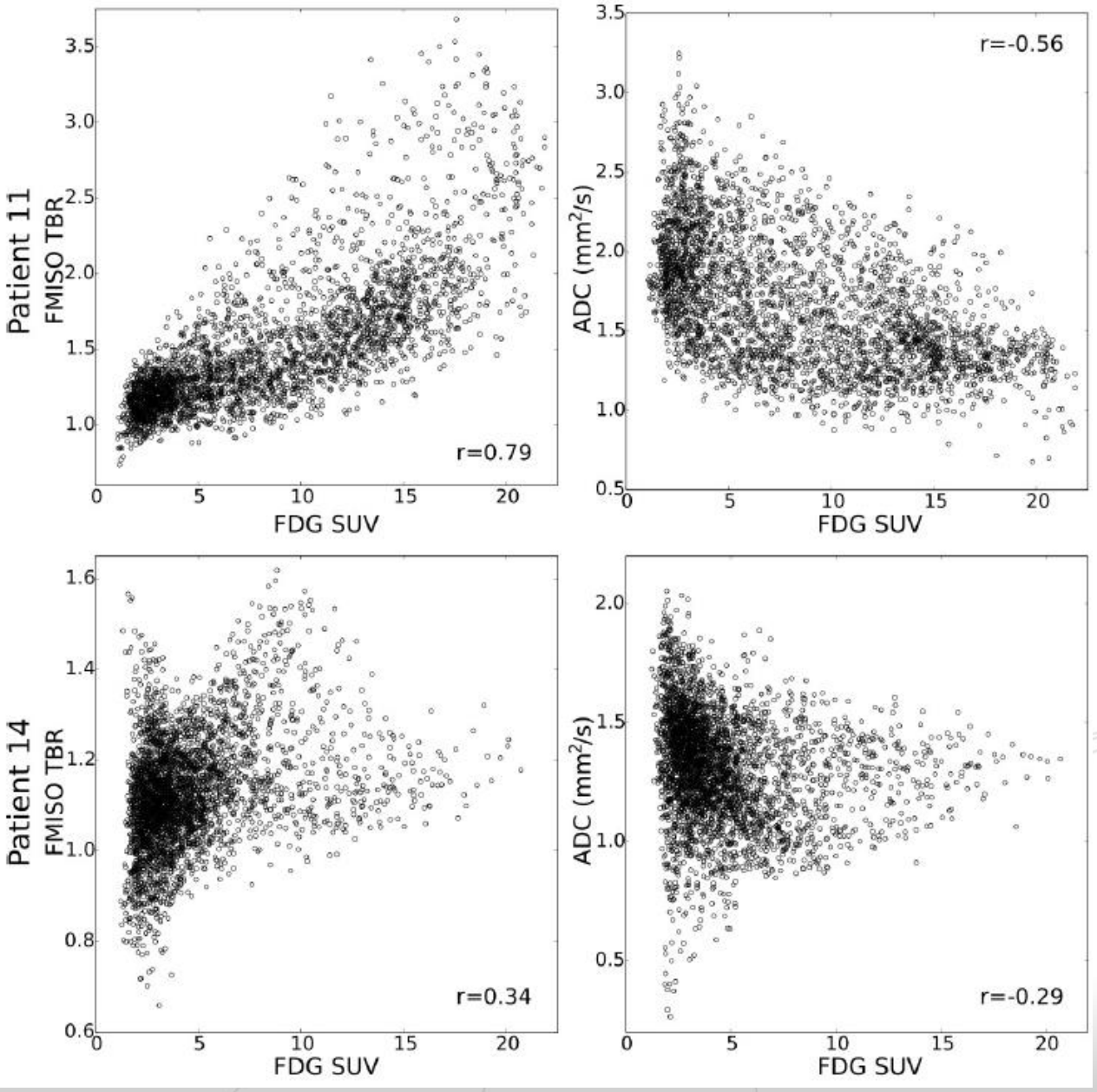
N=15 HNC patients

- FDG PET
- FMISO PET
- DW-MRI
- DCE-MRI

Leibfarth S et al. EJNMMI 2016; 43(7):1199-208.

Assessment of pairwise voxel-based parameter correlations:

Large inter-patient variations of correlation coefficients.



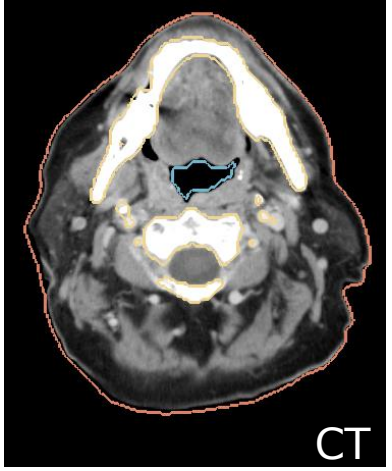
Influence of imperfect deformable image registration

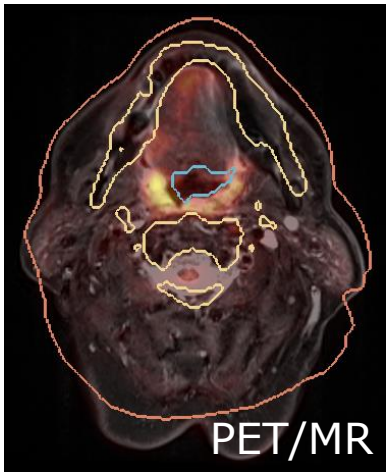
Deformable registration

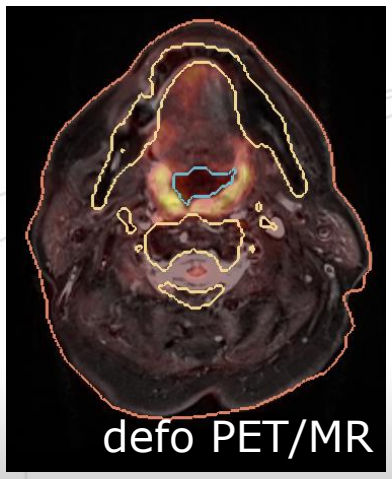
- B-spline
- Local mutual information
- Bending enery penalty term
- Resampling of all data on PET voxel grid
- Residual registration error ~1-3 mm *

➡ **Regional correlation analysis of PET/MR data**

- Definition of sub-regions of 3x3x4 voxels
- 8.4 x 8.4 x 8 mm^3

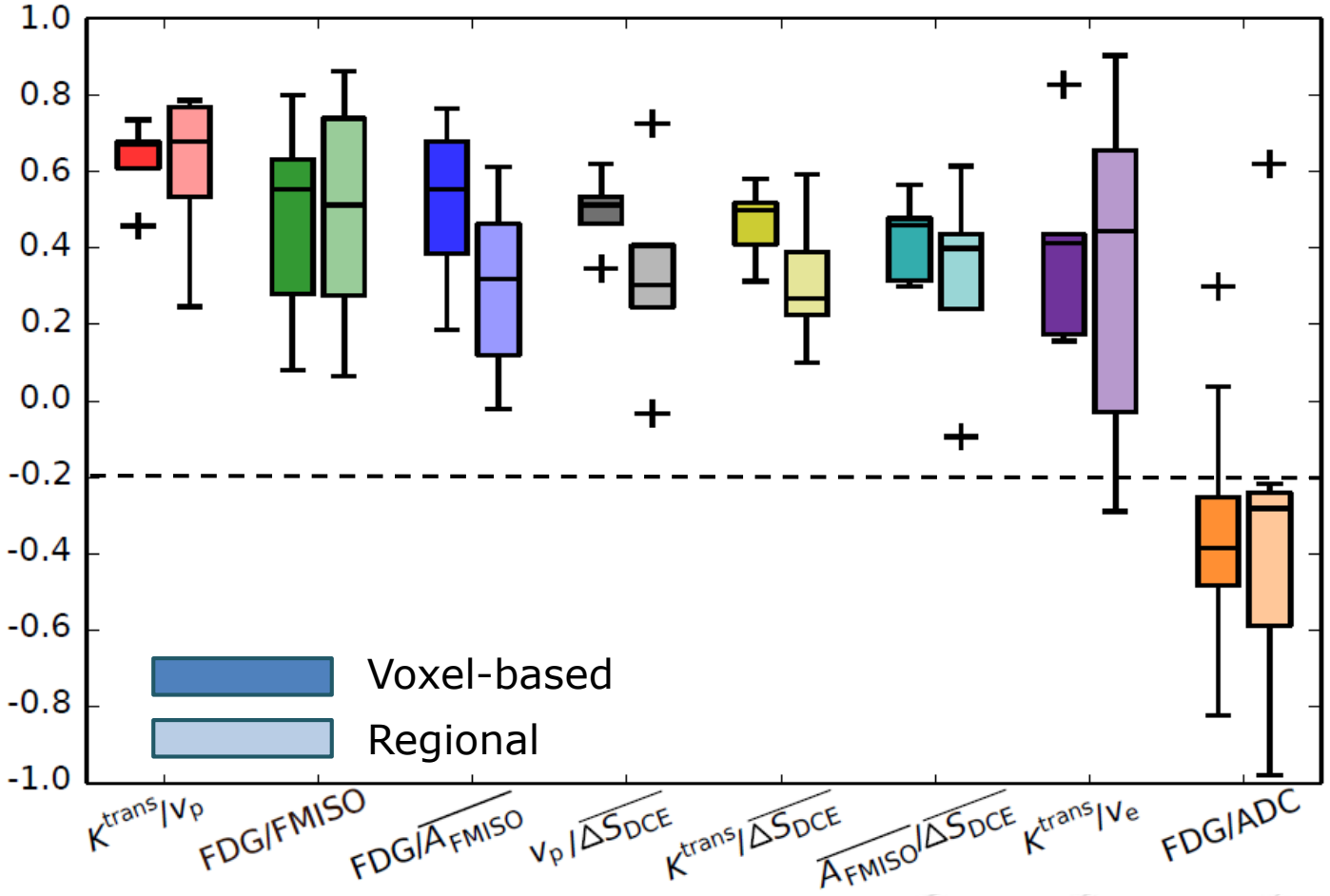




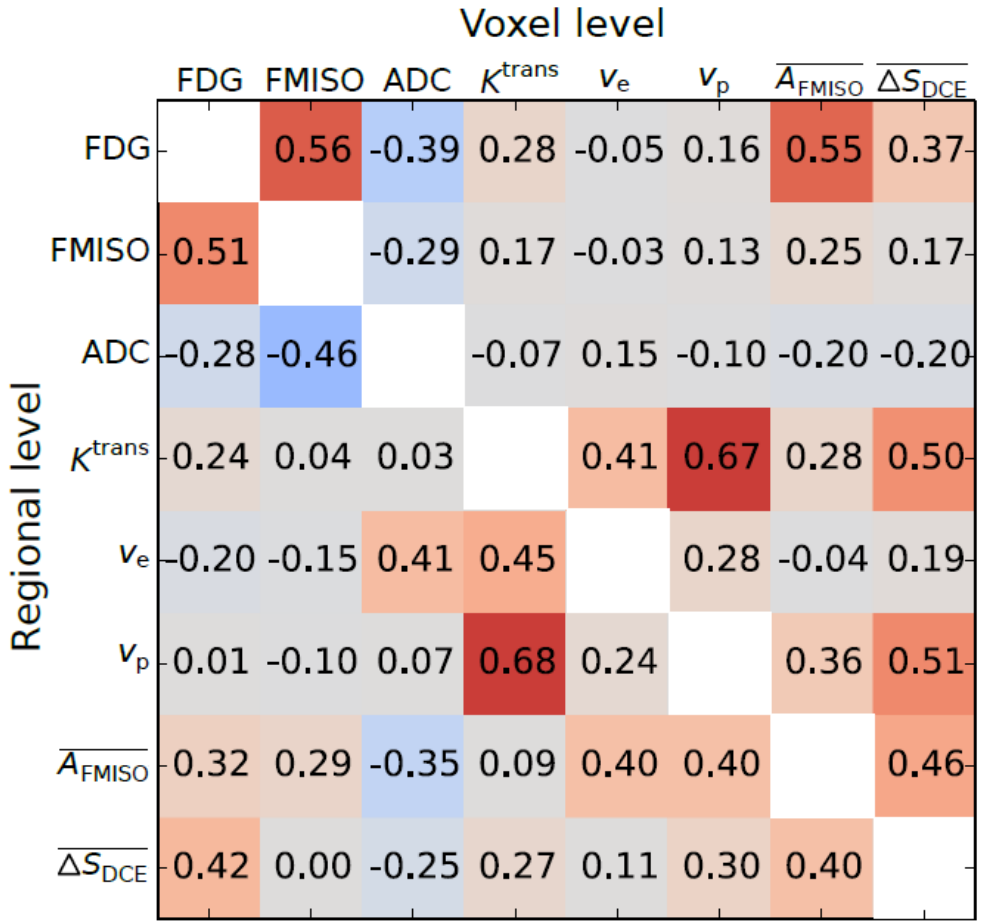


Leibfarth S et al. Acta Oncol 2013;52:1353-9.

Inter-patient variation of pairwise parameter correlations



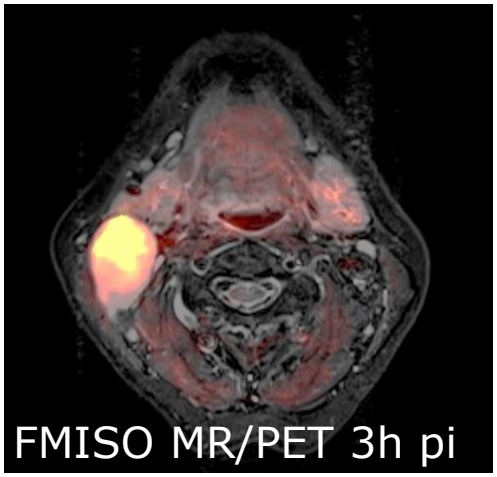
Median Spearmean correlation coefficients of pairwise parameter analysis

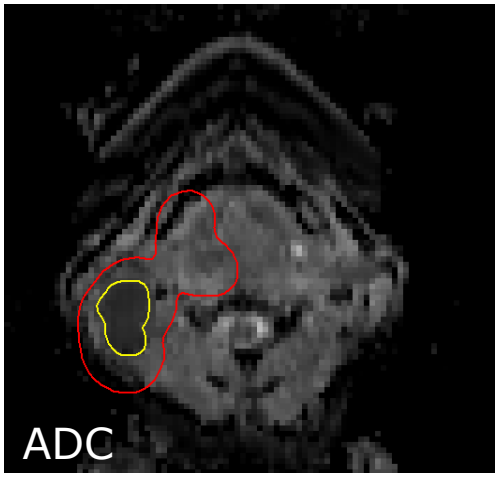


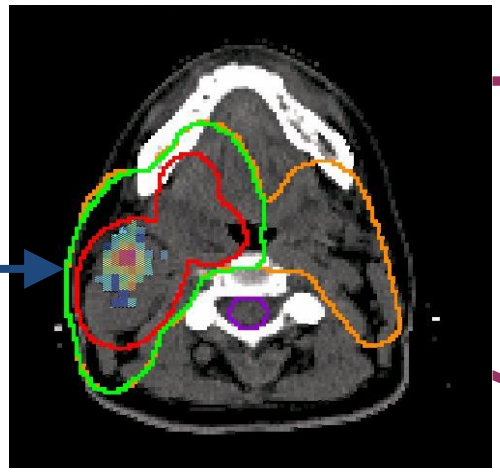
- Moderate to low median correlations
- No difference between voxel-based and regional analysis

Leibfarth S et al. EJNMMI 2016; 43(7):1199-208.

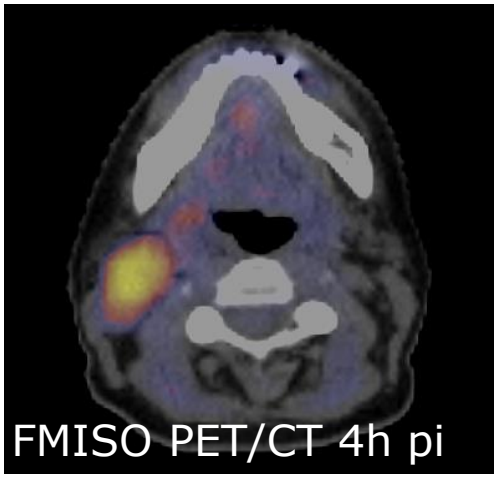
Classification of tumour areas according to multi-parametric molecular and functional imaging

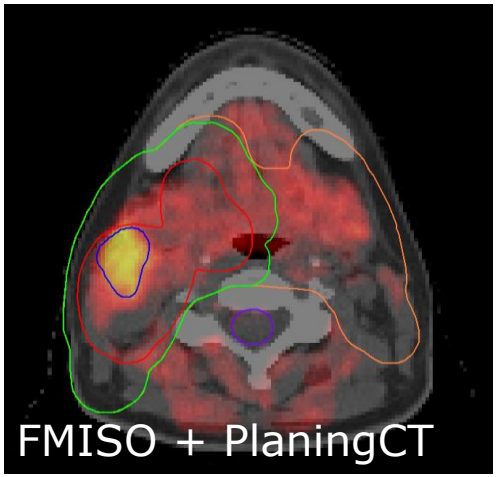




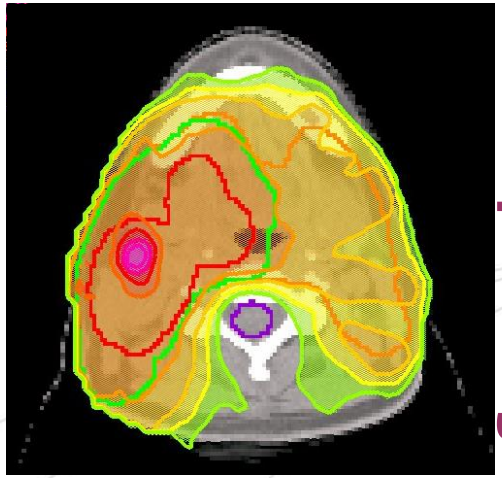


Classification probability





D [Gy]
85
70
45



Dose painting

RT-Contours: PTV_{70Gy}, PTV_{ADC}, PTV_{FMISO}, PTV_{60Gy}, PTV_{54Gy}, Spinal Cord.

ESNM European School of Nuclear Medicine

ESTRO School

Summary/Conclusion

Combined PET/MR offers new possibilities for RT planning

- Accurate contouring by combined information
- Integration of multi-parametric functional information into RTP

RT patient positioning hardware for PET/MR imaging

- Flat table top + mask fixation + RF coil holders
- MR and PET compatible
- CT-based hardware μ-maps available
- Image quality comparable

Multi-parametric functional PET/MR imaging for biologically adapted RT dose prescriptions

- Multi-parametric information potentially usable as basis for PET/MR-based dose escalation
- Potential of hypoxia imaging with PET/MR as a basis for future hypoxia dose painting approaches

Predictive value of MR spectroscopy for glioblastoma and integration in a prospective dose-painting clinical trial

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FRANCE

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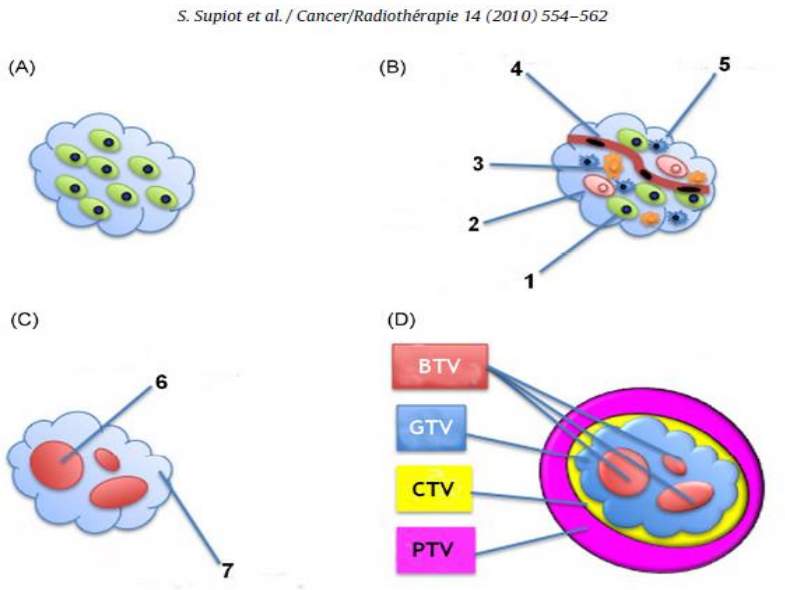
Dose-Painting



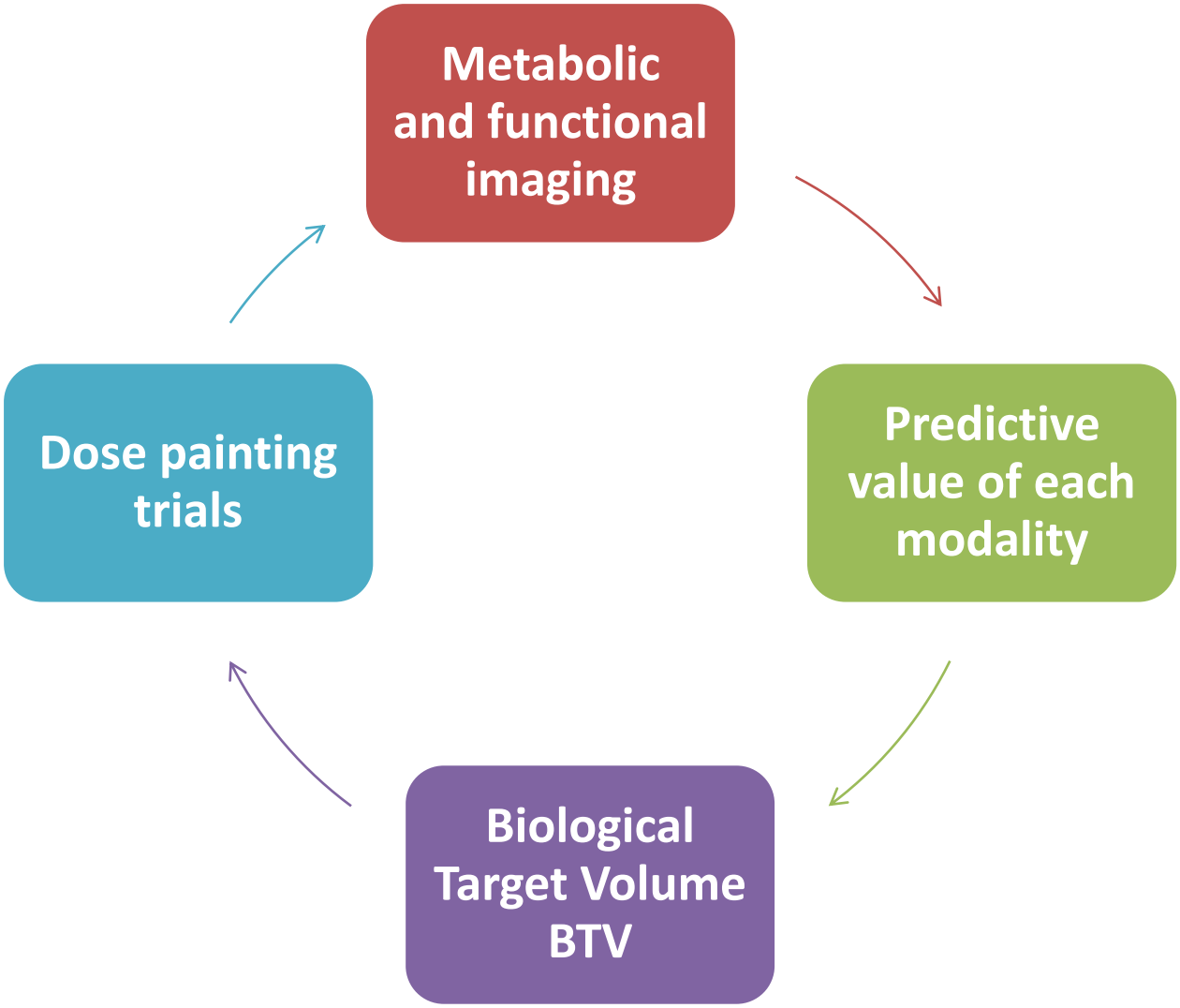
Local relapses can be due to cellular or micro-environment clusters that resist to standard homogeneous dose.

Metabolic imaging can help define radioresistant clusters → Biological Target Volume

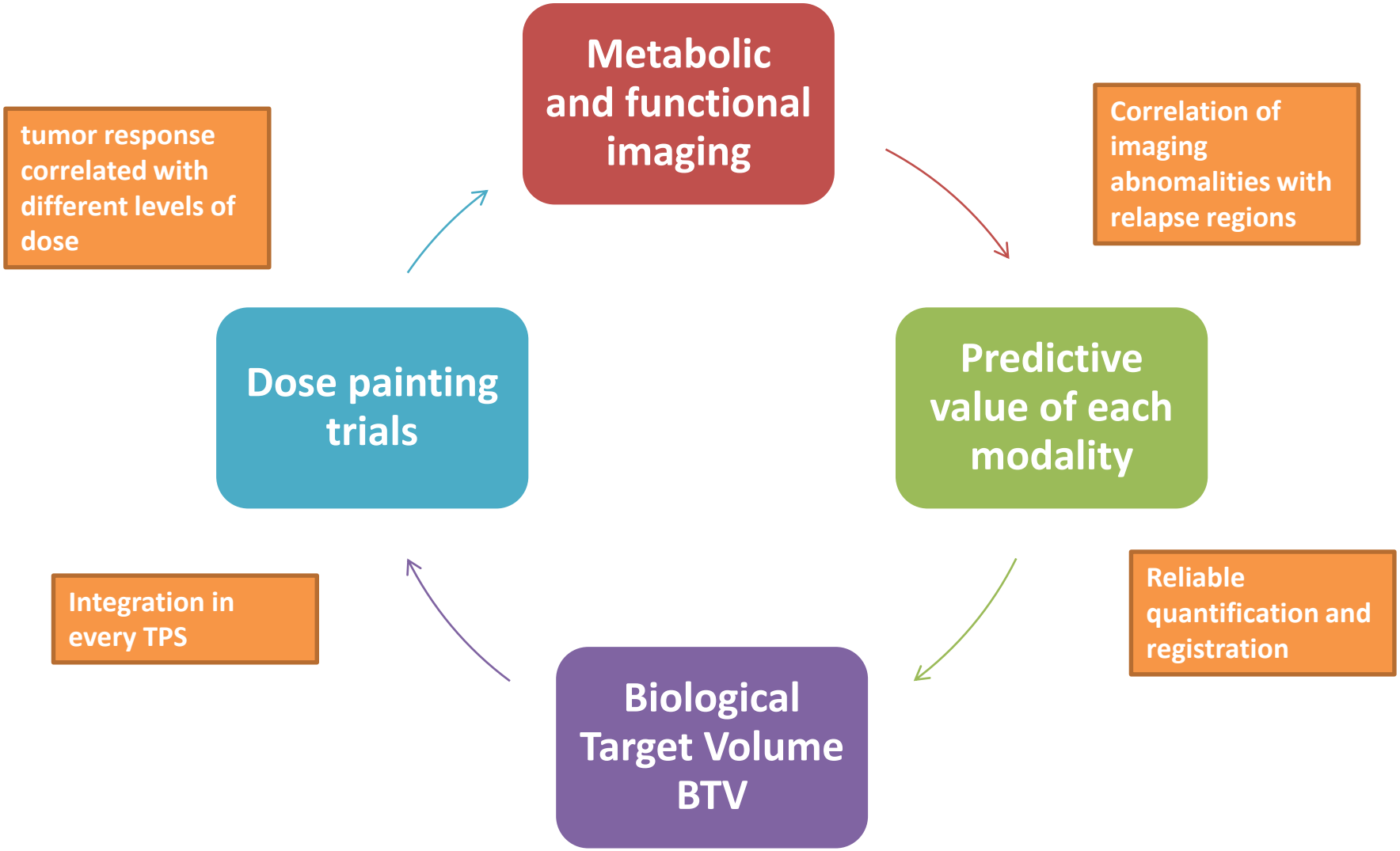
New radiotherapy techniques allow a precise targeting of BTV

Optimisation of radiotherapy can be performed with Dose-painting : delivering heterogenous dose guided by metabolic imaging

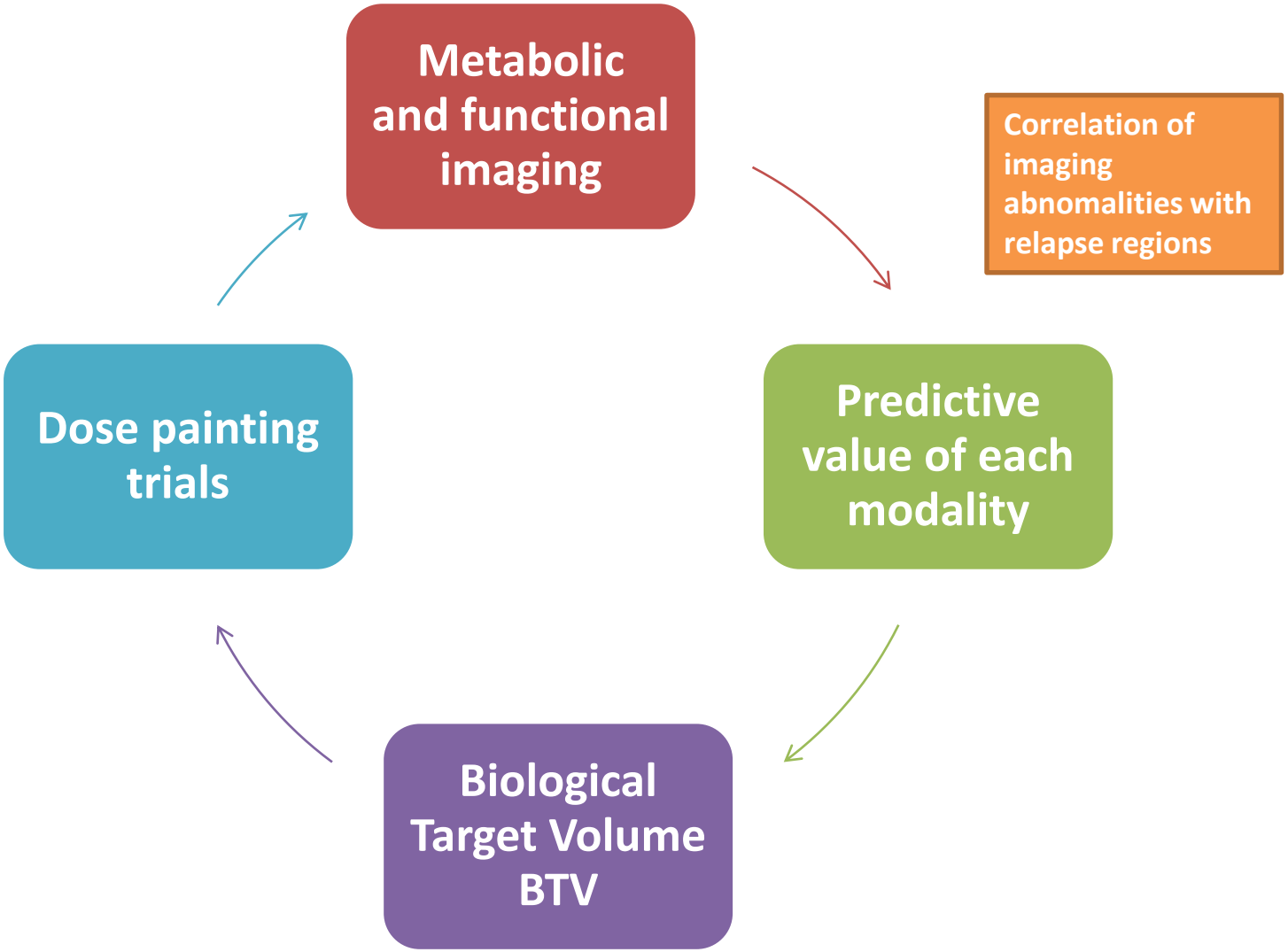
Virtuous circle of dose-painting



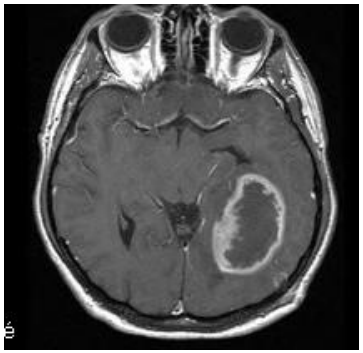
Virtuous circle of dose-painting

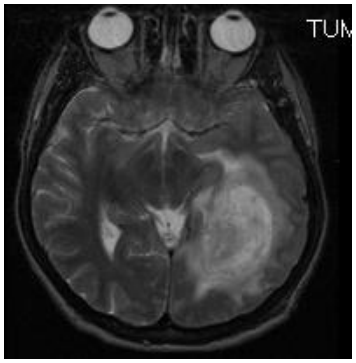


Virtuous circle of dose-painting



Glioblastoma RT volume definition





T1 gado reflects the rupture of hematomeningeal barrier and underestimates tumoral volume

T2 reflects edema and micoscopic invasion and overestimates tumoral volume

Tumor with complex infiltration

Histological series : tumors 2 cm around CE

CTV = CE + 2cm

What is the real tumor extension ?

Q1. Brain metabolic and functional imaging for brain tumors:

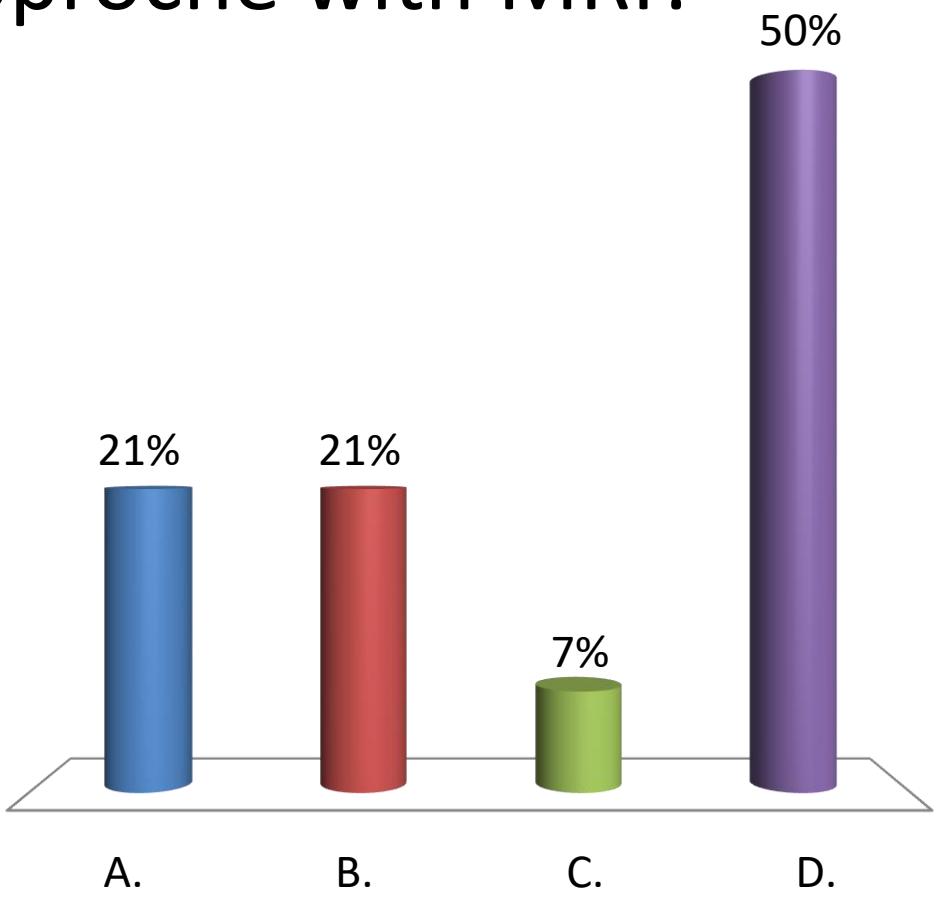
What is **not** a main approche with MRI?

A. Perfusion MRI with DSC analyzing CBV (cerebral blood volume)

B. Perfusion MRI with DCE analysing Ktrans

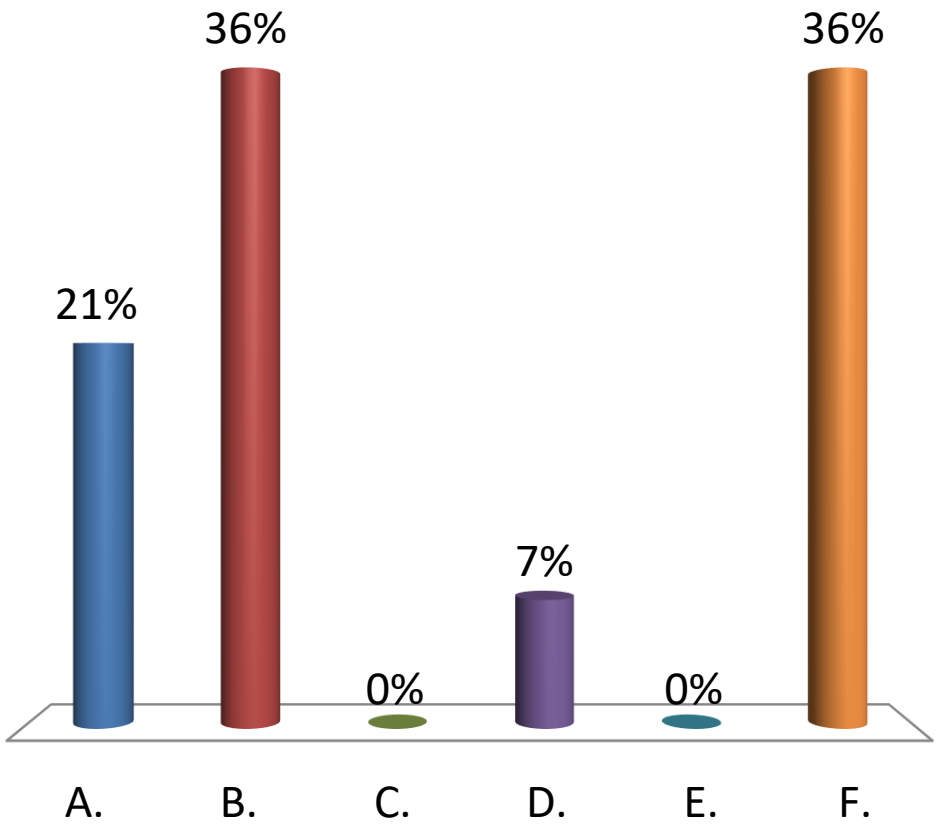
C. Diffusion MRI with ADC analysis (Apparent diffusion coefficient)

D. Proton MR Spectroscopy



Q2. MR spectroscopy

A. Is well known for diagnostic and guiding biopsies
B. Gives information on cellularity and metabolism
C. Gives information on hypoxia
D. May give 2D or 3D imaging
E. Is reproducible whatever the scan-constructor.
F. Was described by several teams as predictive for local relapse site



Glioblastoma RT

RT increases survival whatever age and OMS status : radiosensivity

95% of relapses within irradiated volumes : Radioresistance

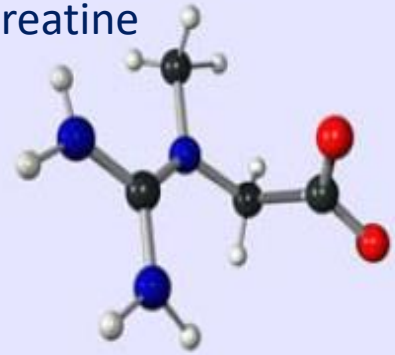
Dose escalation ? Where ?
Metabolic imaging ?

Imaging technique already used in neurosurgery and neuroradiology
Guiding biopsies
Grading tumors
Differenciating necrosis from relapse

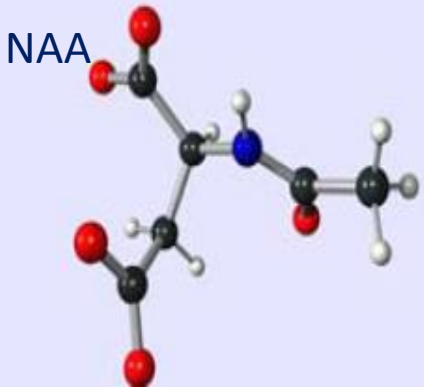
Magnetic Resonance Spectroscopic Imaging

Choline

Creatine



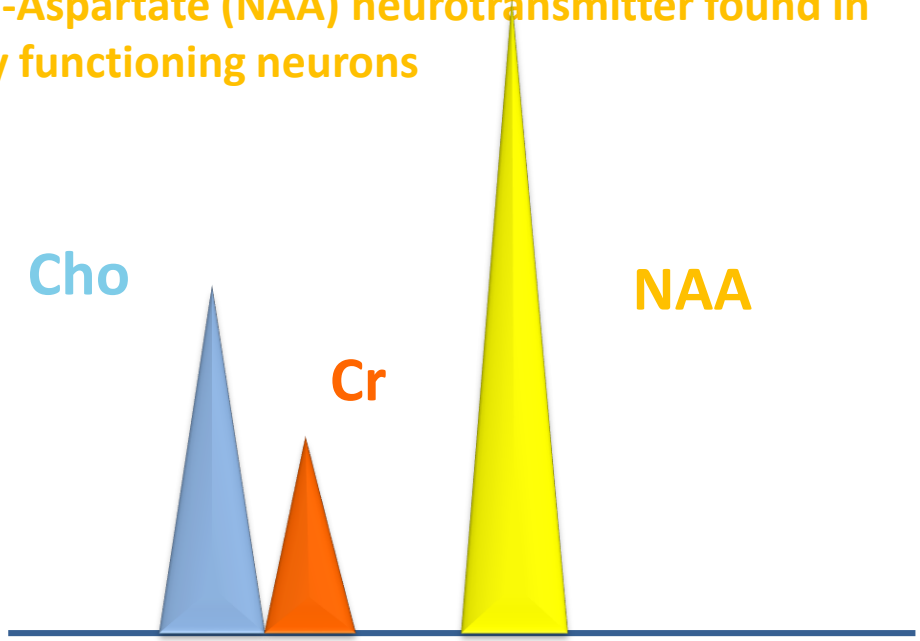
NAA



Choline (Cho) : cellular membranes

Creatine (Cr) : regulation of intracellular

N-Acetyl-Aspartate (NAA) neurotransmitter found in normally functioning neurons



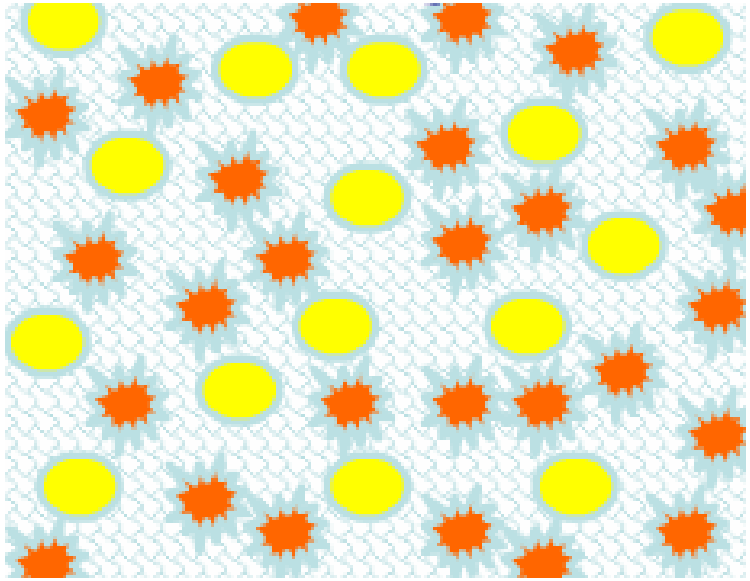
Chemical-shift imaging : CSI- 2D or CSI-3D

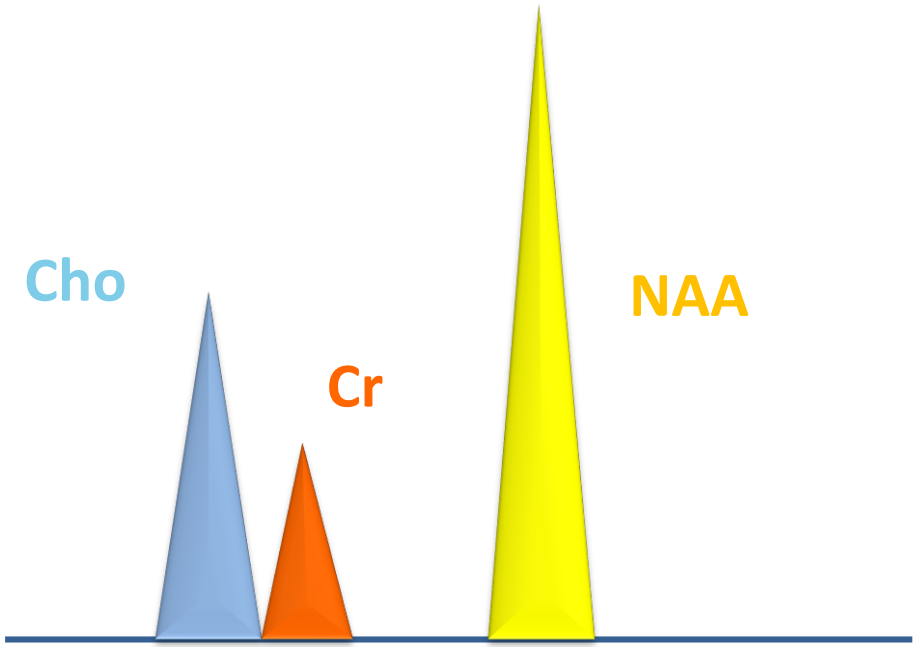
Spectra of the proton depends on its chemical environement

Choline (Cho) : cellular membranes

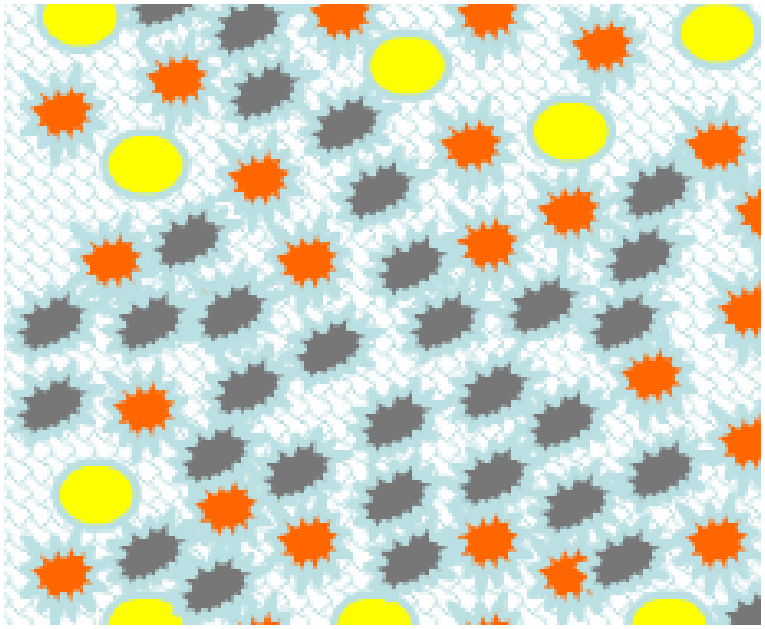
Creatine (Cr) : regulation of intracellular

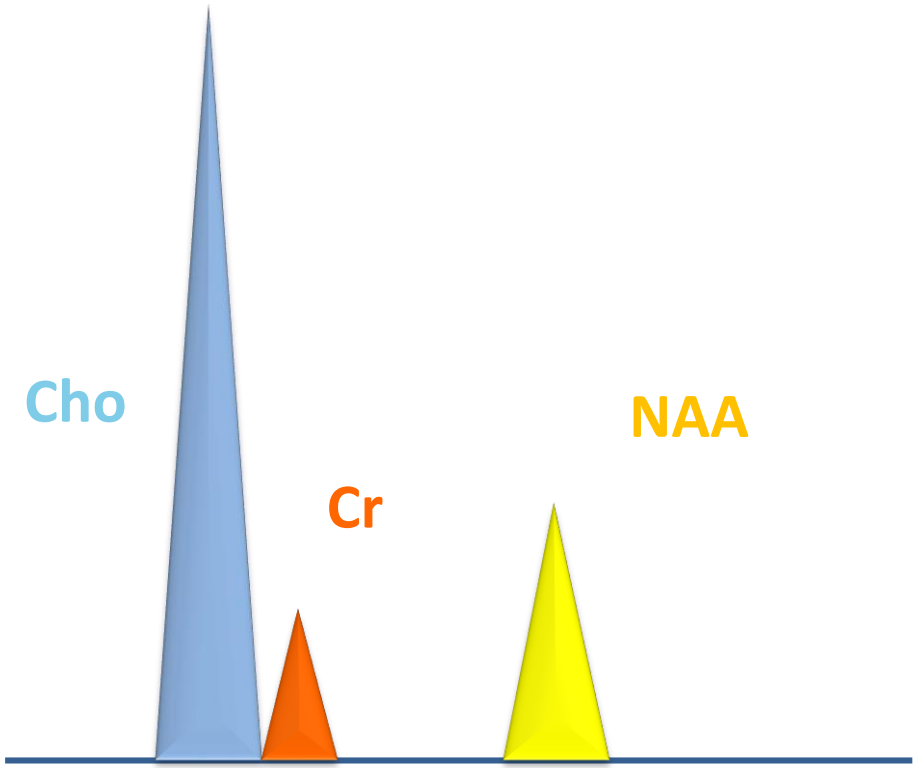
N-Acetyl-Aspartate (NAA) neurotransmitter found in normally functioning neurons

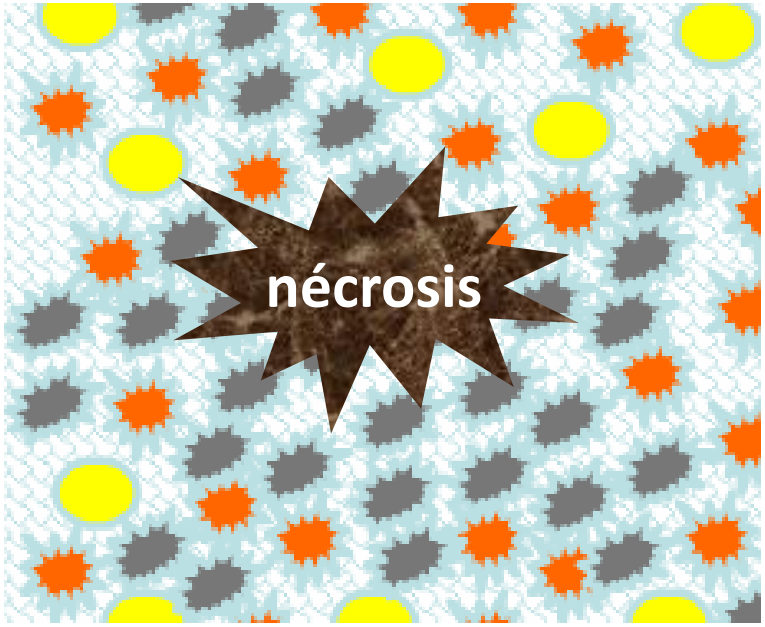


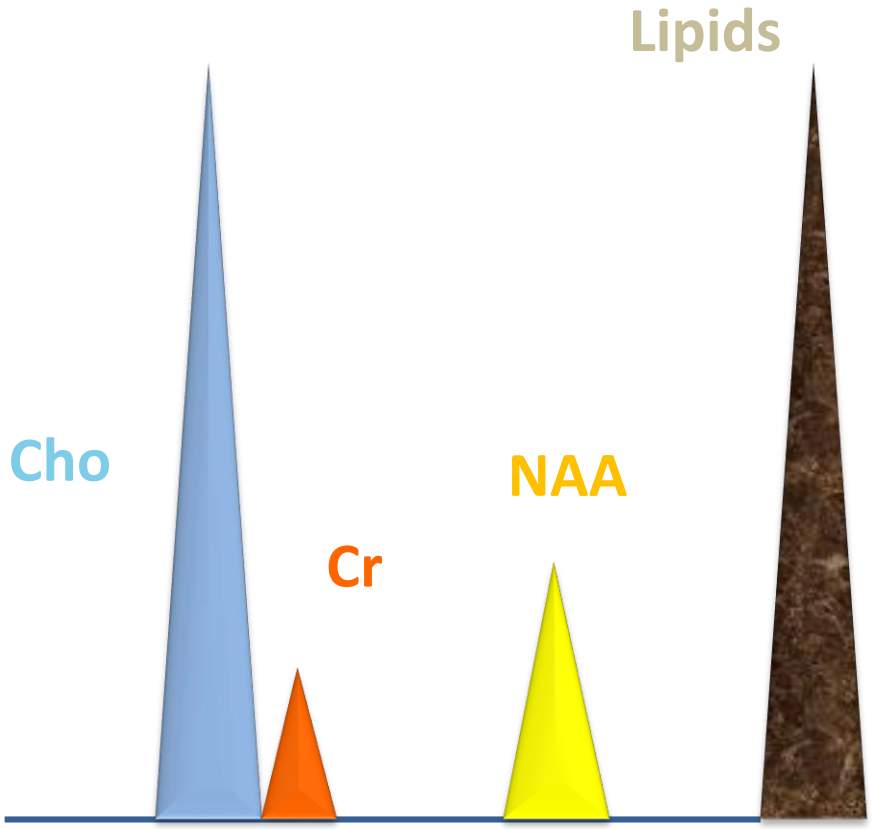


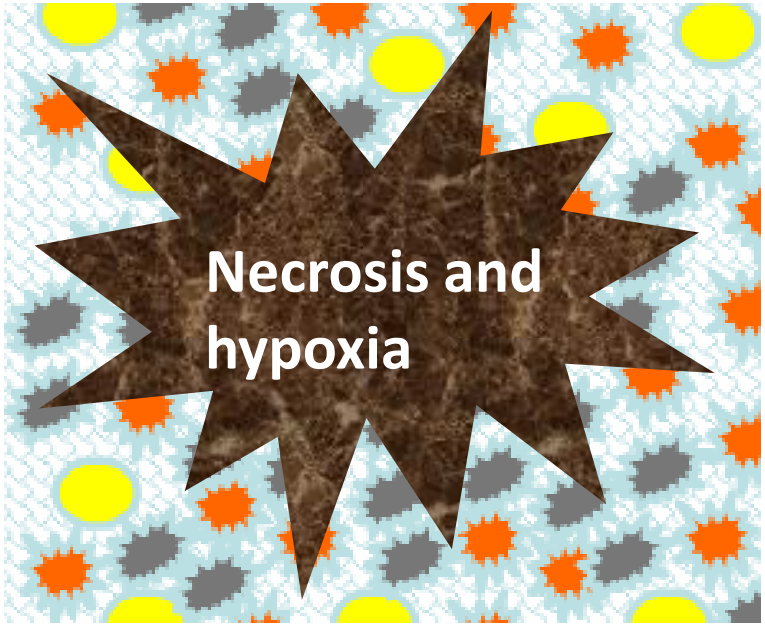
ratios of areas under the curve
Cho/NAA>2 → agressive glioma

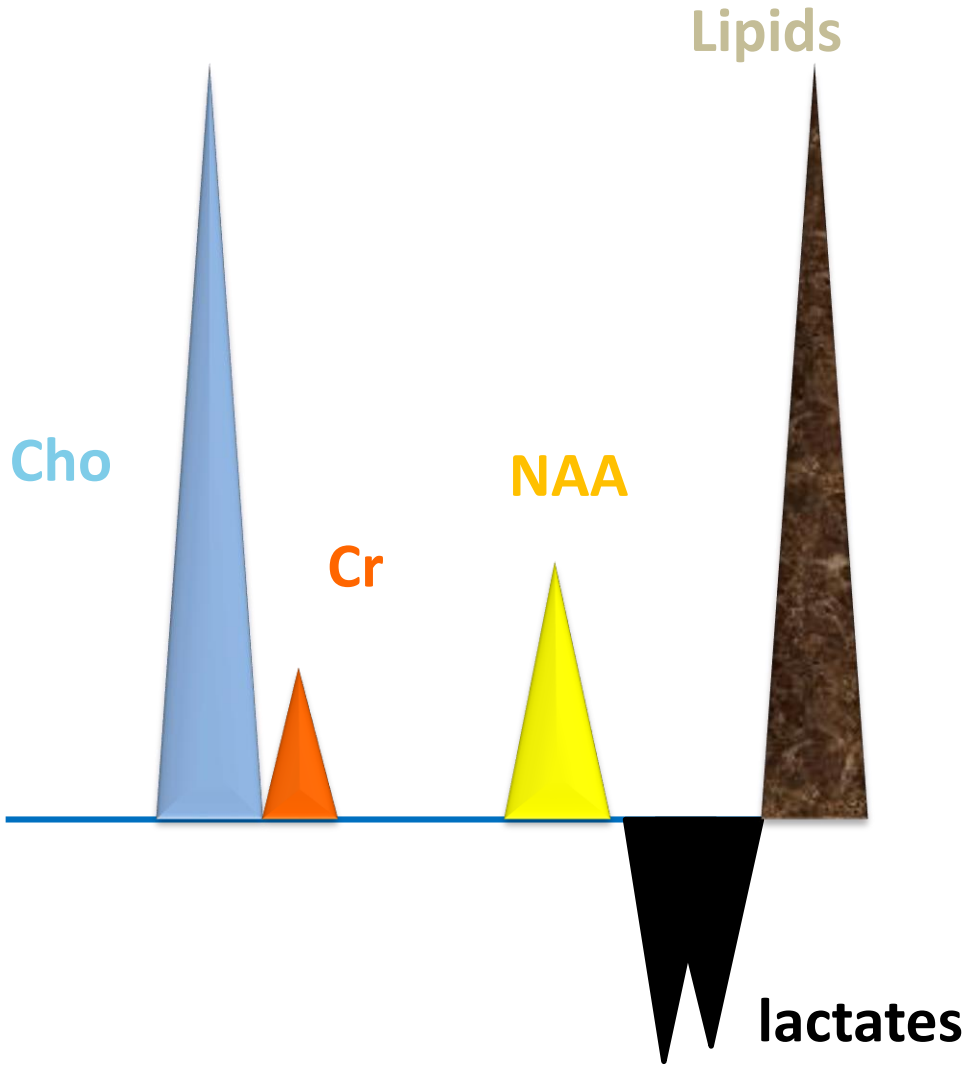




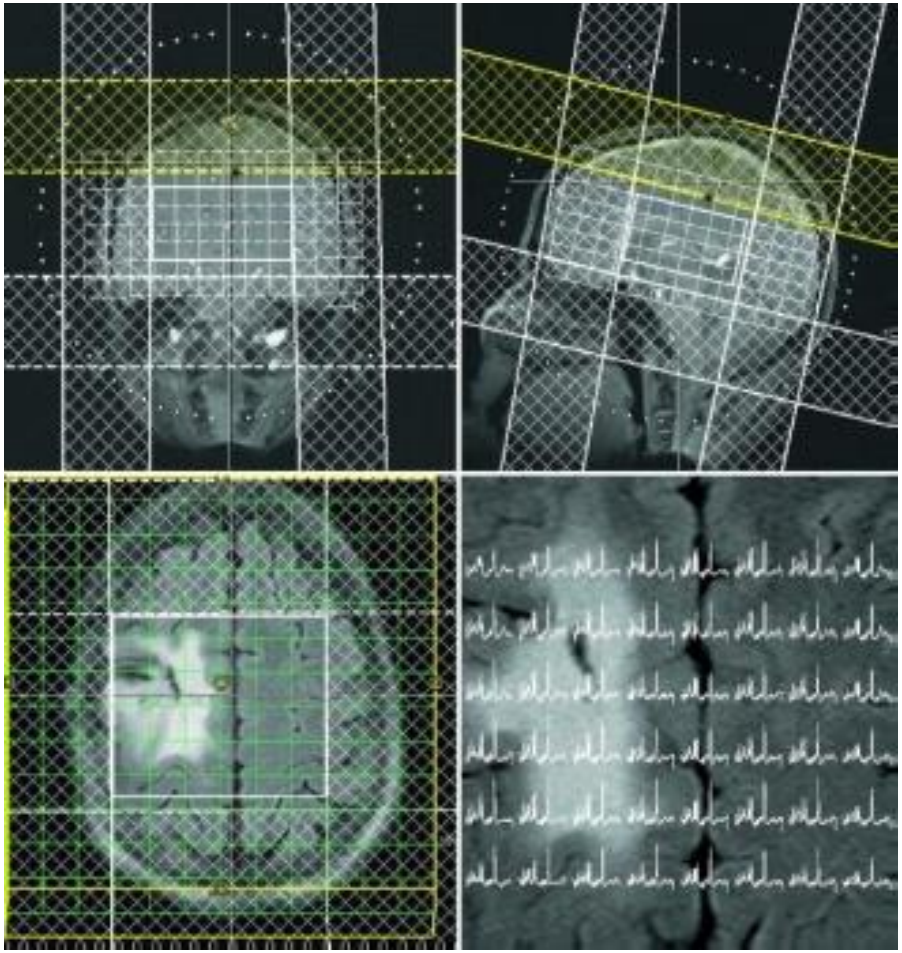

nécrosis

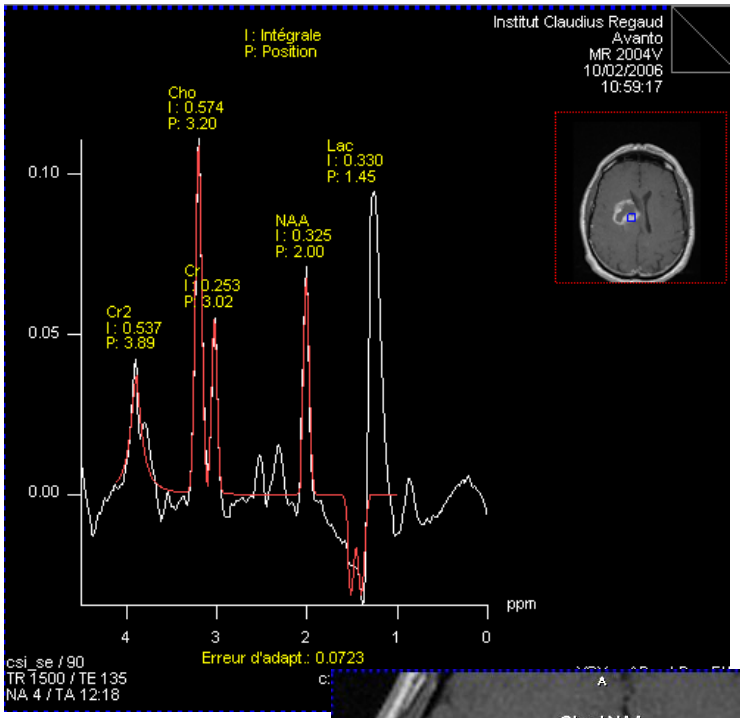

Lipids
Cho
NAA
Cr

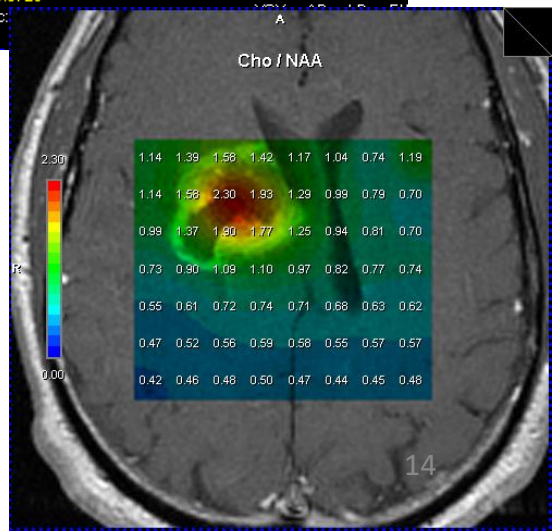

Necrosis and
hypoxia


Lipids
Cho
NAA
Cr
lactates

High grade brain tumors 3D MR spectroscopy

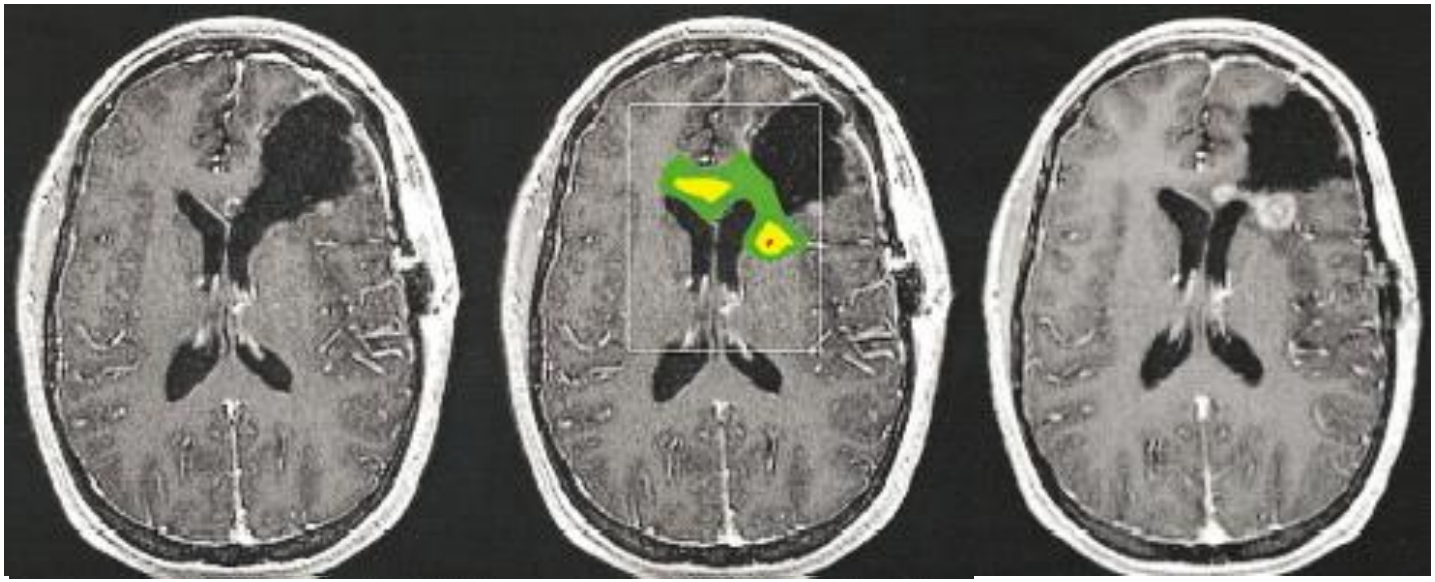






7 minutes exams added to standard MRI examination

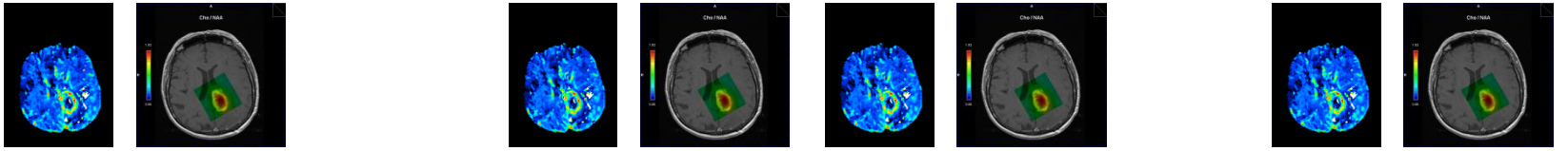
Predictive value of MR spectroscopy for relapse site after RT



A. Pirzkall, et al. IJROBP 2005

MR spectroscopy value for RT ?
Results from imaging performed in the prospective Zarnestra trial

23 2D- spectros , 1207 voxels



Biopsy or surgery | **Radiotherapy +tipifarnib** | 2mois | 4mois | **Relapse**

IRM +spectro | IRM +spectro | IRM +spectro | IRM +spectro

voxel by voxel comparisons

Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–6, 2007

0360-3016/07/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2007.02.043

CLINICAL INVESTIGATION

PHASE I TRIAL OF TIPIFARNIB (R115777) CONCURRENT WITH RADIOTHERAPY IN PATIENTS WITH GLIOBLASTOMA MULTIFORME

Elizabeth Cohen-Jonathan Moyal, M.D., Ph.D.,*† Anne Laprie, M.D.,* Martine Delannes, M.D.,* Muriel Poublanc,‡ Isabelle Catalaa, M.D., Ph.D.,§ Florence Dalenc, M.D., Ph.D.,‖ Delphine Berchery, M.D.,¶ Jean Sabatier, M.D., Ph.D.,# Philippe Bousquet, M.D.,# Peter De Porre, M.D.,** Béatrice Alaux, M.D.,‡ and Christine Toulas, Ph.D.†

Int. J. Radiation Oncology Biol. Phys., Vol. 70, No. 3, pp. 773–781, 2008

0360-3016/08/$–see front matter

ELSEVIER

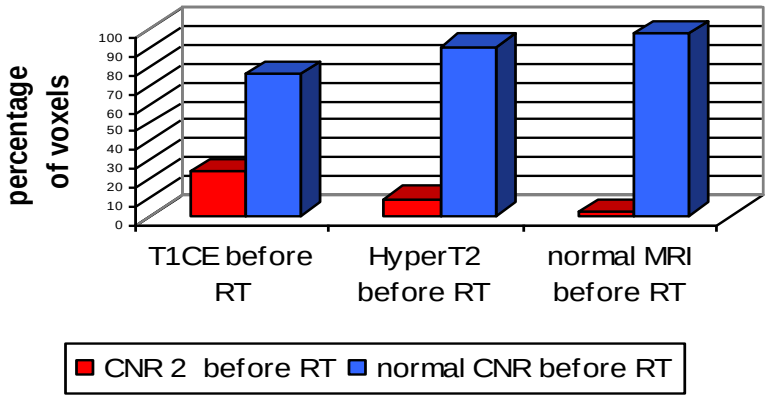
doi:10.1016/j.ijrobp.2007.10.039

CLINICAL INVESTIGATION **Brain**

PROTON MAGNETIC RESONANCE SPECTROSCOPIC IMAGING IN NEWLY DIAGNOSED GLIOBLASTOMA: PREDICTIVE VALUE FOR THE SITE OF POSTRADIOTHERAPY RELAPSE IN A PROSPECTIVE LONGITUDINAL STUDY

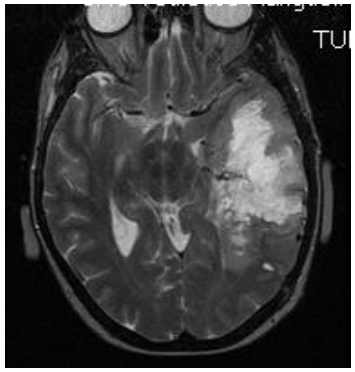
Anne Laprie, M.D., Ph.D,*† Isabelle Catalaa, M.D., Ph.D,†§ Emmanuelle Cassol, Ph.D.,† Tracy R. McKnight, Ph.D.,¶ Delphine Berchery, M.D.,‖ Delphine Marre, Ph.D.,* Jean-Marc Bachaud, M.D.,* Isabelle Berry, M.D., Ph.D,† and Elizabeth Cohen-Jonathan Moyal, M.D., Ph.D*‡

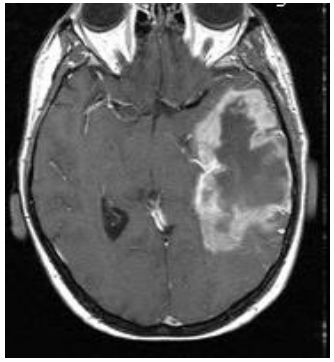
MR spectroscopy value for RT ?
Results from imaging performed in a prospective trial

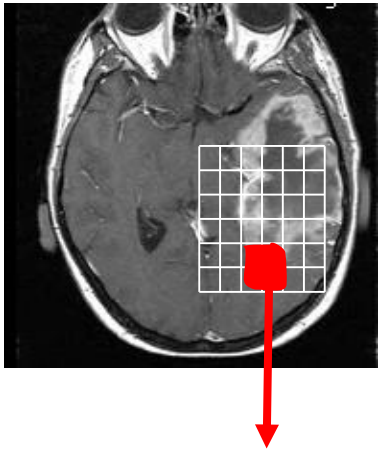


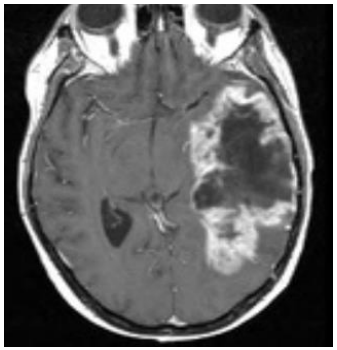
p<0.001

Spectroscopy Abnormal regions are limited compared with conventional imaging regions









Cho/NAA> 2 = CNR2

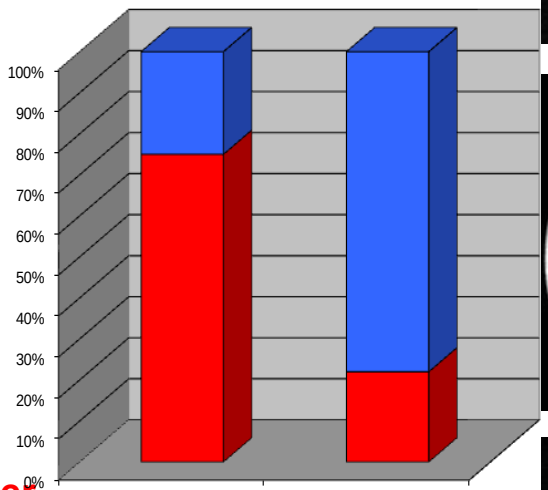
MR spectroscopy value for RT ?
Results from imaging performed in a prospective trial

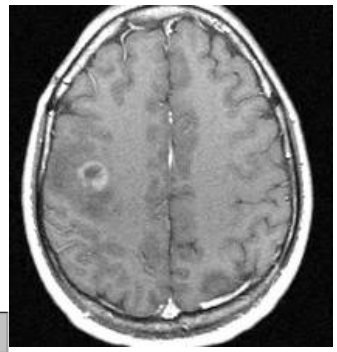
Metabolic maps of CHO/NAA >2

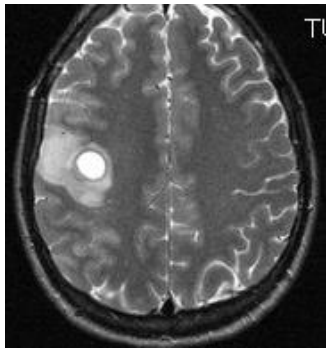
Before RT

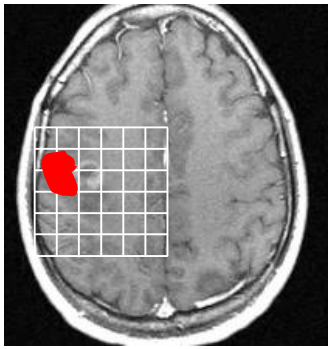
at 4 months

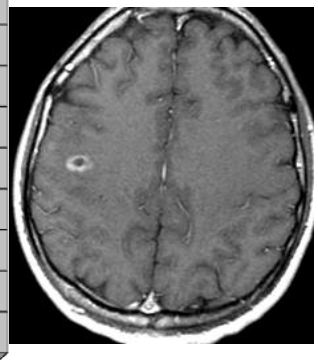
6 months later

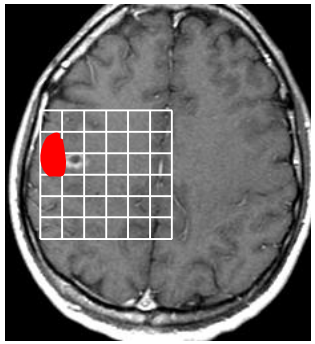


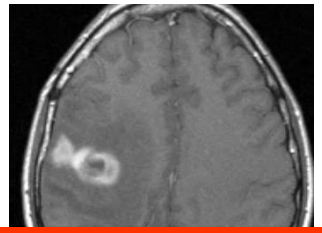


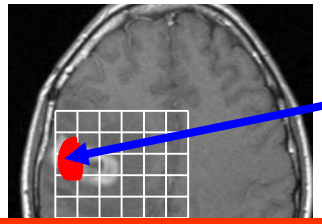


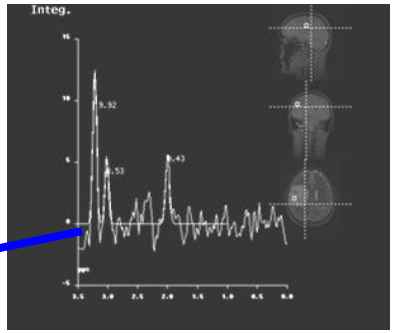






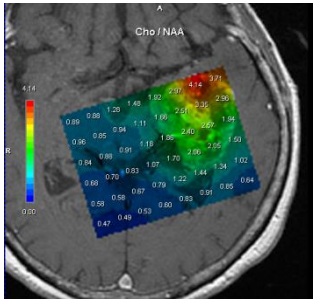






Statistically significant pronostic value compared with conventional imaging
80% of voxels with new contrast enhancing lesions were cho/NAA>2 before RT versus
20% of voxels with new contrast enhancing lesions were cho/NAA<2

MR spectroscopy and glioblastoma RT



MR Spectroscopy abnormality regions represent a minority of MRI anatomical abnormalities regions.

These areas are predictive for the site of post RT relapse

Pirzkall et al, IJROBP 2004

Laprie et al, IJROBP 2008

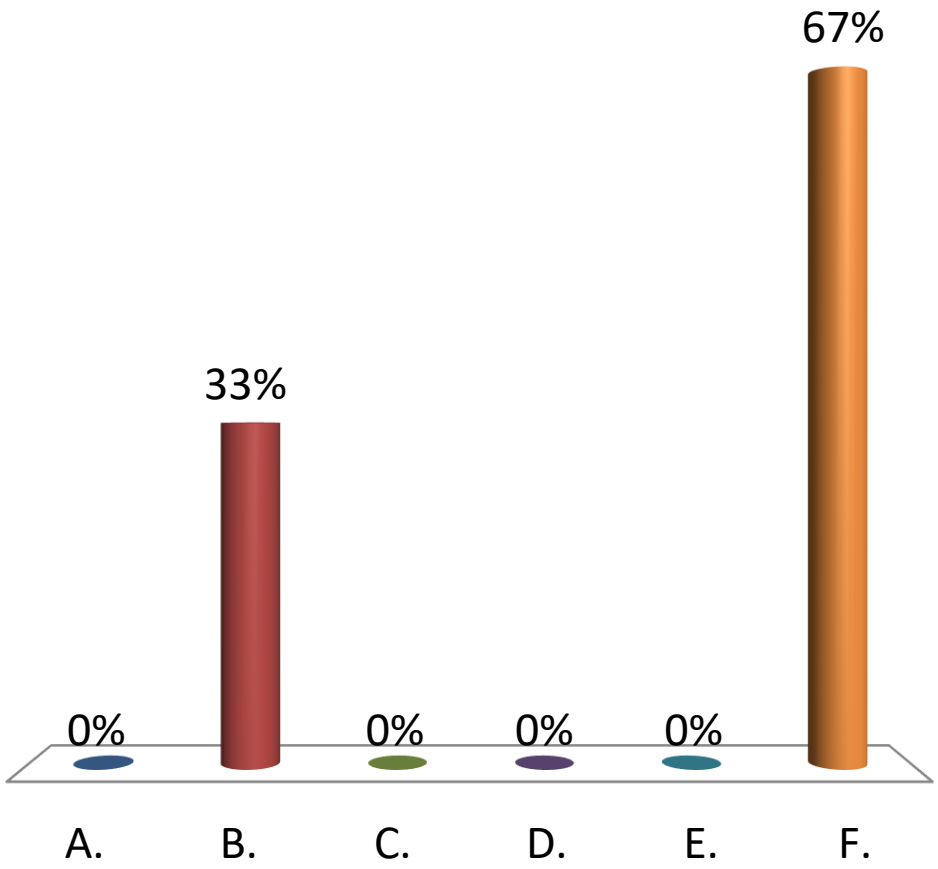
Regions of radioresistance

Dose-increase guided by MR spectroscopy?

Prospective clinical trial SPECTRO-GLIO financed by French national Institute of Cancer

Q2. MR spectroscopy

A. Is well known for diagnostic and guiding biopsies
B. Gives information on cellularity and metabolism
C. Gives information on hypoxia
D. May give 2D or 3D imaging
E. Is reproducible whatever the scan-constructor.
F. Was described by several teams as predictive for local relapse site

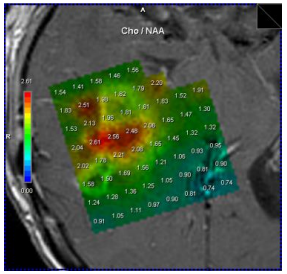


SPECTRO GLIO
Newly Diagnosed Glioblastoma
Prospective multicentric phase III trial
Promoted by Institut Claudius Regaud– financed by French national cancer institute

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

ToNIC Toulouse NeuroImaging Center UMR1214

220 patients – 9 institutions

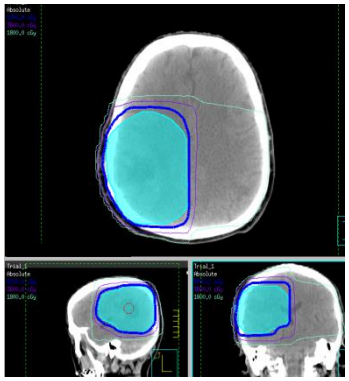


MRI + spectro

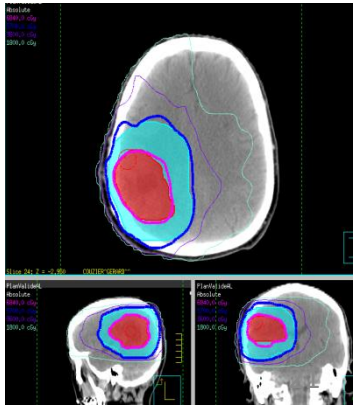
Randomization

60 Gy + TMZ

60 Gy + TMZ + 72 Gy/2,4 Gy
IMRT SIB guided by MR spectroscopy



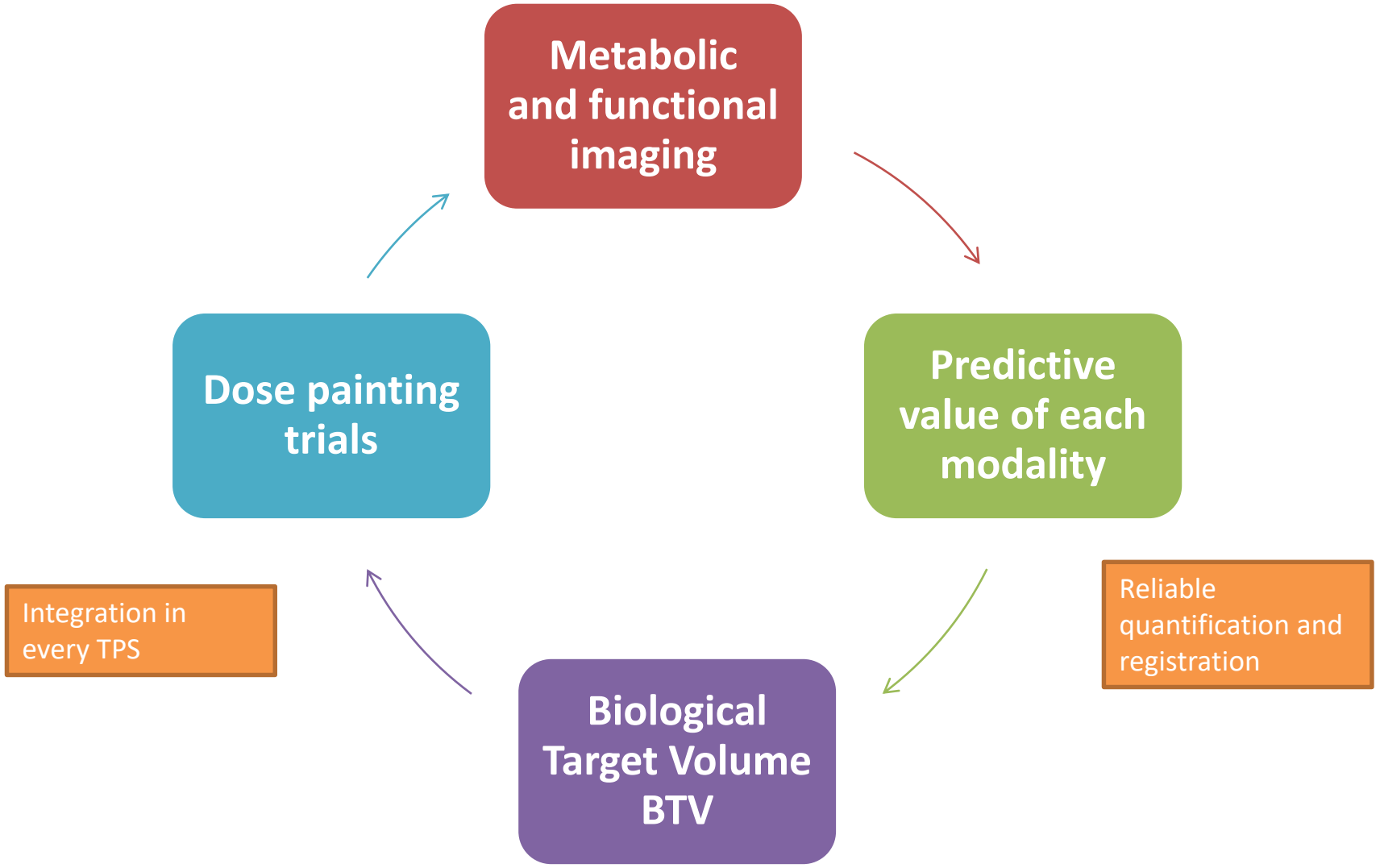
MRI + spectro /2months



Global survival

- Inclusion Criterias
  - Newly diagnosed Glioblastoma
  - Biopsy or surgery
  - Clinical status OMS≤2
  - Age ≥ 18 years
  - Stratification on biopsy or surgery.
  - Stratification on MGMT status
- Exclusion Criterias
  - Uninterpretable spectroscopy
  - GTV > 5 cm
  - Distance-GTV-chiasm < 2 cm

Oncological Focus

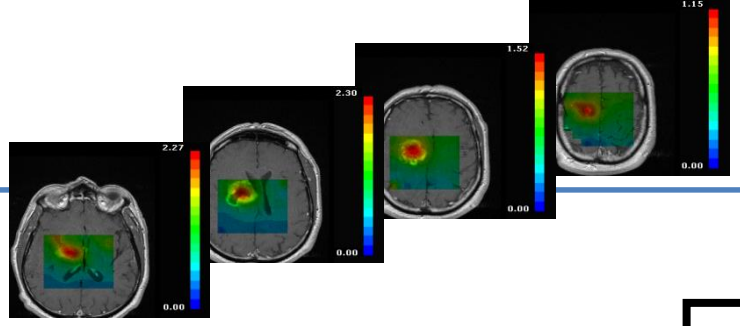


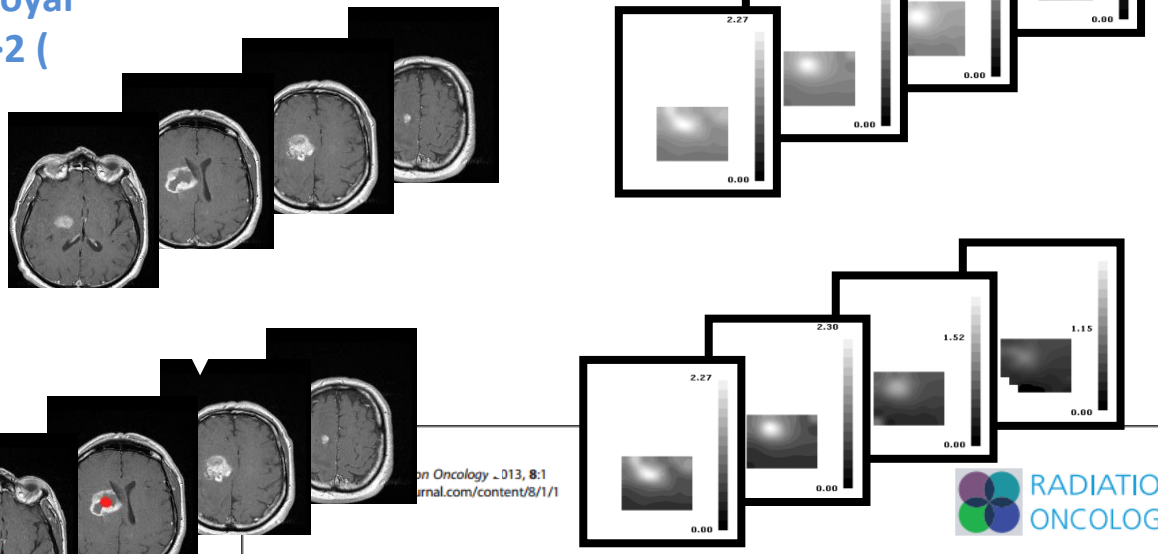
Methods

INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

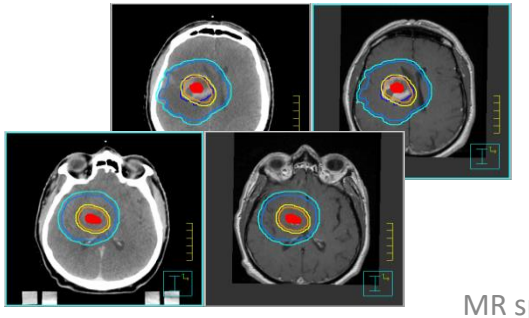
TONIC TOULOUSE NEURO IMAGING CENTER

Anatomic MR imaging and MR Spectroscopy Imaging (MRSI) acquisition of 16 patients enrolled in a previous trial of conventional RT + targeted therapy (Moyal et al, IJROBP 2007). Maps of CHO/Naa>2 (Laprie et al, IJROBP 2008)





Metabolite ratios maps overlaid on anatomic MR images →anatomic-metabolic images



RADIATION ONCOLOGY

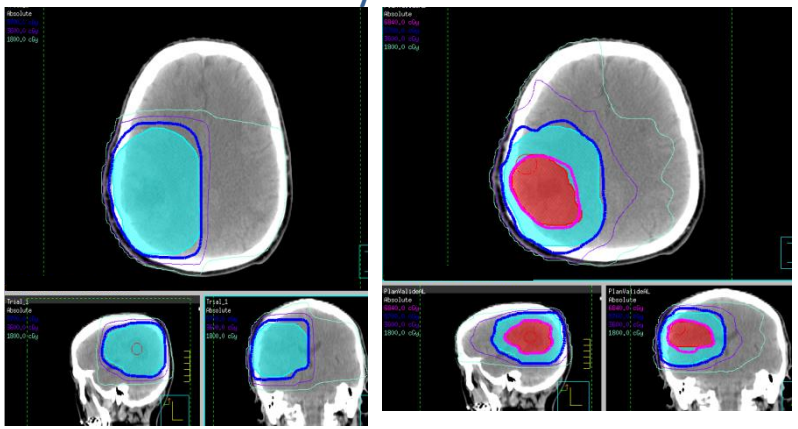
METHODOLOGY Open Access

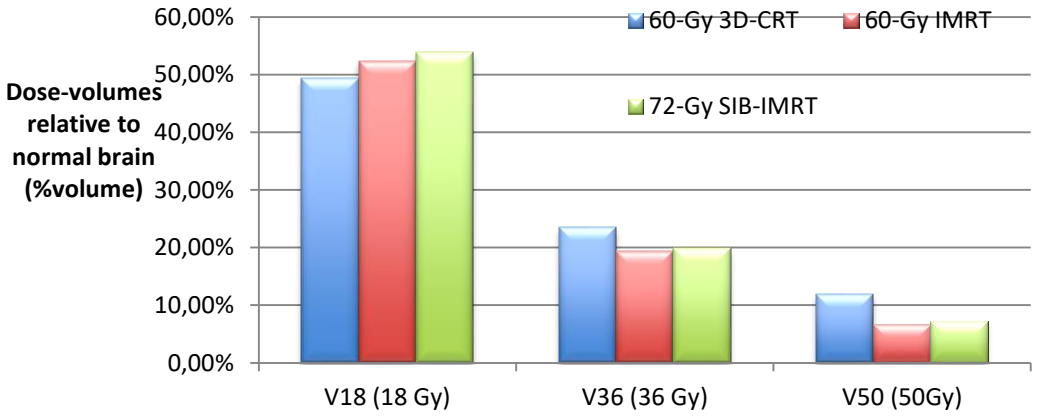
Integration method of 3D MR spectroscopy into treatment planning system for glioblastoma IMRT dose painting with integrated simultaneous boost

Soléakhéna Ken[1,2*], Laure Vieillevigne[1], Xavier Franceries[2], Luc Simon[1], Caroline Supper[1], Jean-Albert Lotterie[2,3], Thomas Filleron[1], Vincent Lubrano[2,3], Isabelle Berry[2,3], Emmanuelle Cassol[2,3], Martine Delannes[1], Pierre Celsis[2], Elizabeth Moyal Cohen-Jonathan[1,4] and Anne Laprie[1,2]

Spectro glio trial

- robust and reproducible technique for MR spectroscopy coregistration with planning CT.
- →Dosimetric comparaison on 16 patients :
- IMRT SIB technique 72 Gy compared with 3D conformal RT 60 Gy :
  - better target coverage,
  - better index conformity
  - better conformation number
  - equivalent or better OARs sparing.





Ken et al, Radiation Oncology 2013

SPECTRO GLIO
Newly Diagnosed Glioblastoma
Prospective multicentric phase III trial
Promoted by IUC Toulouse coordinator A Laprie– financed by French national cancer institute

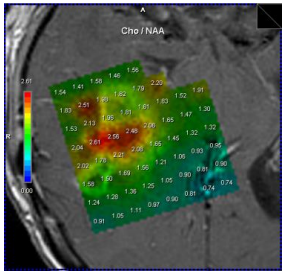
INSTITUT UNIVERSITAIRE DU CANCER DE TOULOUSE Oncopole

ToNIC Toulouse NeuroImaging Center UMR1214

220 patients – 9 institutions

170 patients included

Intermediate analysis 93 events, not reached

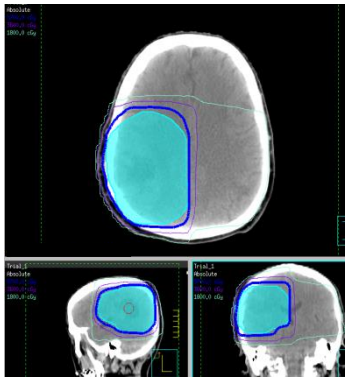


MRI + spectro

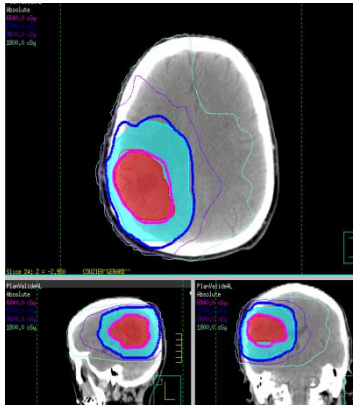
Randomization

60 Gy + TMZ

60 Gy + TMZ + 72 Gy/2,4 Gy
IMRT SIB guided by MR spectroscopy



MRI + spectro /2months

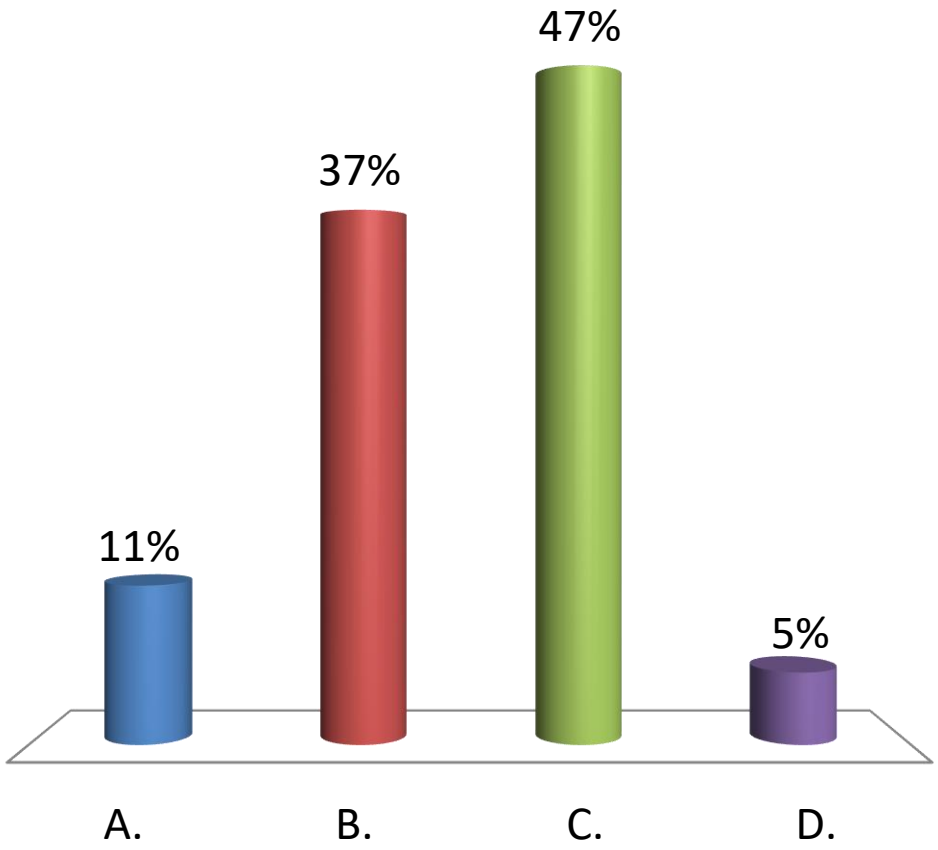


Global survival

MR spectroscopic imaging for dose-painting

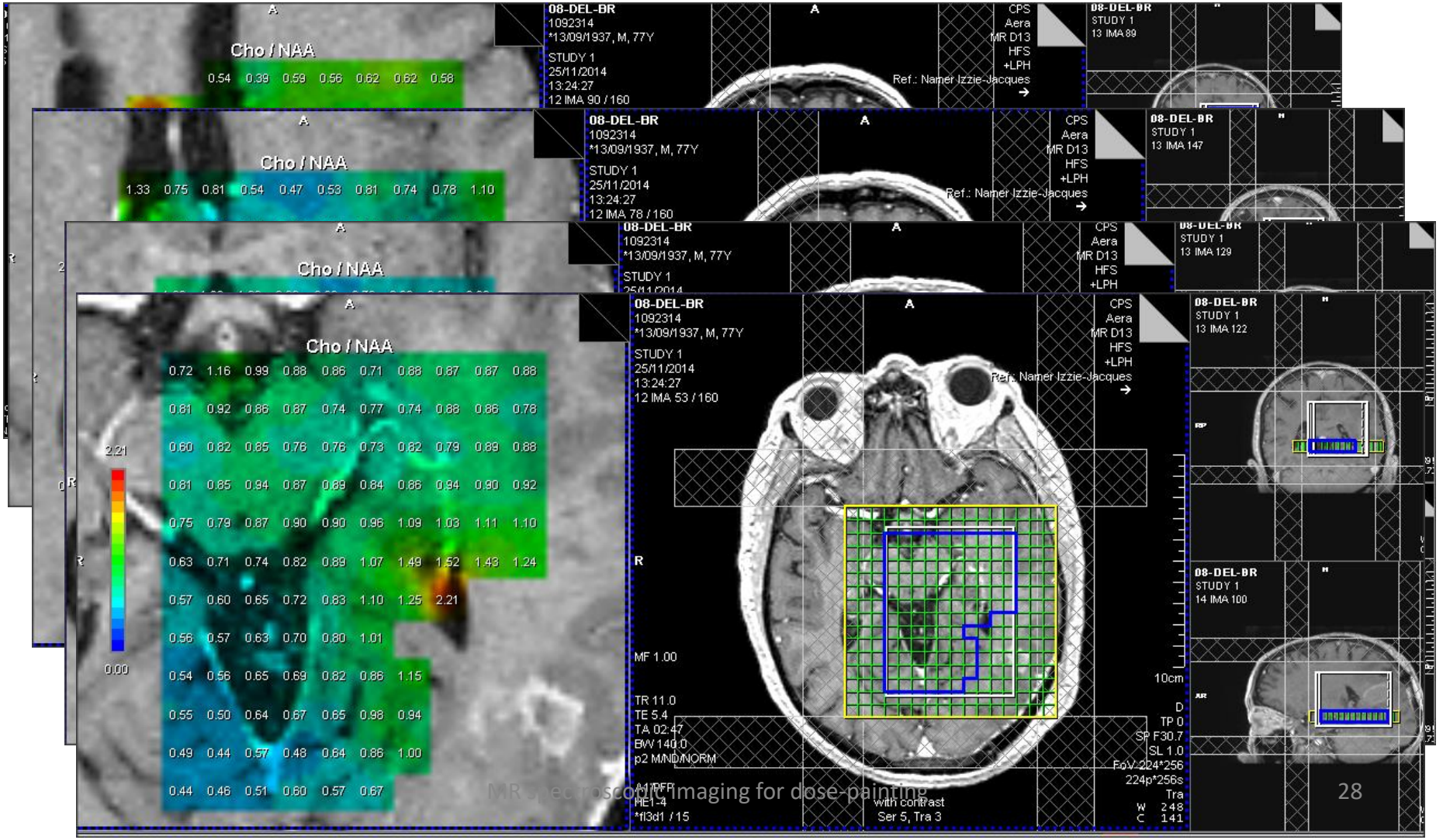
Q3. Dose-painting trials

A. Could be performed on any valuable metabolic imaging
B. Should be performed with metabolic imaging with a predictive value for post-radiotherapy relapse
C. Require quality control
D. Should be widely spread whatever the risk of « killing » the value of a metabolic imaging



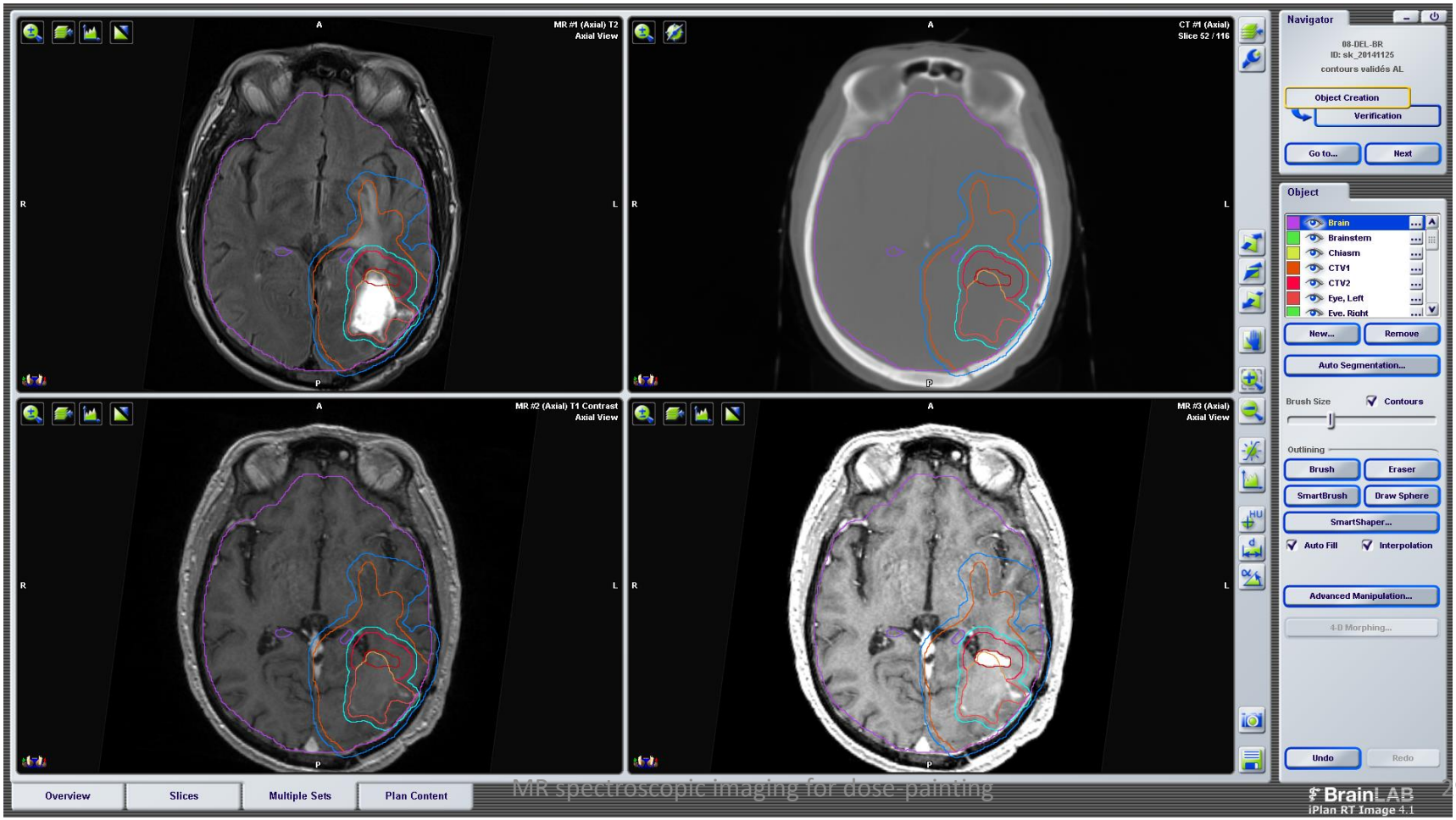
Centralized MR spectroscopy processing and integration

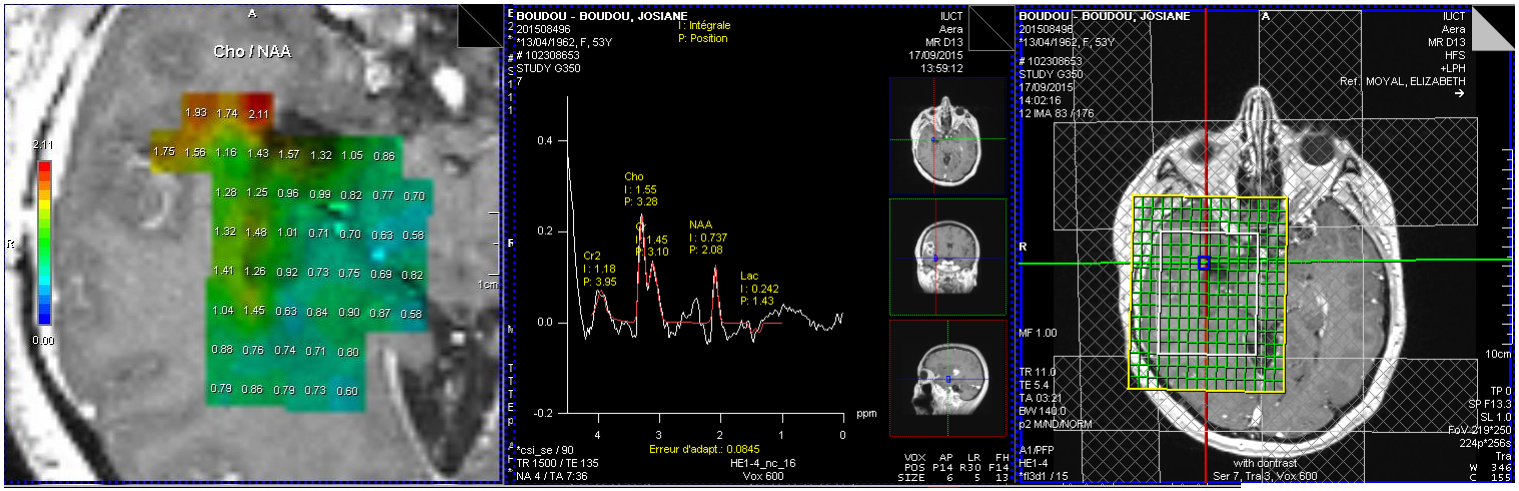
MR spectroscopy maps (1, 5 hour work)

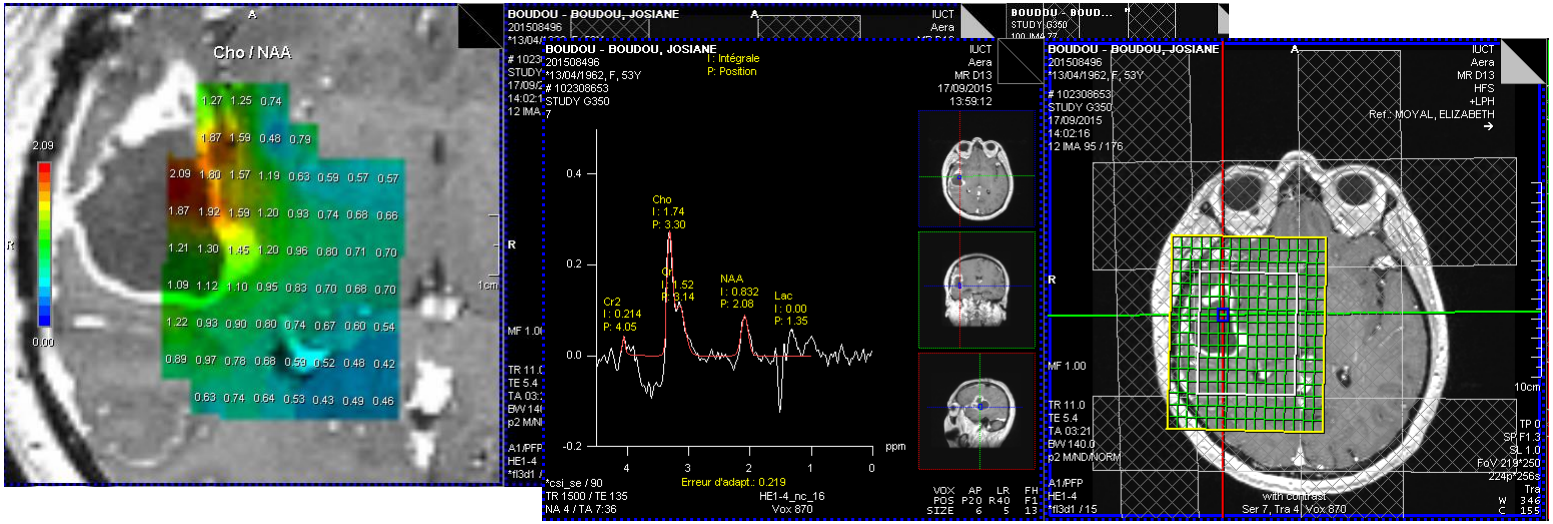


Centralized MR spectroscopy processing and integration

- Map integration to TPS (1 hour)
- Contours of target volumes and organs at risk




Cho / NAA
BOUDOU - BOUDOU, JOSIANE
I: Intégrale
P: Position
Cho
I: 1.55
P: 3.28
Cr2
I: 1.18
P: 3.95
Cr
I: 1.45
P: 3.10
NAA
I: 0.737
P: 2.08
Lac
I: 0.242
P: 1.43
ppm
Erreur d'adapt.: 0.0845
with contrast


Cho / NAA
BOUDOU - BOUDOU, JOSIANE
I: Intégrale
P: Position
Cho
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P: 3.30
Cr2
I: 0.214
P: 4.05
Cr
I: 1.52
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P: 2.08
Lac
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P: 1.35
ppm
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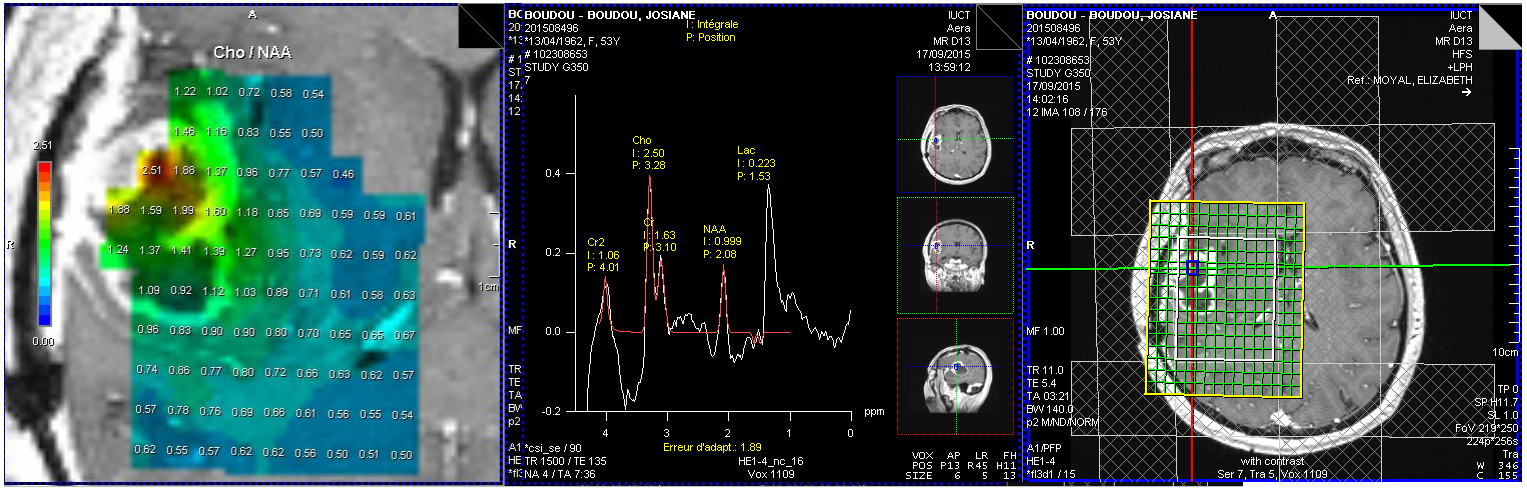
with contrast


Cho / NAA
BOUDOU - BOUDOU, JOSIANE
Cho
I: 2.50
P: 3.28
Lac
I: 0.223
P: 1.53
Cr2
I: 1.06
P: 4.01
Cr
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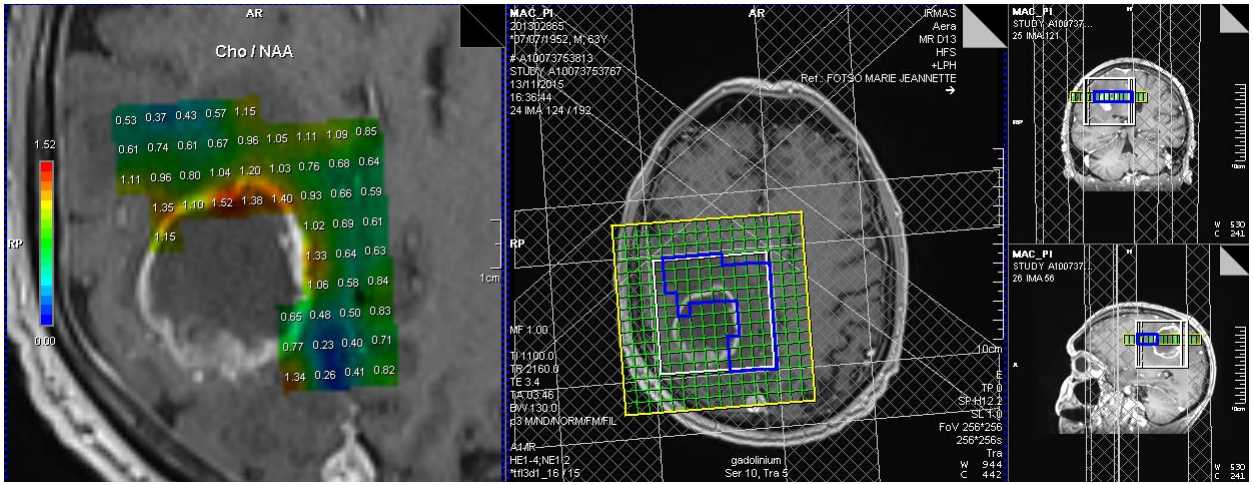
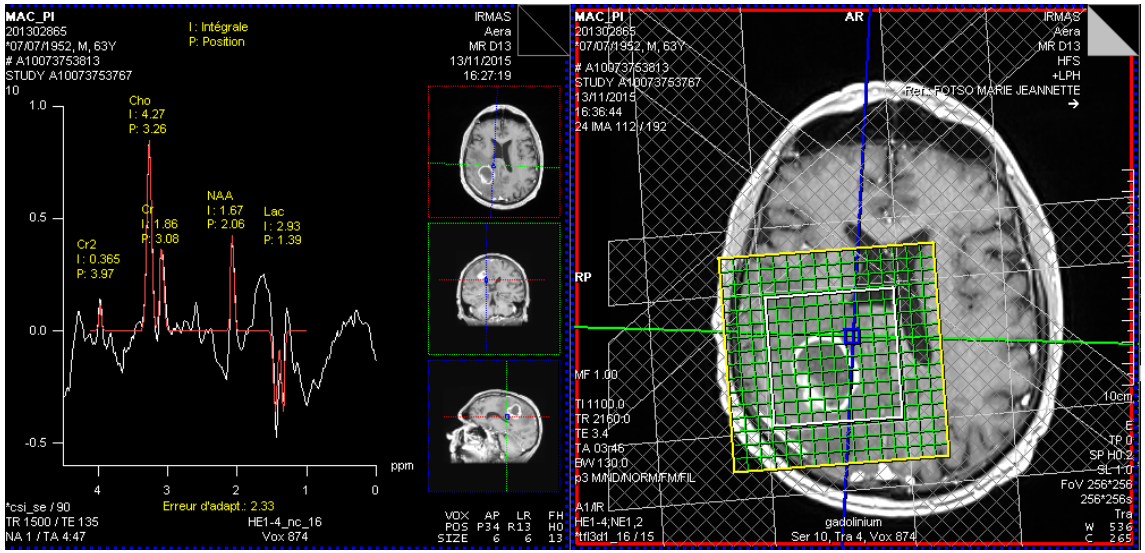
P: 3.10
NAA
I: 0.999
P: 2.08
ppm
Erreur d'adapt.: 1.89
with contrast


AR
Cho / NAA
MAC_PI
IRMAS
Aera
MR D13
HFS
+LPH
Ref.: FOTSO MARIE JEANNETTE
gadolinium
Ser 10, Tra 5


MAC_PI
I : Intégrale
P: Position
IRMAS
Aera
MR D13
13/11/2015
16:27:19
Cho
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P: 3.26
NAA
I: 1.67
P: 2.06
Cr
I: 1.86
P: 3.08
Lac
I: 2.93
P: 1.39
Cr2
I: 0.365
P: 3.97
ppm
Erreur d'adapt.: 2.33
TR 1500 / TE 135
NA 1 / TA 4:47
HE1-4_nc_16
Vox 874
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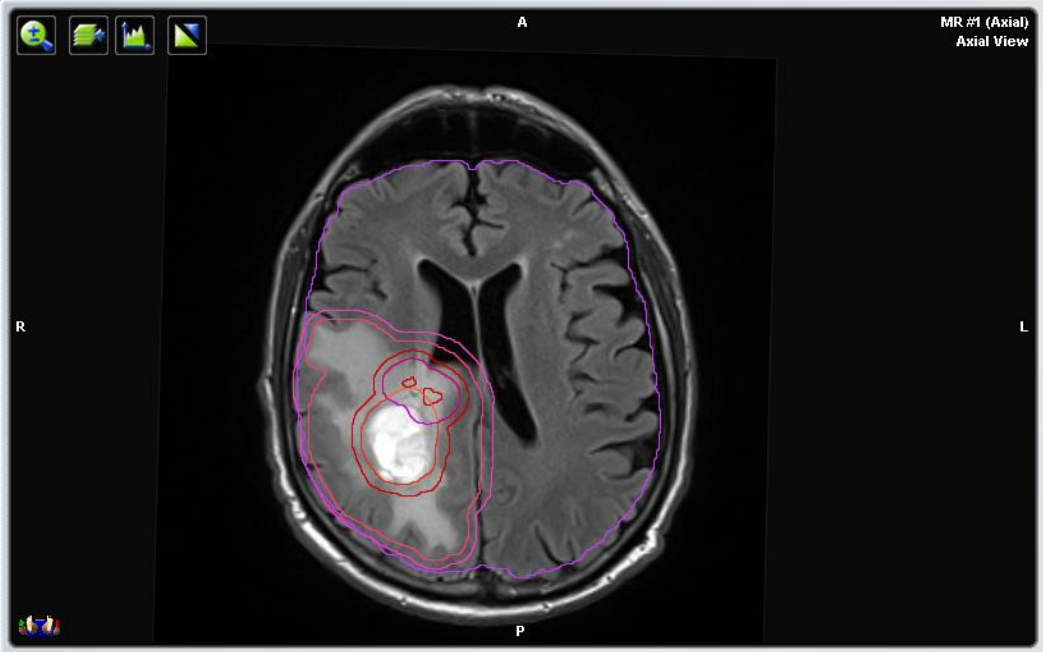
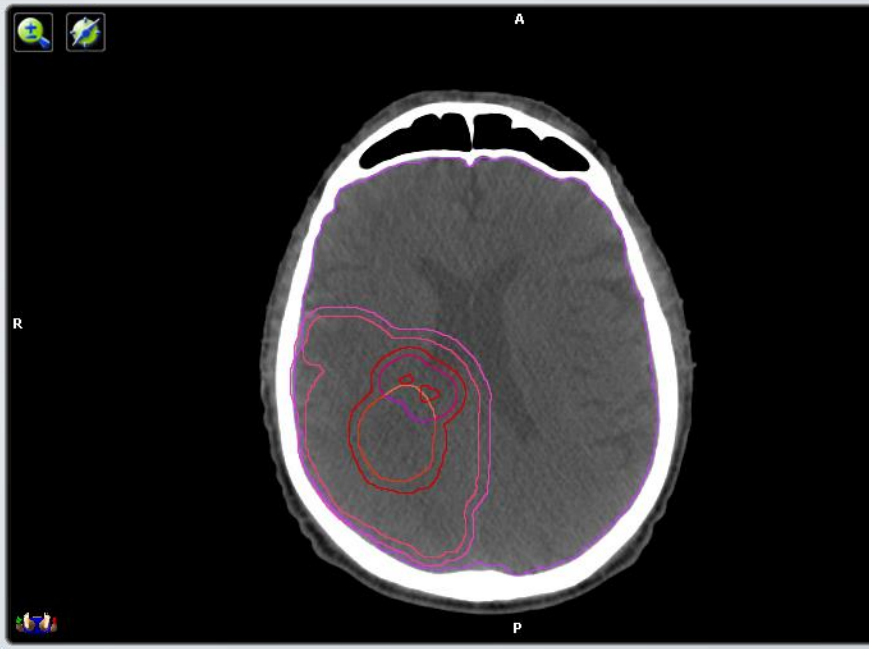
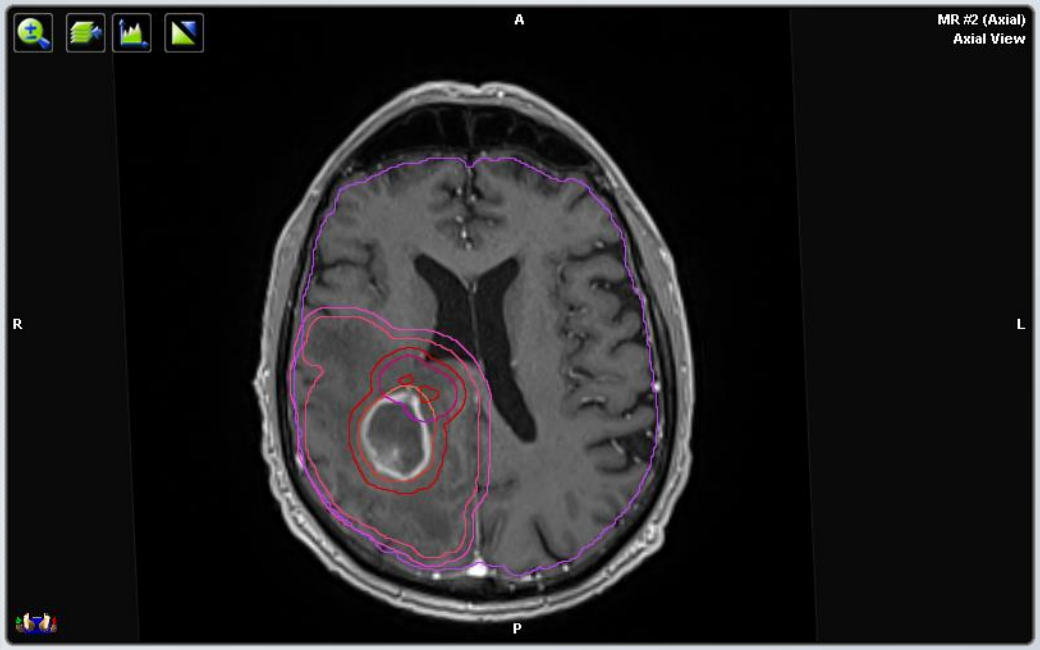
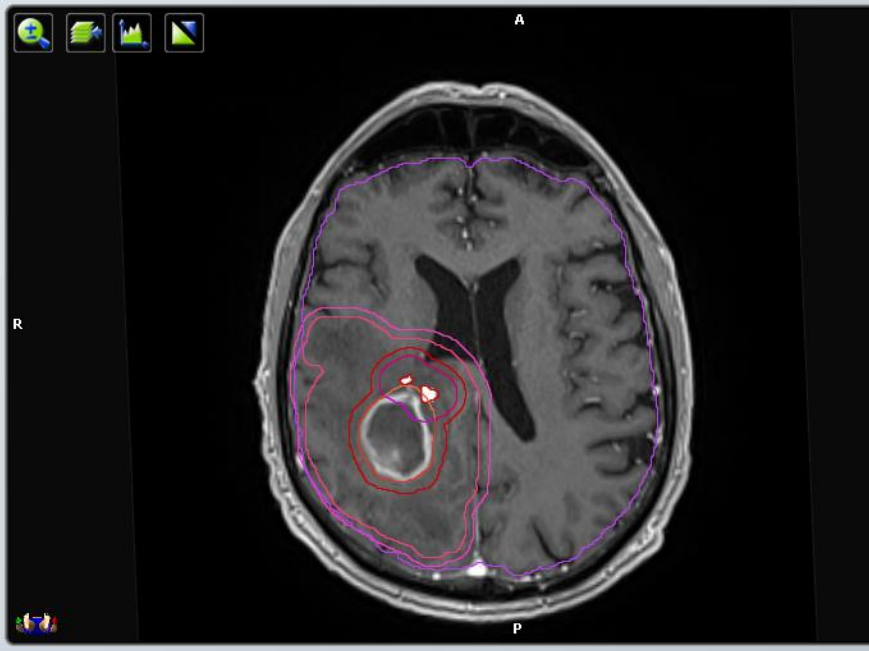
Ref.: FOTSO MARIE JEANNETTE
gadolinium
Ser 10, Tra 4, Vox 874









Overview | Slices | Multiple Sets | Plan Content

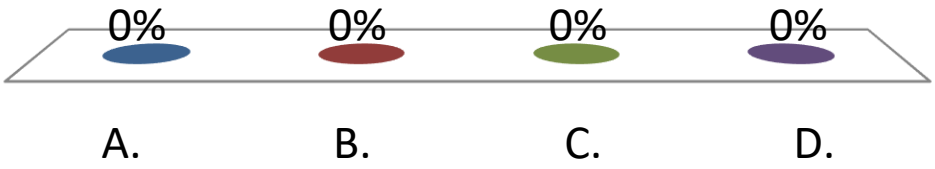
Q3. Dose-painting trials

A. Could be performed on any valuable metabolic imaging

B. Should be performed with metabolic imaging with a predictive value for post-radiotherapy relapse

C. Require quality control

D. Should be widely spread whatever the risk of « killing » the value of a metabolic imaging



Radiotherapy Protocol Deviations and Clinical Outcomes: A Meta-analysis of Cooperative Group Clinical Trials

Nitin Ohri, Xinglei Shen, Adam P. Dicker, Laura A. Doyle, Amy S. Harrison, Timothy N. Showalter

Table 1. Summary of trials included in the meta-analysis*

Trial name, enrollment period (reference)	Disease	Study design	Definition of RT deviation	No. of patients without RT deviation (%)	No. of patients with RT deviation (%)	Endpoints evaluated for association with RT deviation
RTOG 73-01, 1973–1978 (20)	Non-small-cell lung cancer	40 Gy split course vs 40 Gy vs 50 Gy vs 60 Gy	"Major" variation: recalculated dose variation >10%, no margin on primary target, or partial treatment of elective target	277 (92)	24 (8)	OS
SWOG 7628, 1976–1979 (21)	Small-cell lung cancer	RT preceded by one of four chemotherapy regimens	"Major" variation: included incorrect dose, ≥5% underdosing of involved target, ≥10% underdosing of elective target, ≥10% overdosing of critical normal structure	96 (69)	44 (31)	OS
POG 8346, 1983–1988 (24)	Ewing sarcoma	Chemotherapy followed by whole bone vs involved field RT	"Minor" or "major" deviation: <2 cm margin or >5% deviation from the recommended dose	52 (79)	14 (21)	Local control
SFOP 93/94, 1992–1998 (22)	Medulloblastoma	Risk-adapted chemotherapy followed by craniospinal RT	"Minor" or "major" deviation: ≤5 mm margin (cranial fields) or ≤ 0 mm margin (spinal fields)	49 (29)	120 (71)†	Relapse
POG 9031, 1990–1996 (23)	Medulloblastoma	Chemotherapy before or after craniospinal RT	"Major" deviation: ≥10% underdosing of brain, posterior fossa, or spine	69 (43)	91 (57)	OS, EFS
SIOP/UKCCSG PNET-3, 1992–1999 (16)	Supratentorial PNET	Chemotherapy followed by craniospinal RT vs craniospinal RT alone	Deviation: <3 mm margin (cribriform fossa) or <8 mm margin (skull base)	28 (67)	14 (33)	OS, EFS
TROG 02.02, 2002–2005 (10)	Head and neck cancer	Chemoradiotherapy with or without tirapazamine	"Deficiencies predicted to have a major adverse impact on tumor control"	723 (88)‡	97 (12)	OS, locoregional control
RTOG 97-04, 1998–2002 (9)	Pancreatic adenocarcinoma	5-FU + RT, preceded and followed by gemcitabine vs 5-FU	Less than per protocol (included field borders and dose delivered)	216 (52)	200 (48)	OS, failure

Impact of quality control on survival in prospective trials

VOLUME 28 · NUMBER 18 · JUNE 20 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

Lester J. Peters, Brian O'Sullivan, Jordi Giralt, Thomas J. Fitzgerald, Andy Trotti, Jacques Bernier, Jean Bourhis, Kally Yuen, Richard Fisher, and Danny Rischin

See accompanying editorial on page 2941 and article on page 2989

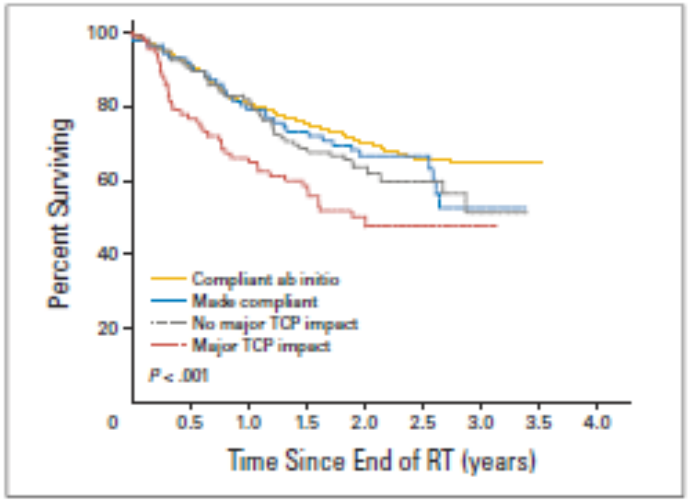


Fig 2. Overall survival by deviation status: (1) compliant from the outset (n = 502), (2) made compliant following a review by the Quality Assurance Review Center (n = 86), (3) noncompliant but without predicted major adverse impact on tumor control (n = 105), and (4) noncompliant with predicted major adverse impact on tumor control (n = 87). Overall $P < .001$. Pair-wise tests: not statistically significant except for cohort 1 versus cohort 4 ($P < .001$), cohort 2 versus cohort 4 ($P = .041$), and cohort 3 versus cohort 4 ($P = .006$). TCP, tumor control probability; RT, radiotherapy.

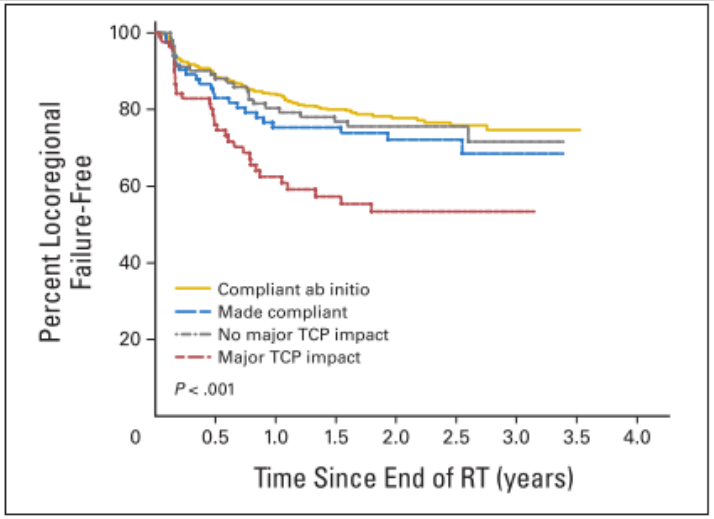
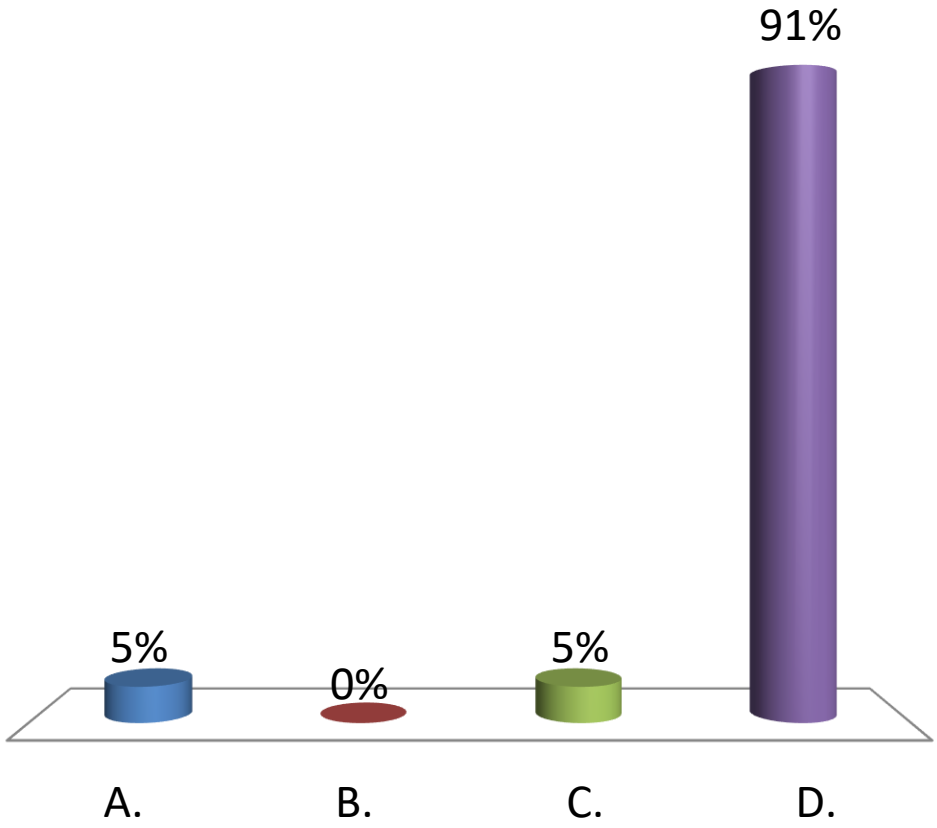


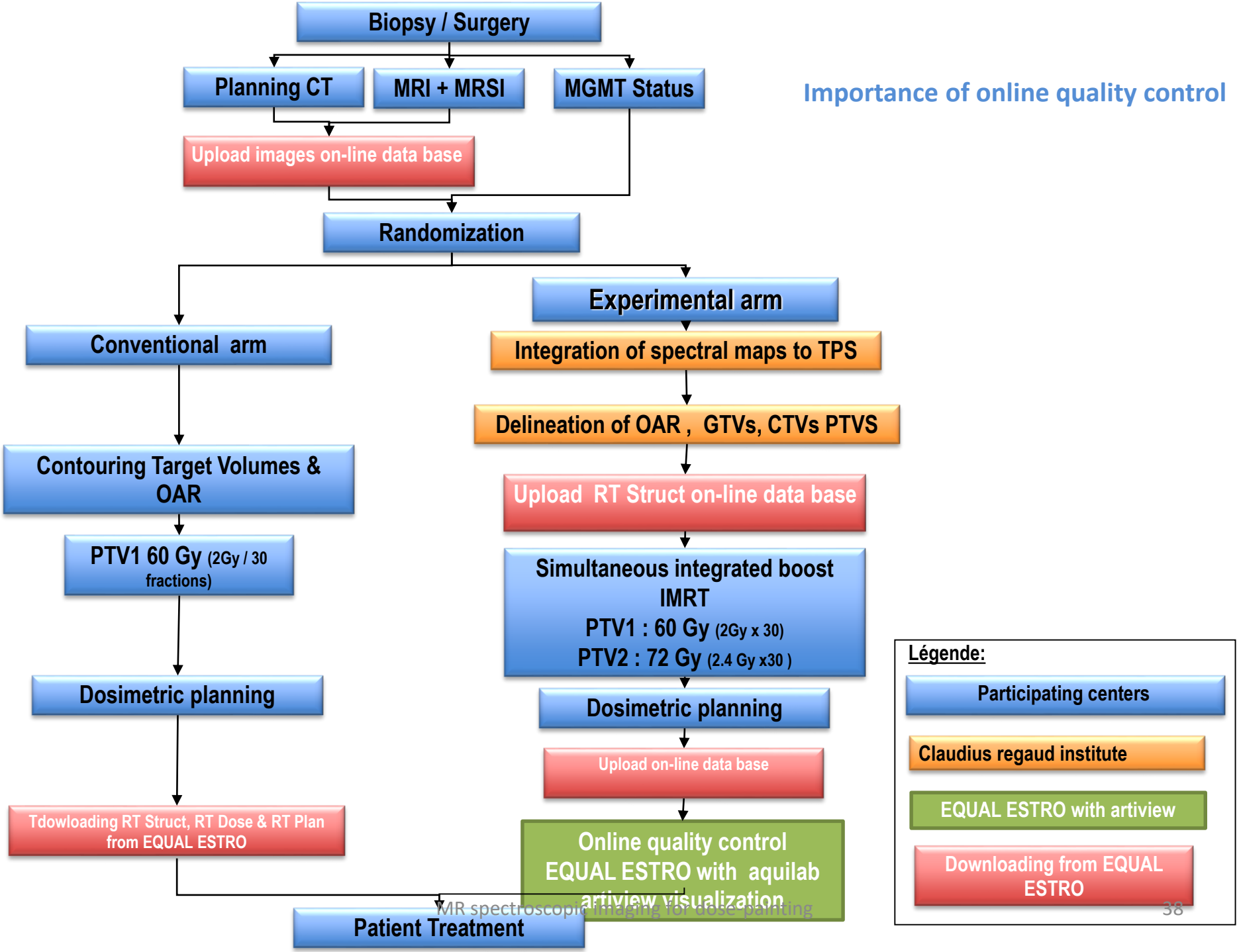
Fig 3. Time to locoregional failure by deviation status. The four cohorts are (1) compliant from the outset (n = 502), (2) made compliant following a review by the Quality Assurance Review Center (n = 86), (3) noncompliant but without predicted major adverse impact on tumor control (n = 105), and (4) noncompliant with predicted major adverse impact on tumor control (n = 87). Overall $P < .001$. Pair-wise tests were not statistically significant except for cohort 1 versus cohort 4 ($P < .001$), cohort 2 versus cohort 4 ($P = .004$), and cohort 3 versus cohort 4 ($P = .006$). TCP, tumor control probability; RT, radiotherapy.

Q4. Quality control in clinical trials

A. Quality control has no impact on survival
B. Online quality control systematically delays the start of treatment
C. Retrospective quality control is sufficient
D. online quality control of contours and dosimetry should be performed in prospective clinical trials



Importance of online quality control



Q4. Quality control in clinical trials

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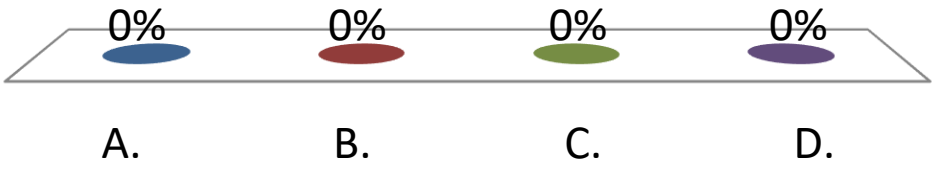
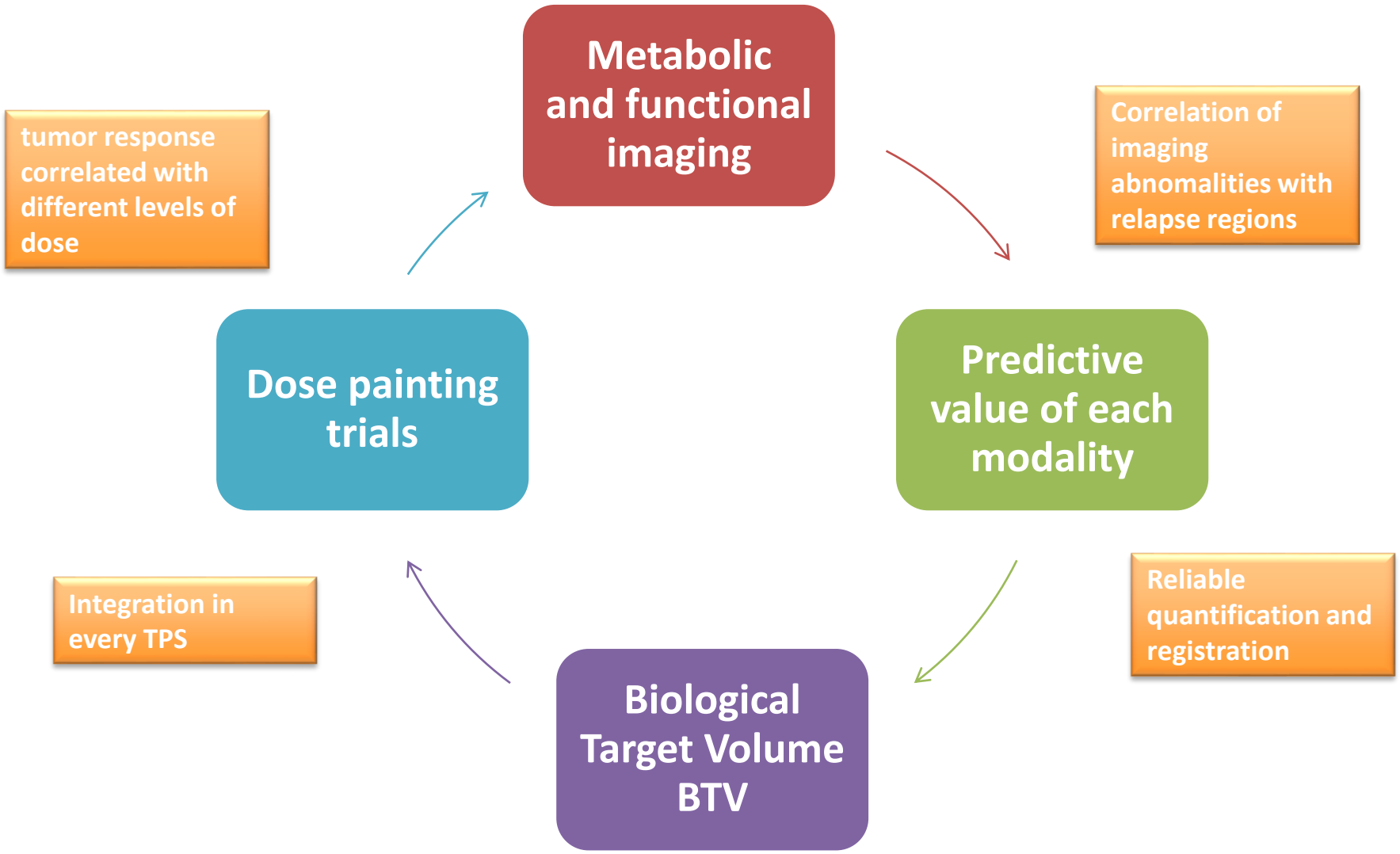


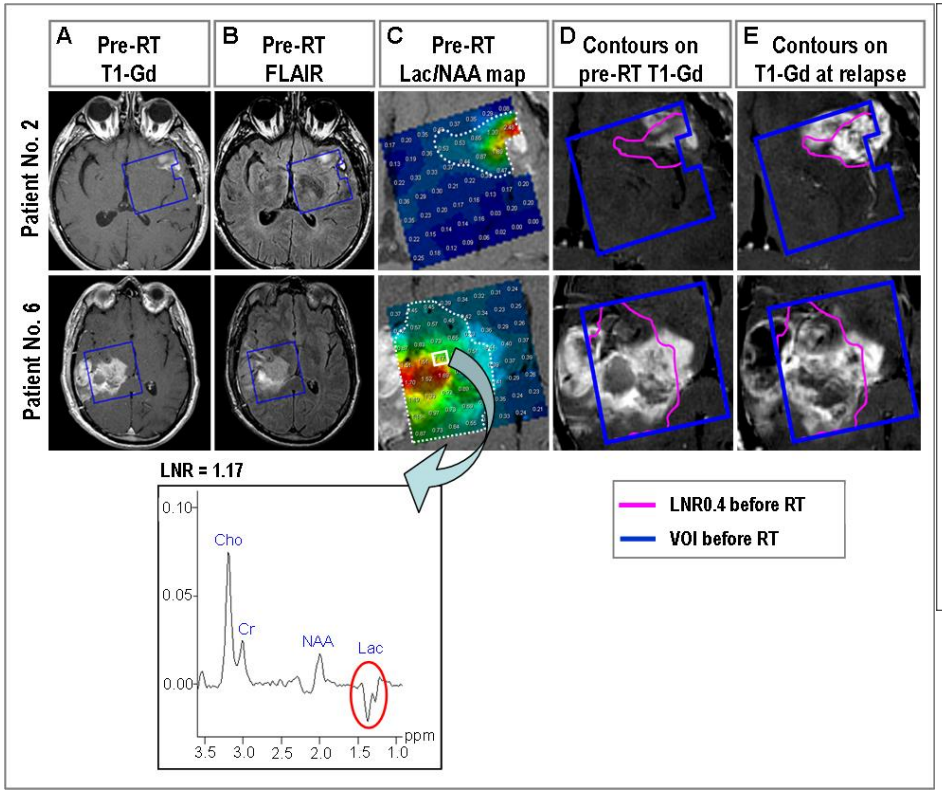
Dose painting virtuous circle



Needs and difficulties for a dose painting trial

- Easy imaging exchanges
- Reliable integration of metabolic imaging :
  - Turn MR spectroscopy map into DICOM format
  - For trials limitation to one manufacturer ,
  - spectral analysis is operator dependant
- Transfer of contours to the treatment center
- Online quality control
- Quick and reliable retrieval of data in order to rapidly perfom the analysis of relapse at the end of the trial → radiomics concept

Predictive value of MR spectroscopy lactate/Naa ratio ?



- Surrogate of tumor hypoxia
- 4 millions voxels analysed, data from previous trial Zarnestra
- Definition of a significant threshold of Lactates/NAA > 0.4 using ROC curves
- Statistically significant predictivity for relapse
  - 71% of voxels with LNR0,4 are contrast enhancing at relapse vs 10% with LNR<0,4.
- tendency for EFS

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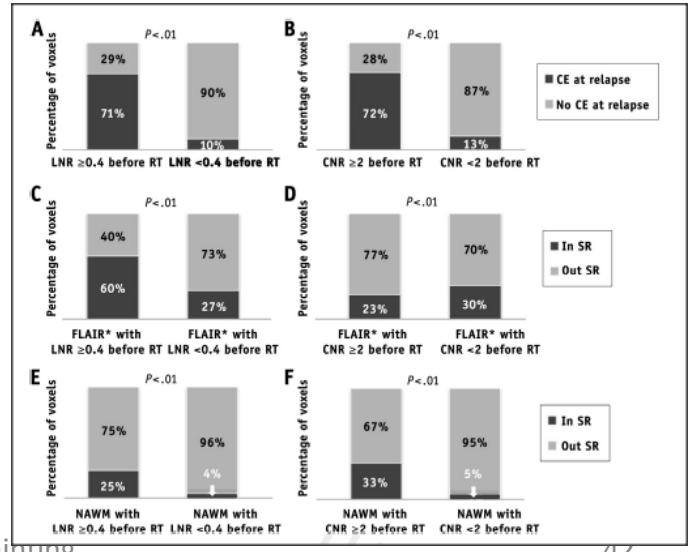
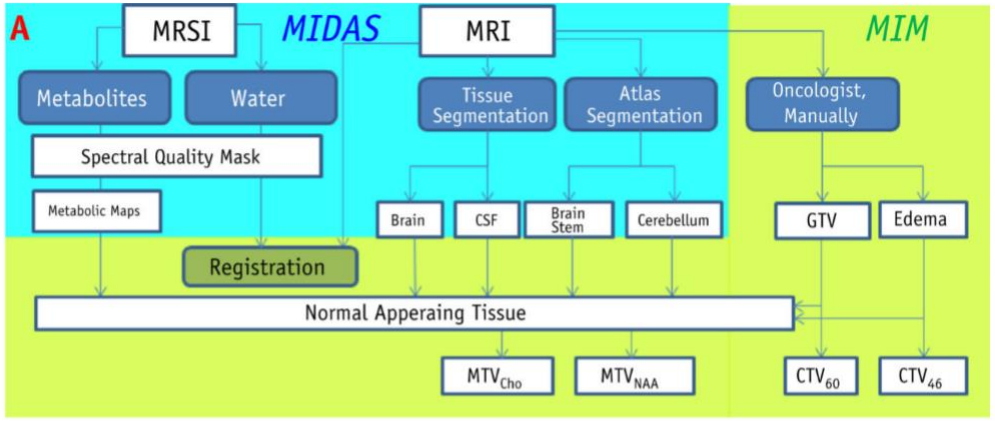
Clinical Investigation

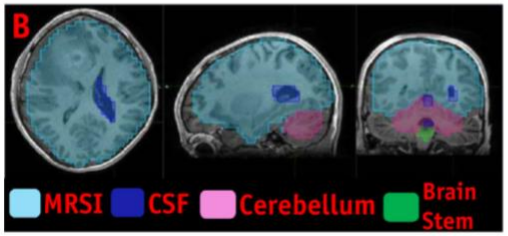
Evaluation of the Lactate-to-*N*-Acetyl-aspartate Ratio Defined With Magnetic Resonance Spectroscopic Imaging Before Radiation Therapy as a New Predictive Marker of the Site of Relapse in Patients With Glioblastoma Multiforme

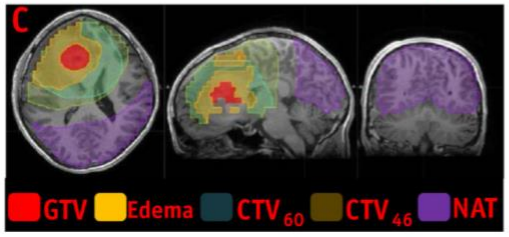
Alexandra Deviers, DVM, PhD,*,†,‡ Soléakhéna Ken, PhD,*,† Thomas Filleron, PhD,§ Benjamin Rowland, PhD,* Andrea Laruelo, MSc,* Isabelle Catalaa, MD, PhD,†,|| Vincent Lubrano, MD, PhD,†,|| Pierre Celsis, MD, PhD,† Isabelle Berry, MD, PhD,†,||,# Giovanni Mogicato, DVM, PhD,†,‡ Elizabeth Cohen-Jonathan Moyal, MD, PhD,*,¶,# and Anne Laprie, MD, PhD*,†

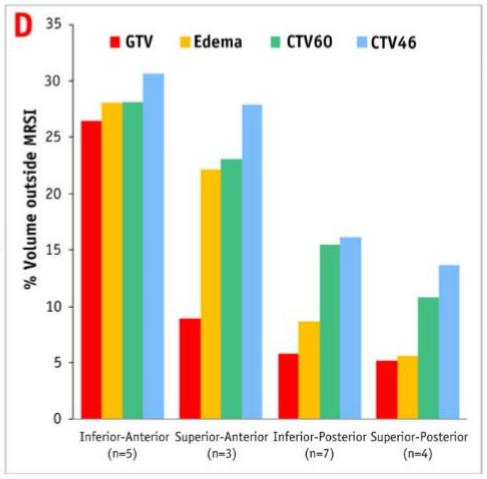


Perspectives : whole brain MR spectroscopy



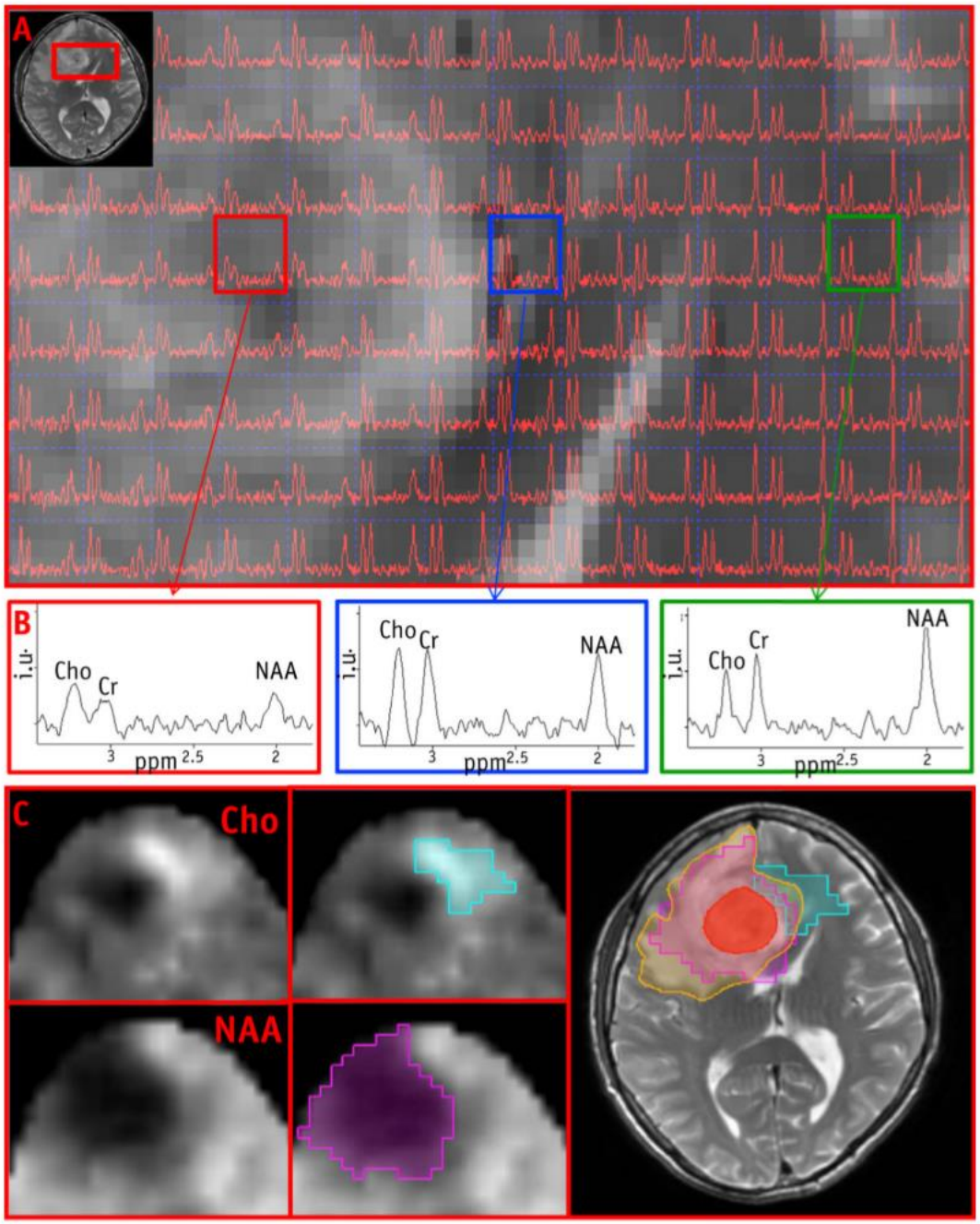






- first comprehensive evaluation of magnetic resonance spectroscopic imaging covering the entire brain

Parra et al, IJROBP 2010



Volumes related to active and infiltrative tumor were outside of the treatment area in one-third of them

Parra et al, IJROBP 2010

Parametric maps analysis

10 patients from spectro glio trial

A learning system based on support vector machines : SVM

T1-Gd and FLAIR image intensities, Choline-over-NAA(CNI), Choline

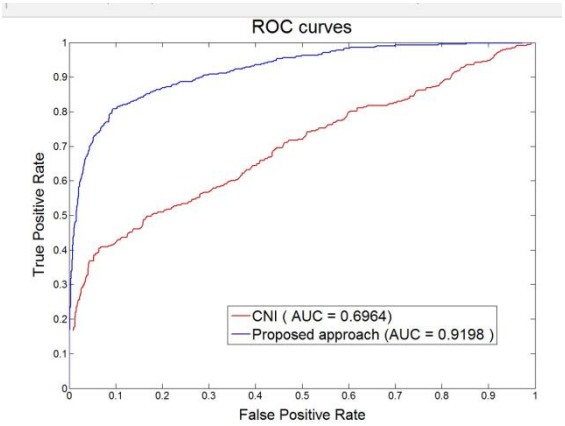
over-Creatine and Lac-over-NAA metabolite ratios, and metabolite heights

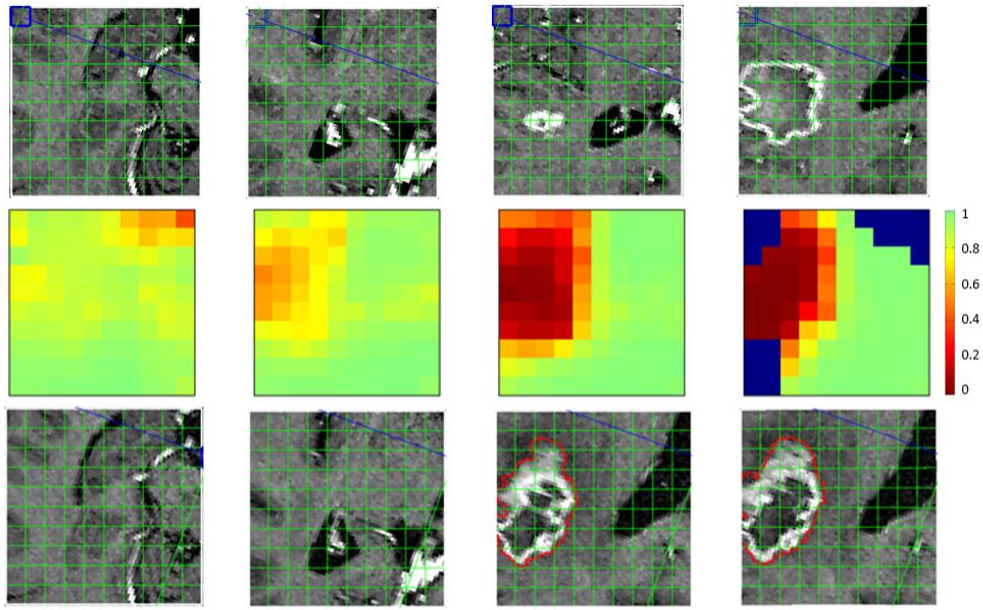
The sensitivity and specificity of the proposed system were 0.80 (0.19) and 0.87 (0.09), respectively.

Choline-to-NAA index (CNI) achieved a sensitivity of 0.62 (0.25) and a speci ficity of 0.63 (0.13).

In addition, the receiver operating characteristic (ROC)outperforms CNI

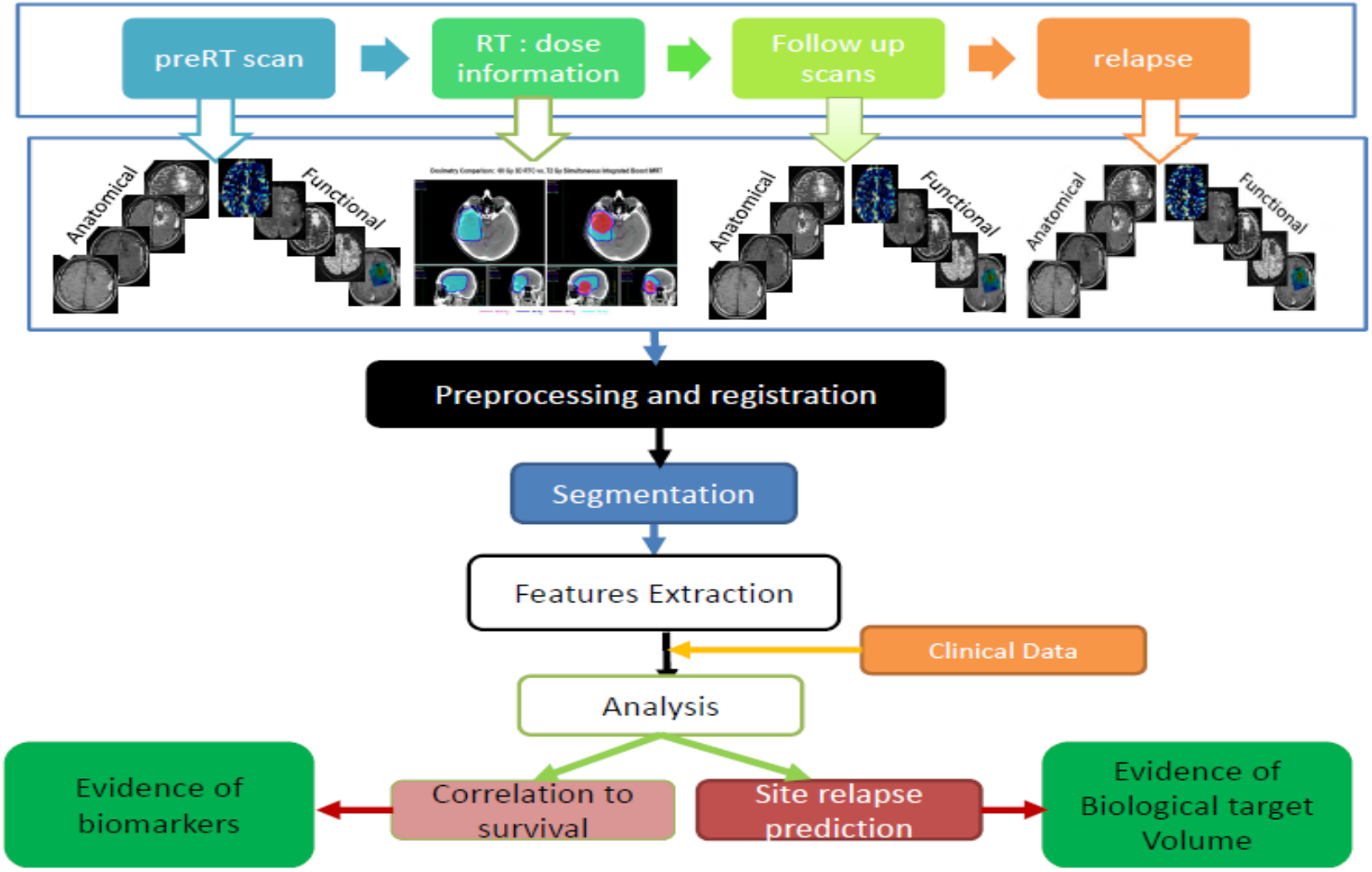
this learning scheme can provide a probability map of the area of relapse of GBM in a stable and accurate manner



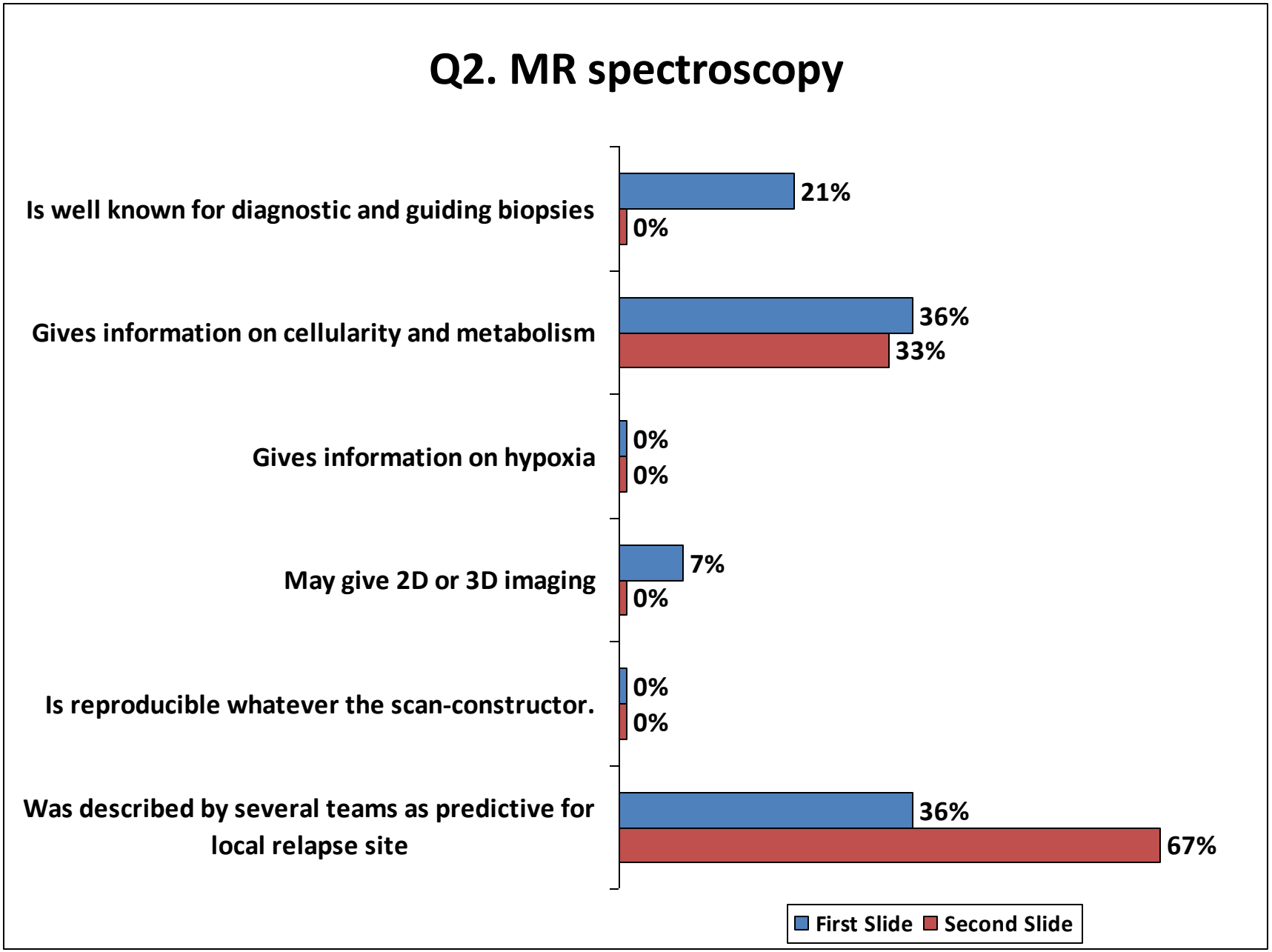


Laruelo et al, ESTRO 2016

GLIOMICS Project



Q2. MR spectroscopy



Q3. Dose-painting trials

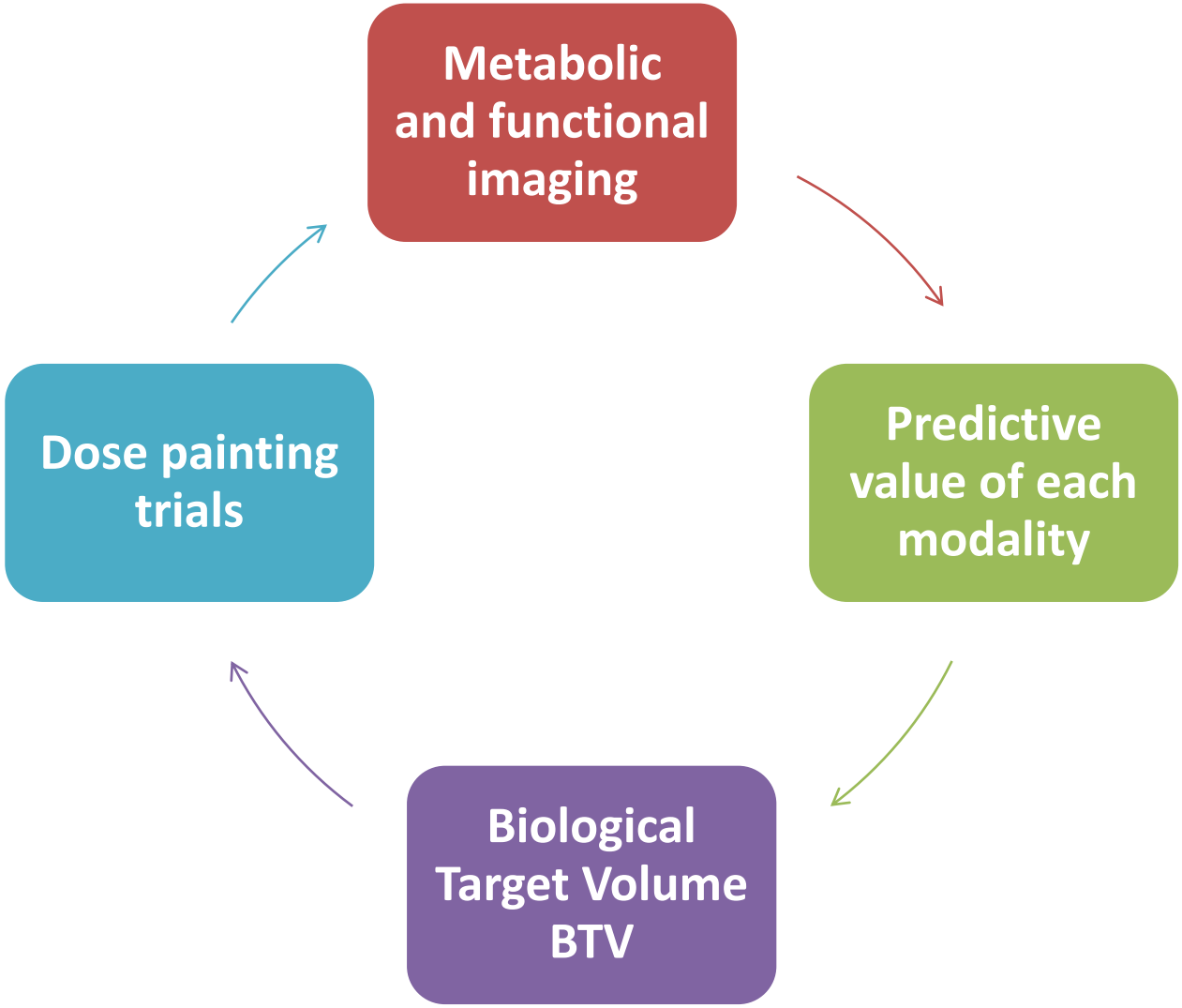
Q4. Quality control in clinical trials

MR spectroscopic imaging for dose-painting in newly diagnosed GBM - Take Home Message

- Predictive value of MR spectroscopy with CHO/NAA>2 is well-known and of LAC/NAA> 0.4 was recently described .

- 170 patients have been already included in SPECTRO GLIO , a prospective multicentric clinical dose-painting trial MR spectroscopy volumes of CHO/NAA > 2 comparing standard 60 Gy with SIB IMRT at 72 Gy

- From the ongoing SPECTRO GLIO trial, longitudinal spectroscopy, perfusion and diffusion MRI studies will allow the confirmation and/or definition of new Biological Target Volume(s) for further dose-painting trials


Metabolic and functional imaging
Predictive value of each modality
Biological Target Volume BTV
Dose painting trials