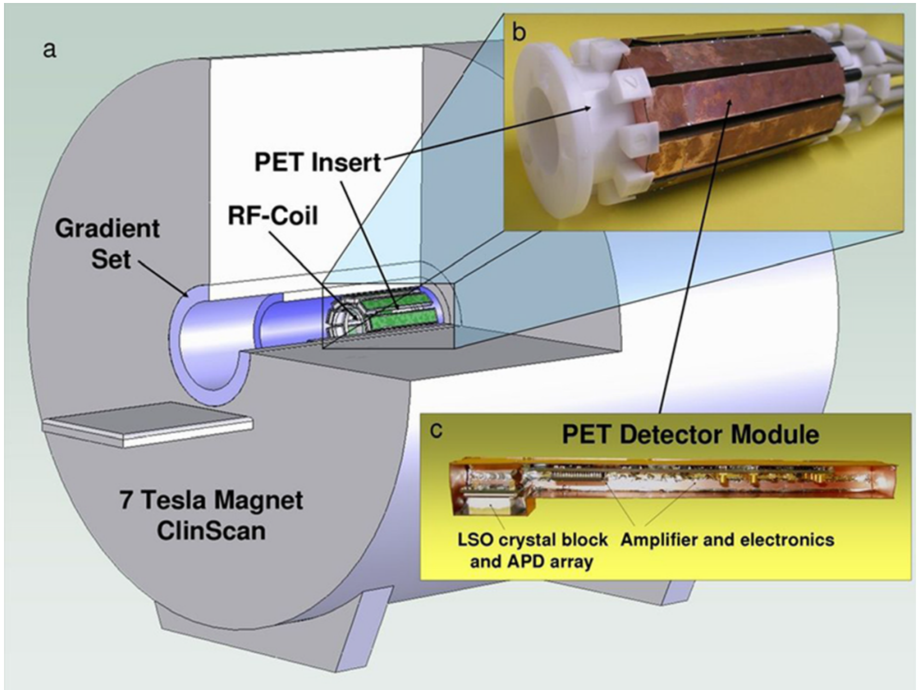
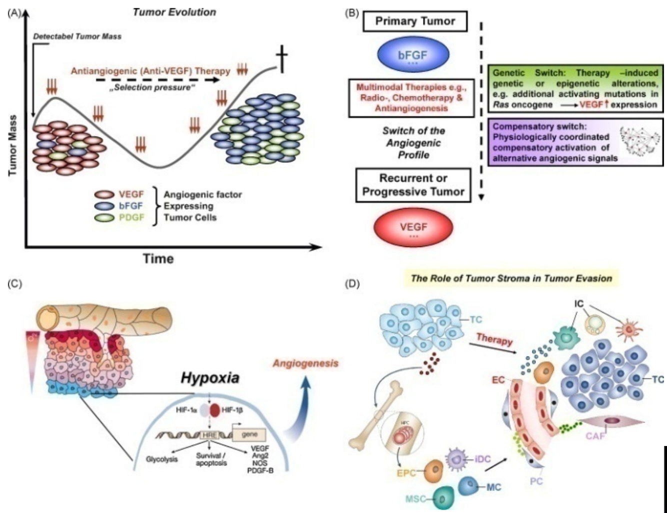
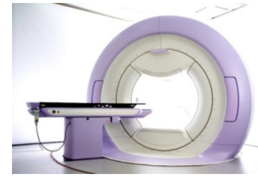


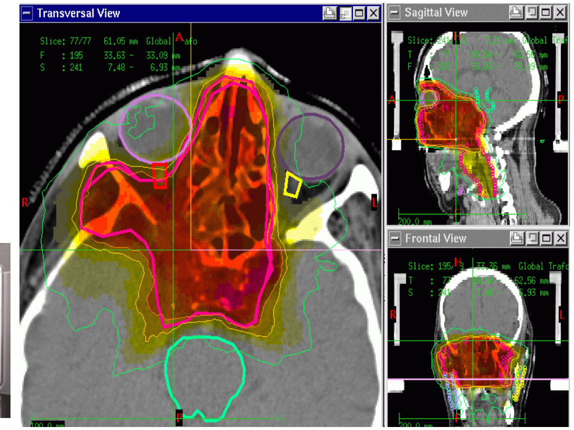
RM-PET in Radioterapia: le attese del clinico e le prospettive di impiego

Marco Krengli
Cattedra di Radioterapia
Università del Piemonte Orientale "Amedeo Avogadro"
Azienda Ospedaliero-Universitaria "Maggiore della Carità"
Novara

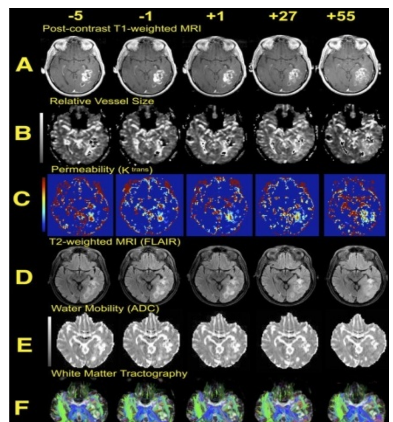
Evoluzione delle conoscenze biologiche





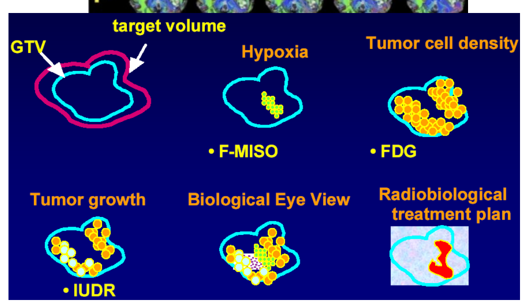


Evoluzione delle tecniche di radioterapia e dei risultati clinici



Evoluzione tecnologica

Evoluzione tecnologica



Evoluzione dell'imaging (GTV-CTV → BTV)

Metabolic and Functional Imaging

Available at present:

- Increased/decreased content of molecules
  - Active transport of metabolites → PET/SPECT
  - Passive diffusion of molecules → PET/SPECT
  - Different concentration of normal molecules → MRS
- Different distribution of H_2O → DW-MRI
- Increased blood flux (angiogenesis) → PW-MRI, P-CT

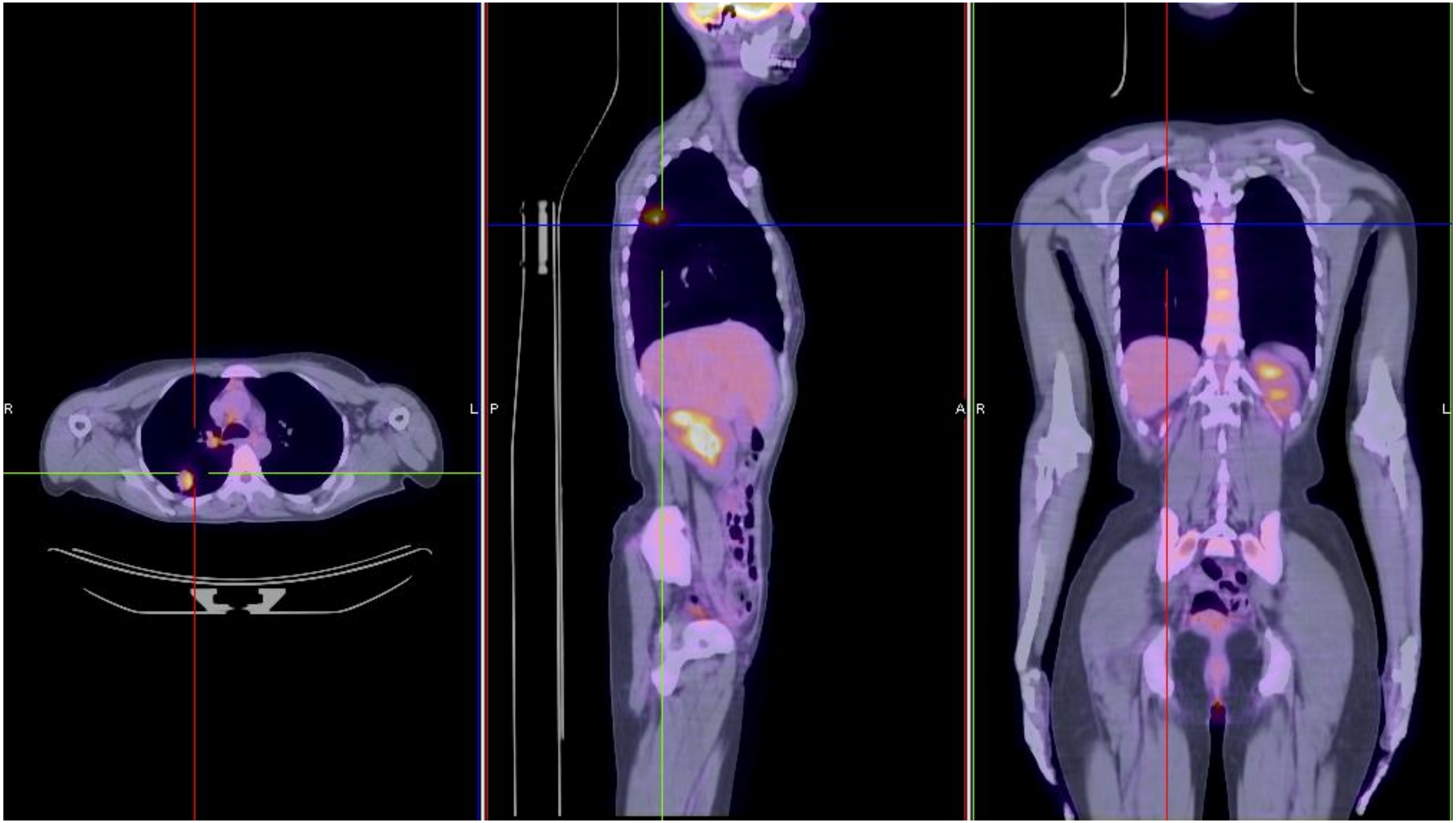
Optimal:

- Specific markers of tumor stem cells → ???

MOLECULAR IMAGING: PET TRACERS

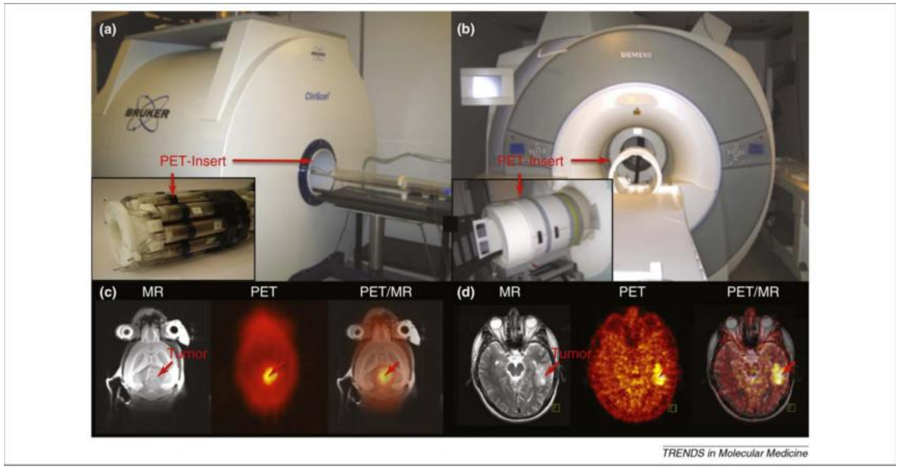
FUNCTION/METABOLISM	TRACER
Glucose metabolism	**^{18}F-fluoro-deoxy-glucose (FDG)**
DNA replication/cellular proliferation	^{11}C-carbon-thymidine ^{18}F-fluoro-thymidine (FLT)
Protein synthesis, amino acid transport	^{11}C-carbon-methionine (MET) ^{18}F-fluoro-ethyl-tyrosine (FET)
Membrane lipid synthesis	^{18}F-fluoro-acetate **^{11}C-carbon-choline** **^{18}F-fluoro-choline (FCH)**
Hypoxia	^{18}F-fluoro-misonidazole (FMISO) ^{64}Cu-copper-ATSM
Apoptosis	^{18}F-fluoro-annexin V
Angiogenesis	^{18}F-fluoro-galacto-RDG
Reporter genes	^{18}F-fluoro-deoxy-arabinofuranosyl nucleosides
Tumor therapy control	^{18}F-fluoro-uracil (FU)
Receptor binding (estrogen)	^{18}F-fluoro-estradiol (FES)
Receptor binding (somatostatine)	^{68}Ga-gallium-DOTATOC/DOTANOC

PET/CT



Limitations of PET/CT

- Sequential acquisition
- Low soft tissue contrast
- Use of ionizing radiation
- Availability of biological imaging only from PET



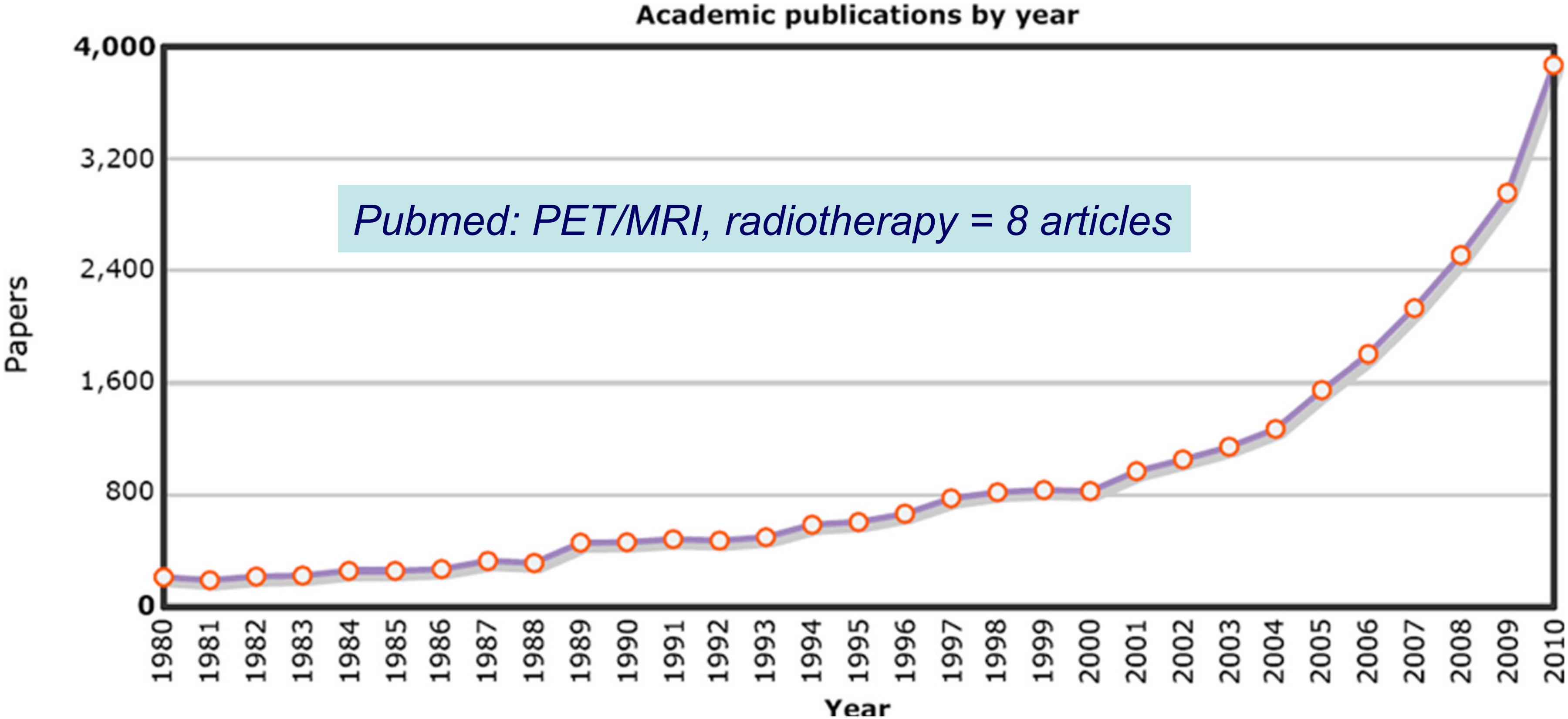
Advantages of PET/MRI

- Simultaneous acquisition
- Excellent soft tissue contrast
- Use of non-ionizing radiation
- Availability of biological imaging from both PET and MRI (MRS) and also functional imaging from fMRI

<u>Moreover:</u>

- PET image quality can be improved using magnetic fields .
- The temporal correlation of different, simultaneously acquired, functional parameters, such as receptor binding and perfusion, might new options for investigating pharmacokinetics in pre-clinical studies.

Increasing number of annual peer-reviewed publications reporting on the use of PET/MR fusion



Zaidi and Del Guerra, Med Phys, 2011

Potential added-value of new imaging modality (MRI-PET) in radiation oncology

- Radiation Therapy -

1
Diagnosis, staging and predictive / prognostic evaluation

2
GTV/CTV/PTV selection/ delineation

3
Dose/fractionation painting

4
Early response evaluation and adaptive RT

5
Final response evaluation

6
Early detection of recurrence

1 – Diagnosis, Staging and Predictive / Prognostic Evaluation

Diagnosis and Staging

- T - MRI for soft tissue contrast (standard),
  DW-MRI, PW-MRI and MRS
  PET (NSCLC)
- N - PET and MRI
- M - PET and DW-MRI

Predictive / Prognostic value

- PET for head&neck, lung, esophagus, rectum, anal canal

Use of metabolic imaging for target selection / delineation

Validation by pathology:

- FDG-PET showed smaller and more accurate target than CT and MRI in laryngeal and hypopharyngeal cancer (Daisne 2005)
- No difference between MRI and FDG-PET/CT which were larger than pathology in oral and oropharyngeal cancer (Seitz 2009)
- FDG-PET/CT was more accurate than CT in head & neck cancer (Burri 2008)
- FDG-PET/CT correlates well with pathology in esophageal cancer (Mamede 2007)
- DW-MRI correlates with nodal involvement in head & neck cancer (Dirix 2010)
- DW-MRI and DCE-MRI correlates with pathology in prostate cancer (Greonendaal 2011)

PET/MRI in Oral Cavity Cancer

- 17 pts: PET/MRI, PET/CT and pathology correlation (max diam.)

	CT	MRI	PET/CT	PET/MRI
Sensitivity (%)	55.0	80.0	80.0	90.0
Specificity (%)	81.8	79.5	84.1	90.9
Level of confidence (%)	73.4	85.9	70.0	85.9

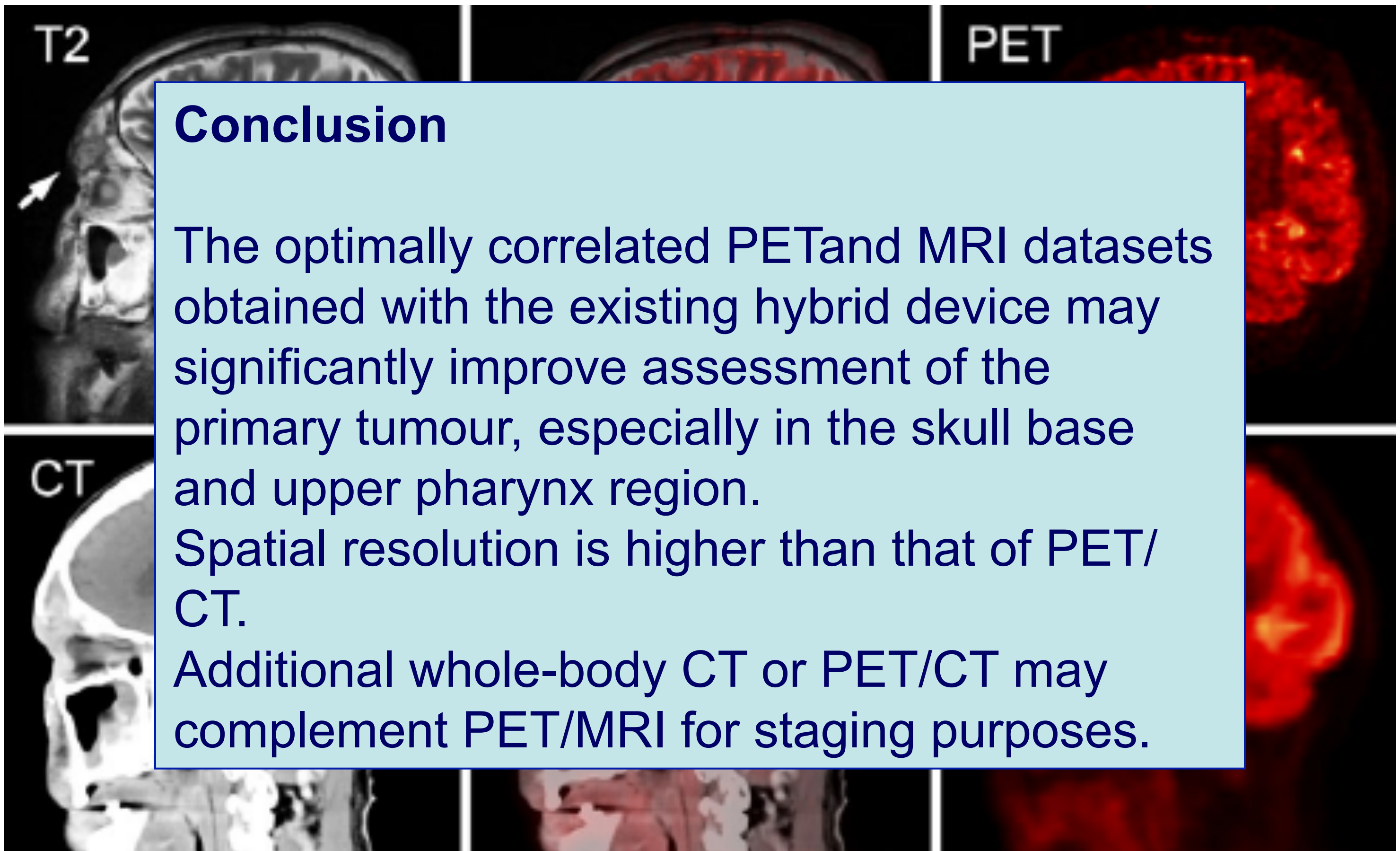
Huang 2011

Eur Radiol, 2011

Head & Neck

Feasibility of simultaneous PET/MR imaging in the head and upper neck area

Andreas Boss · Lars Stegger · Sotirios Bisdas · Armin Kolb · Nina Schwenzer · Markus Pfister · Claus D. Claussen · Bernd J. Pichler · Christina Pfannenberg



Conclusion

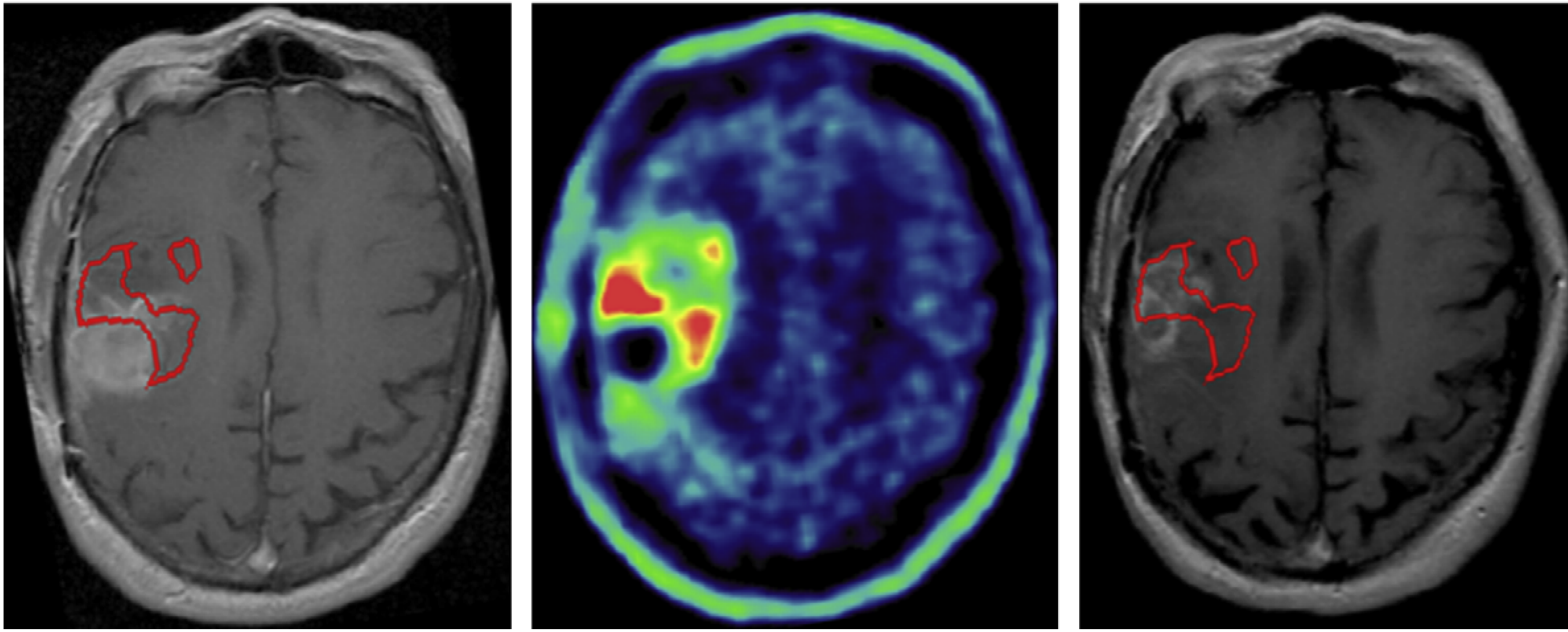
The optimally correlated PETand MRI datasets obtained with the existing hybrid device may significantly improve assessment of the primary tumour, especially in the skull base and upper pharynx region.
Spatial resolution is higher than that of PET/CT.
Additional whole-body CT or PET/CT may complement PET/MRI for staging purposes.

8 pts studied with a hybrid PET/MRI of the head and upper neck region

Supraorbital metastasis of a nasopharyngeal carcinoma

PET/MRI shows a better delineation of intraorbicular muscles

Brain Glioma: Retrospective study by MET-PET on marginal relapse



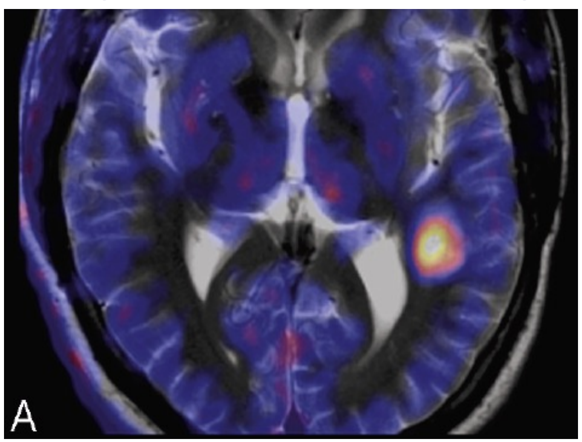
- 26 pts, GTV outlined by MRI; 5 pts had MET uptake outside the GTV
- 5/5 marginal relapses when the MET+ volume was not included in the GTV vs. 2/21

Lee et al. IJROBP 2009

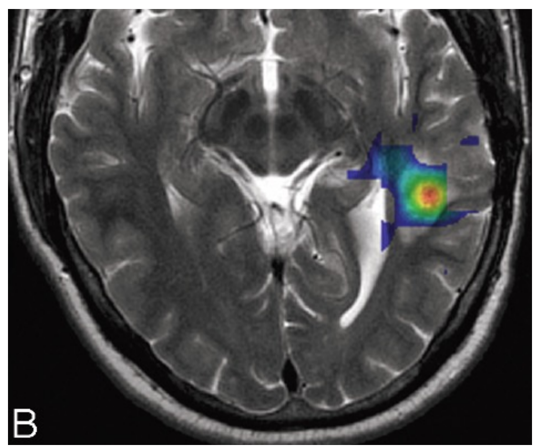
Brain Tumors

- Tracers including amino acids (e.g., 18F-fluoro-ethyl-tyrosine and 11C-methionine) can be used in conjunction with anatomical MRI for biological tumor volume delineation for the purpose of radiation therapy treatment planning (Vees 2009)

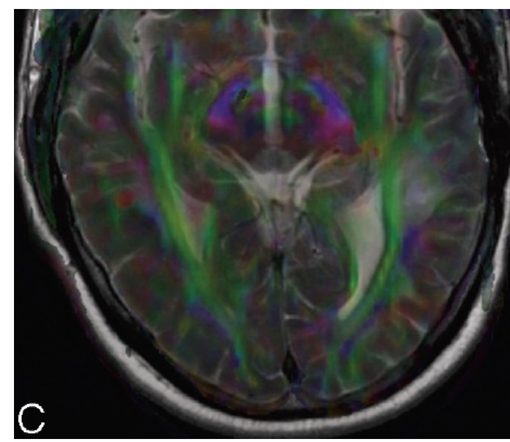
Atypical Neurocytoma



^{11}C-methionine PET/MRI



Proton MR spectroscopy



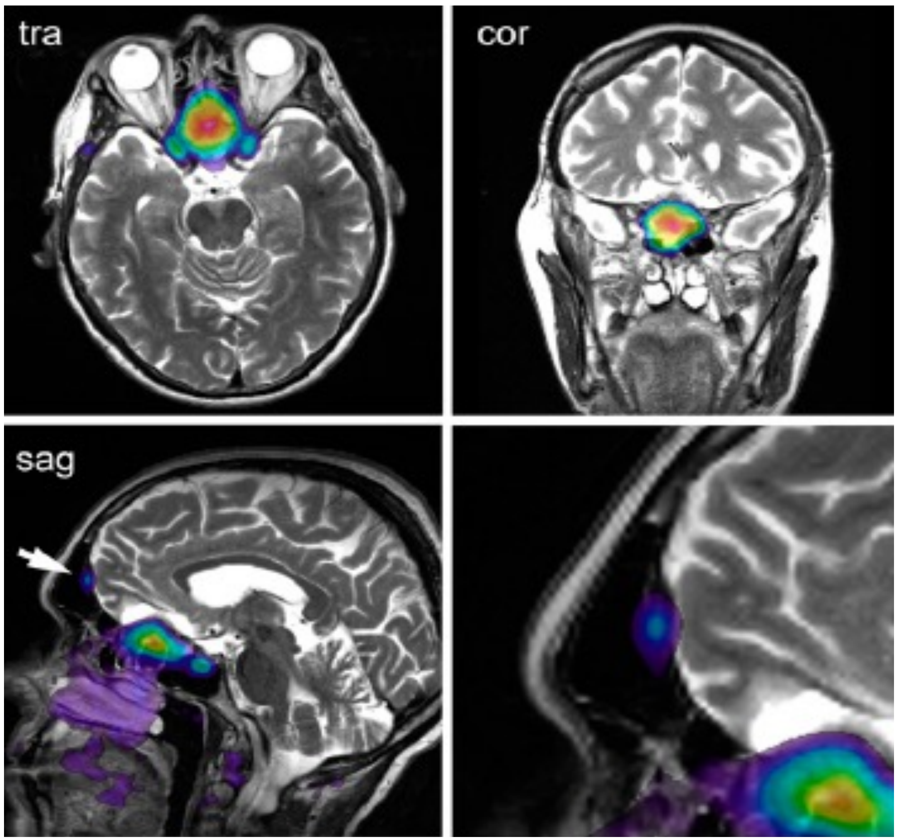
Diffusion Tensor Imaging

Bisdas, 2010

J Nucl Med 2010; 51:1198–1205

Hybrid PET/MRI of Intracranial Masses: Initial Experiences and Comparison to PET/CT

Andreas Boss*[1,2], Sotirios Bisdas*[3], Armin Kolb[2], Matthias Hofmann[2,4], Ulrike Ernemann[3], Claus D. Claussen[1], Christina Pfannenberg[1], Bernd J. Pichler[2], Matthias Reimold[5], and Lars Stegger[1,6]



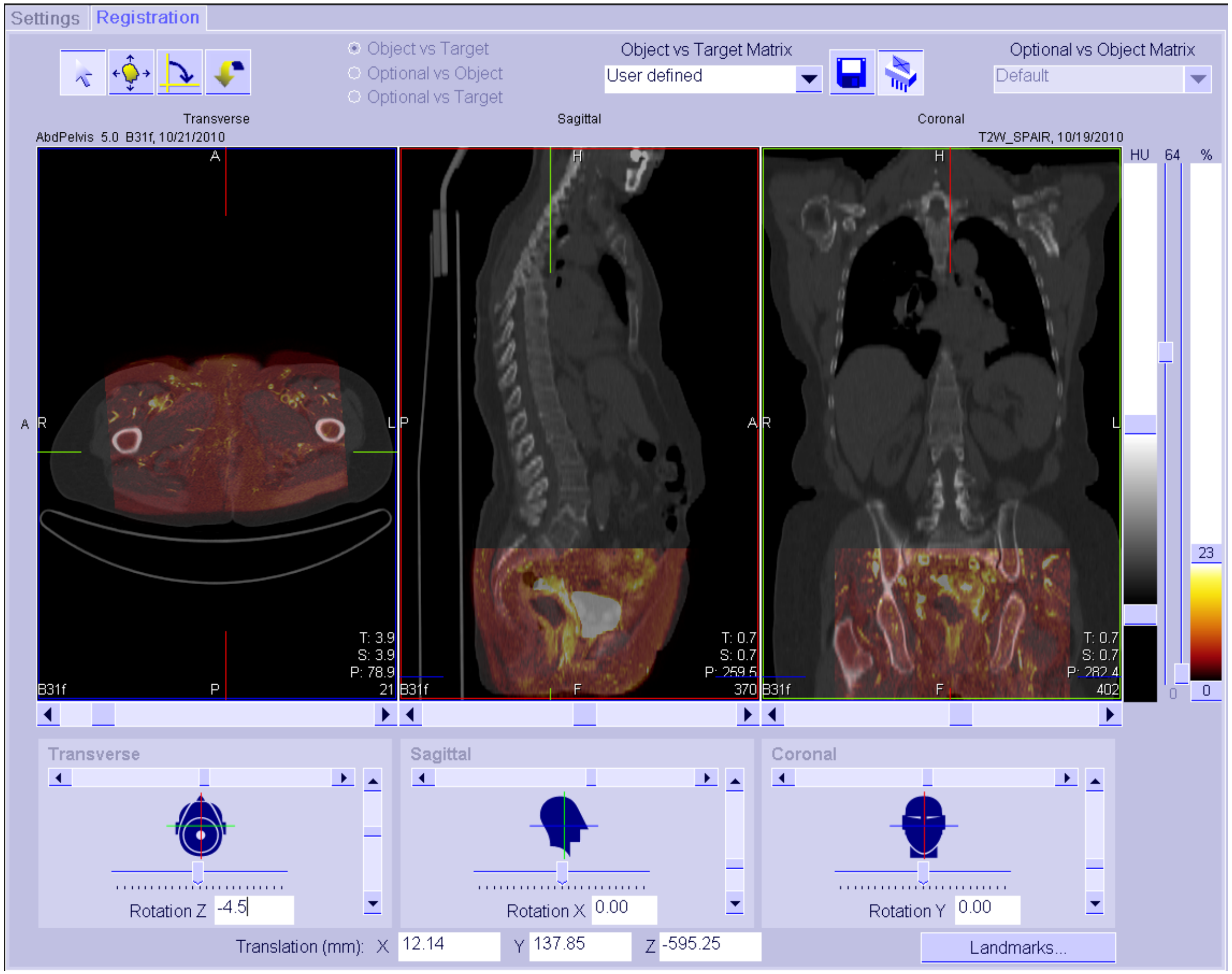
PET/MR images of patient with meningioma, extending from olfactory sulcus to sphenoidal and ethmoidal paranasal sinus. T2-MRI are fused with 68Ga-DOTATOC PET.

In sagittal image: small satellite lesion is visible in dorsal area of frontal sinus; lower-right-side image shows enlargement of this area.

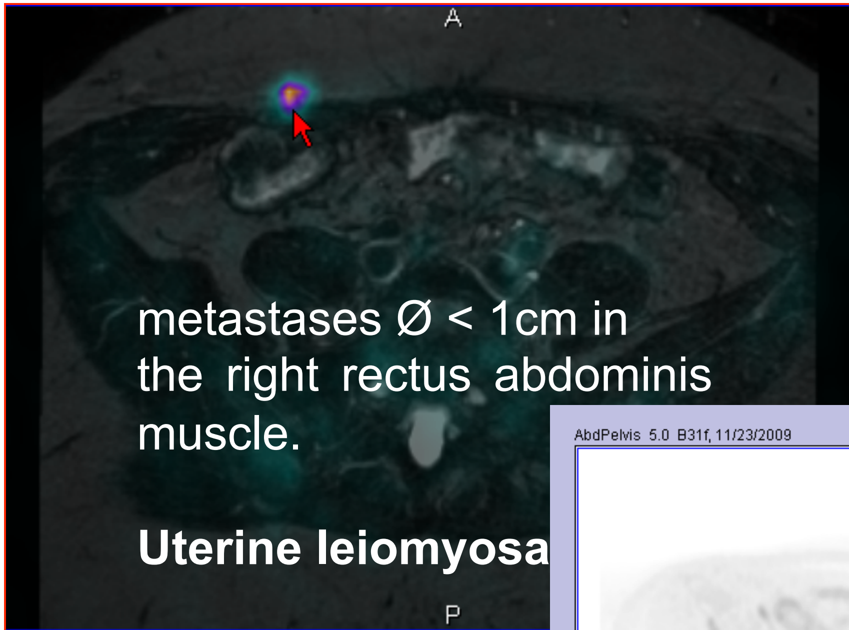
This satellite lesion was detected only on PET, and was included in irradiation field

Pelvic staging in gynecologic malignancies: correlation between 18F-FDG PET/CT, MR (T2-FS) and DWI

25 pts with gynecologic malignancies (9 cervical, 7 ovarian, 7 endometrial and 2 vaginal cancers)

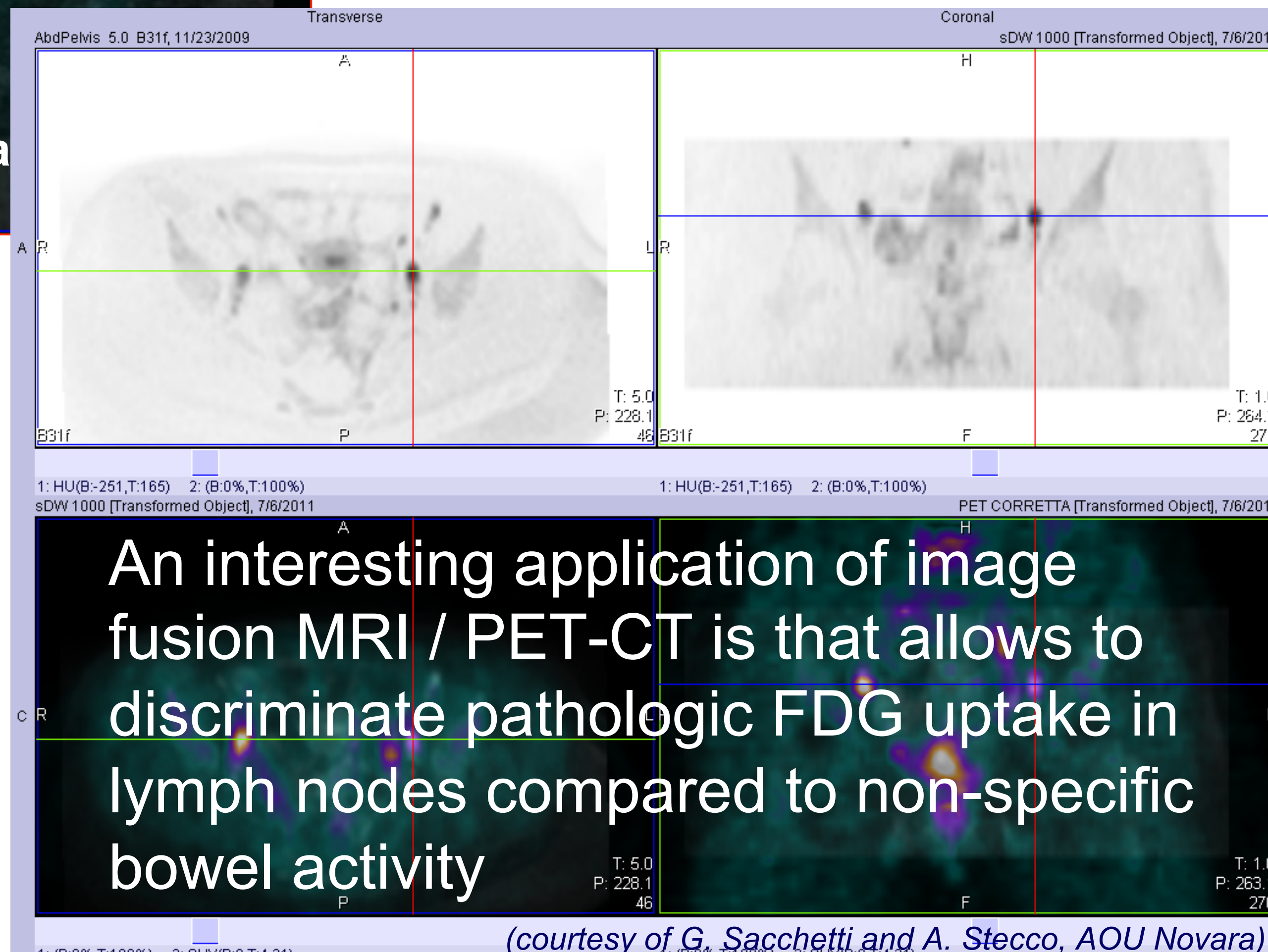


(courtesy of G. Sacchetti and A. Stecco, AOU Novara)



metastases Ø < 1cm in the right rectus abdominis muscle.

Uterine leiomyosa



An interesting application of image fusion MRI / PET-CT is that allows to discriminate pathologic FDG uptake in lymph nodes compared to non-specific bowel activity

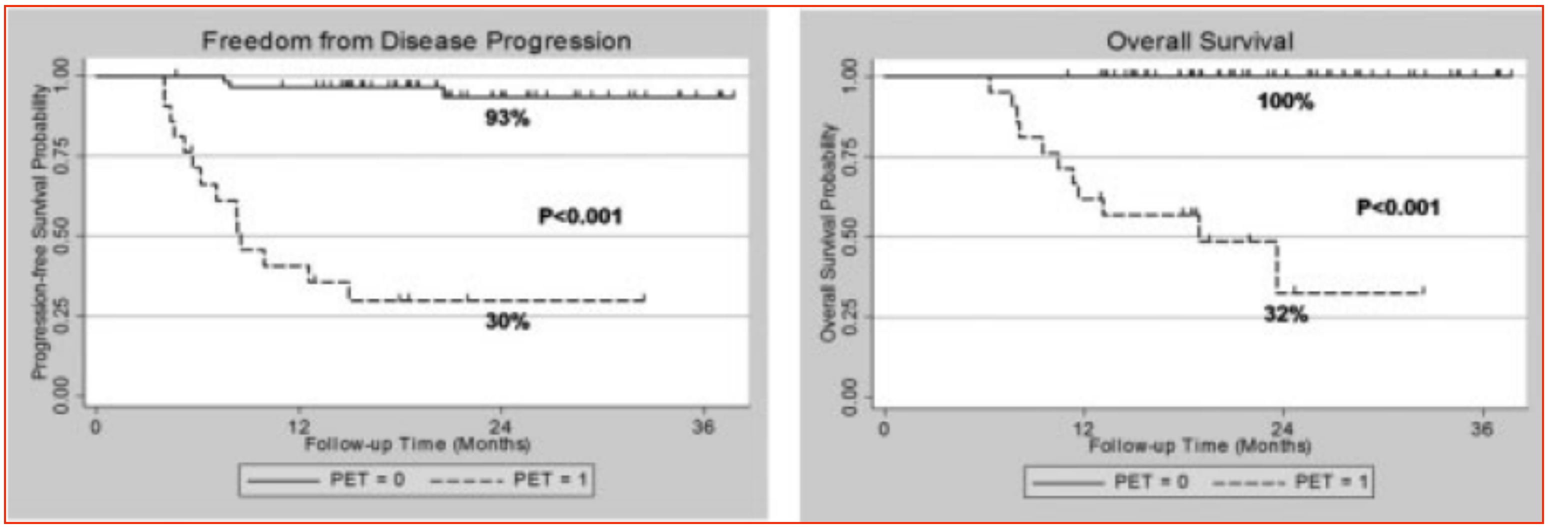
(courtesy of G. Sacchetti and A. Stecco, AOU Novara)

Predictive and prognostic value of molecular imaging

Kao J et al. Cancer 2009

The Diagnostic and Prognostic Utility of Positron Emission Tomography/ Computed Tomography-Based Follow-Up After Radiotherapy for Head and Neck Cancer

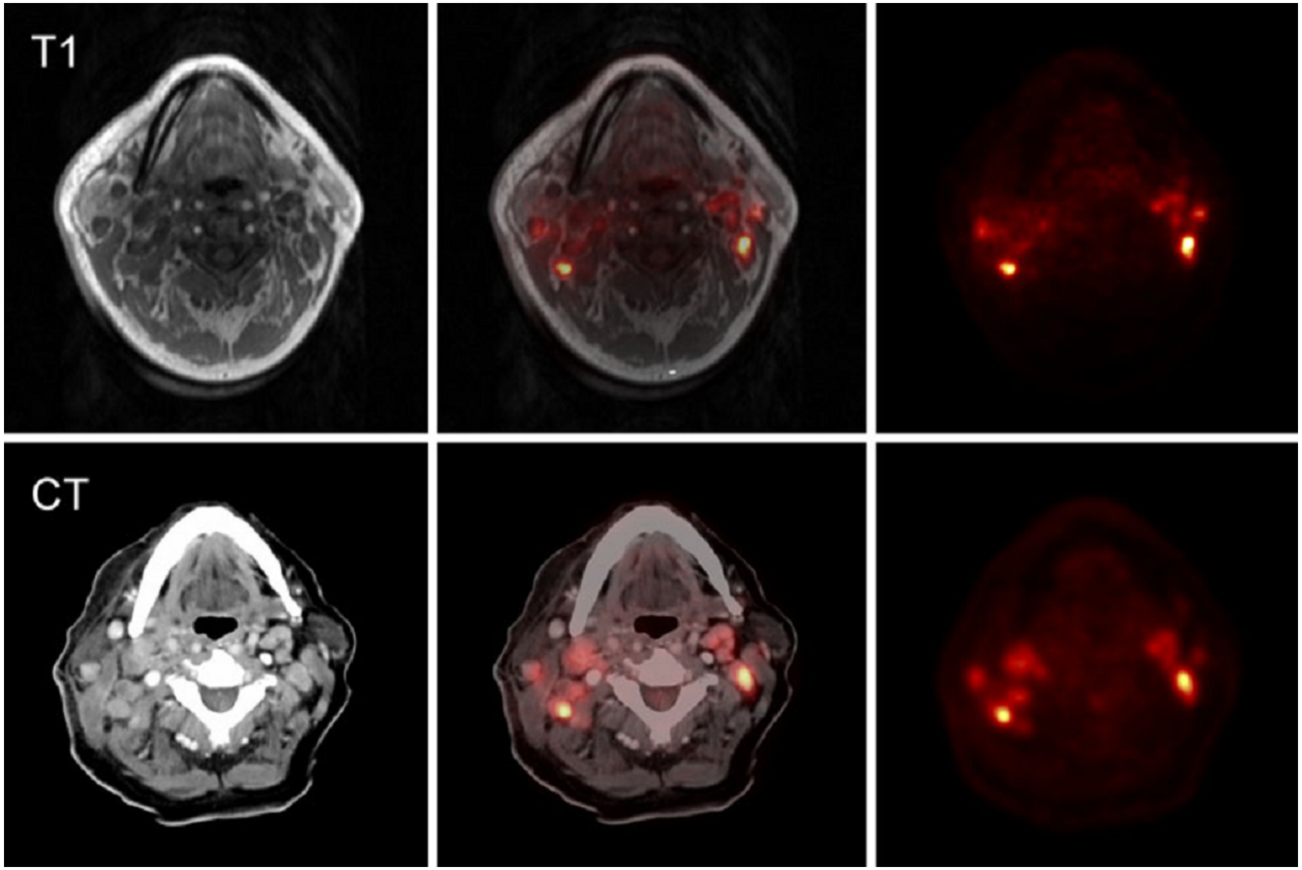
- **80 pts, stage II-IV**
- **Definitive RT to 41 pts**
  Adjuvant RT to 39 pts
- **Serial PET/CT *2-4* months and *4-6* months after IMRT**



Negative PET/CT within 6 months after RT were associated with improved:

- 2 years locoregional control (97% vs 49%, p< 0.001)
- distant disease control (95% vs 46%, p< 0.001)
- OS (100% vs 32%, p< 0.001)

2 – GTV, CTV, PTV Selection and Delineation



- PET/MRI + CT or PET/CT + MRI ?

HEAD & NECK—DOI 10.1002/hed April 2009

USE OF SINGLE MRI AND 18F-FDG PET-CT SCANS IN BOTH DIAGNOSIS AND RADIOTHERAPY TREATMENT PLANNING IN PATIENTS WITH HEAD AND NECK CANCER: ADVANTAGE ON TARGET VOLUME AND CRITICAL ORGAN DELINEATION

Miriam Gardner, MD, PhD,[1] Philippe Halimi, MD,[2] Danielle Valinta, PhD,[1]
Marie-Madeleine Plantet, MD,[3†] Jean-Louis Alberini, MD,[4] Myriam Wartski, MD,[4] Alain Banal, MD,[5]
Stephane Hans, MD,[6] Jean-Louis Floiras, MD,[1] Martin Housset, MD,[7] Alain Labib, MD[1]

Change of treatment volume:

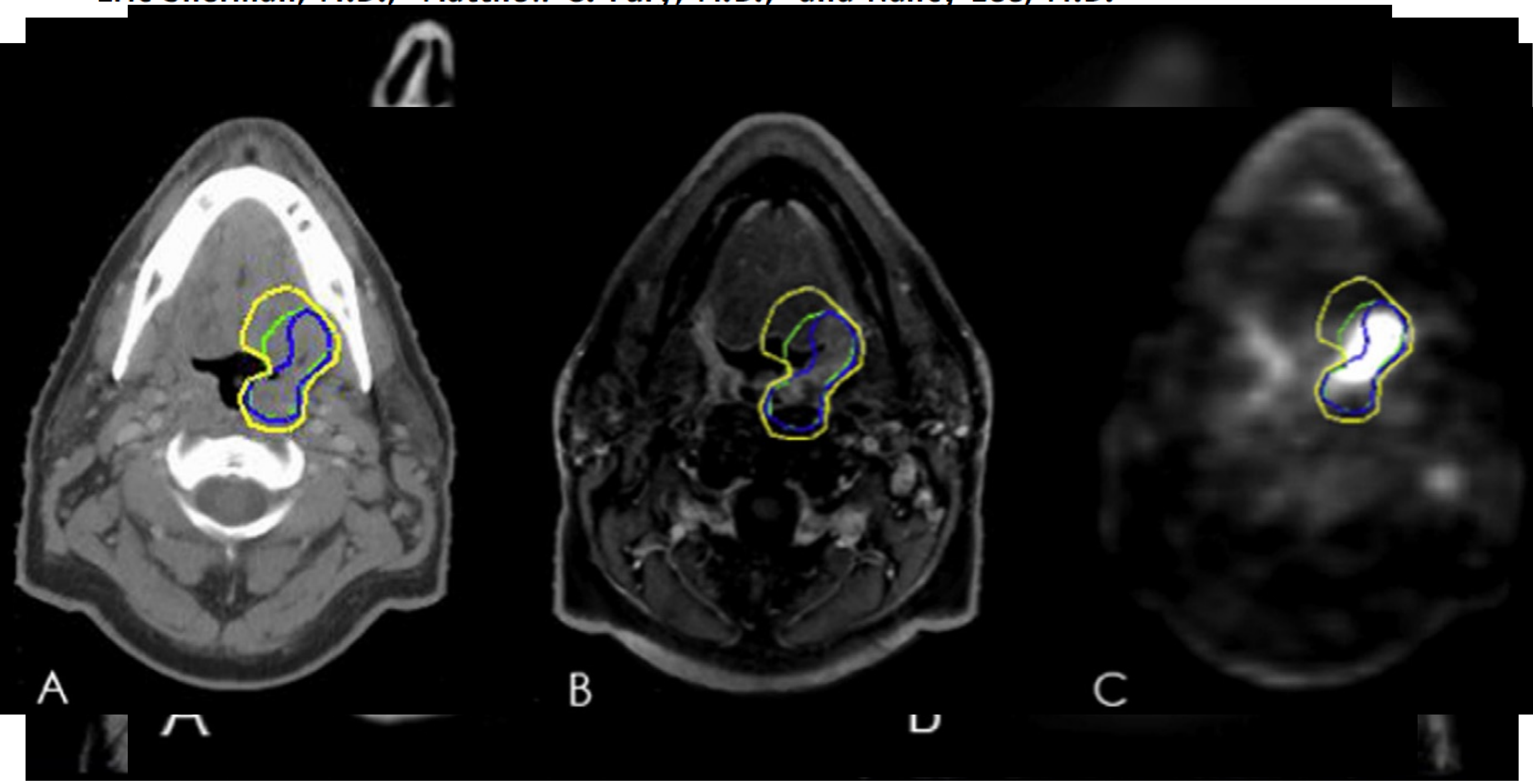
• GTV (FDG-PET/CT)	15/35	43 %
• Parotid glands (MRI)	12/35	34 %
• Optic pathway (MRI)	7/35	20 %

Advantages: *intracranial tumor extension, heavy denta work, contraindication for contrast-enhanced CT*

Int J Radiation Oncol Biol Phys, Vol. ■, No. ■, pp. 1–8, 2011

Target Volume Delineation in Oropharyngeal Cancer: Impact of PET, MRI, and Physical Examination

Anuradha Thiagarajan, M.D.,* Nicola Caria, M.D.,* Heiko Schöder, M.D.,† N. Gopalakrishna Iyer, M.D.,‡ Suzanne Wolden, M.D.,* Richard J. Wong, M.D.,‡ Eric Sherman, M.D.,§ Matthew G. Fury, M.D.,§ and Nancy Lee, M.D.*



RM E FDG PET-TC PER LA DELINEAZIONE DEL VOLUME TARGET DEI CARCINOMI DELL'OROFARINGE E DELLA RINOFARINGE TRATTATI CON IMRT.

L. Masini, L. Deantonio, T. Caltavuturo, C. Pisani, G. Loi, M. Brambilla, M. Krengli - AOU "Maggiore della Carità", Novara

(Poster AIRO Genova 2011)

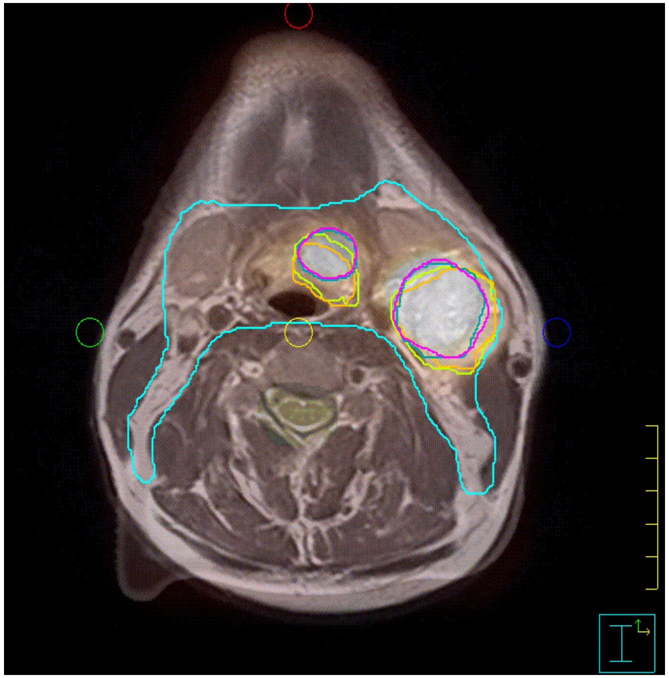
- 21 pazienti affetti da carcinoma spinocellulare in stadio II-IV (13 orofaringe, 8 rinofaringe)
- Tx: IMRT concomitante a chemioterapia con cisplatino.
- PET-TC acquisita in posizione di trattamento.
- Le immagini in T1 e T2 della RM sono state co-registrate con quelle della PET-CT utilizzando i reperi ossei.
- GTV e CTV sono stati contornati sulla PET-TC e sulla RM da due operatori.

Risultati:

- **In 6 pazienti (22%), la PET-TC ha modificato lo stadio di N:**
  - **3 casi con N+ nel collo controlaterale**
  - **3 casi con N+ nel collo omolaterale**

- la RM ha diagnosticato l'estensione in base cranica in 2 casi di rinofaringe, dove la PET rimaneva dubbia (T3 _ T4).

- Per quanto riguarda la delineazione dei volumi:
  - Il volume RM-GTV mediano è di 53,8 cc (range 6,5-62,6 cc) e il volume PET-TC-GTV mediano è di 41,2 cc (3,2-50,3 cc).
  - Il volume PET-TC-GTV risulta inferiore del volume RM-GTV con una differenza media di 6,2 cc (range 12,2-3,2 cc).
  - Variabilità interosservatore media è stata di 2,2 cc (range 1,9-2,5 cc) con la RM e di 1,3 cc (range 0,9-2,5 cc) con la PET-TC.

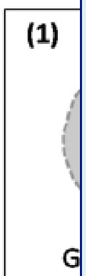


Ca G3 base lingua, cT2N2b
RM-GTV e PET-GTV identintificati dal 1° radioterapista
RM-GTV e PET-GTV identificati dal 2° radioterapista

Int J Radiation Oncology Biol Phys, 2011

SIMULTANEOUS ^{68}GA-DOTATOC-PET/MRI FOR IMRT TREATMENT PLANNING FOR MENINGIOMA: FIRST EXPERIENCE

Case



This preliminary investigation showed that due to its improved PET resolution, simultaneous PET/MR imaging allows a more detailed visualization of meningiomas, especially in small infiltrative regions that might not be detected with larger PET systems resulting in a change of the GTV, CTV and PTV.

GTV$_{MRI}$;
GTV$_{PET2}$;

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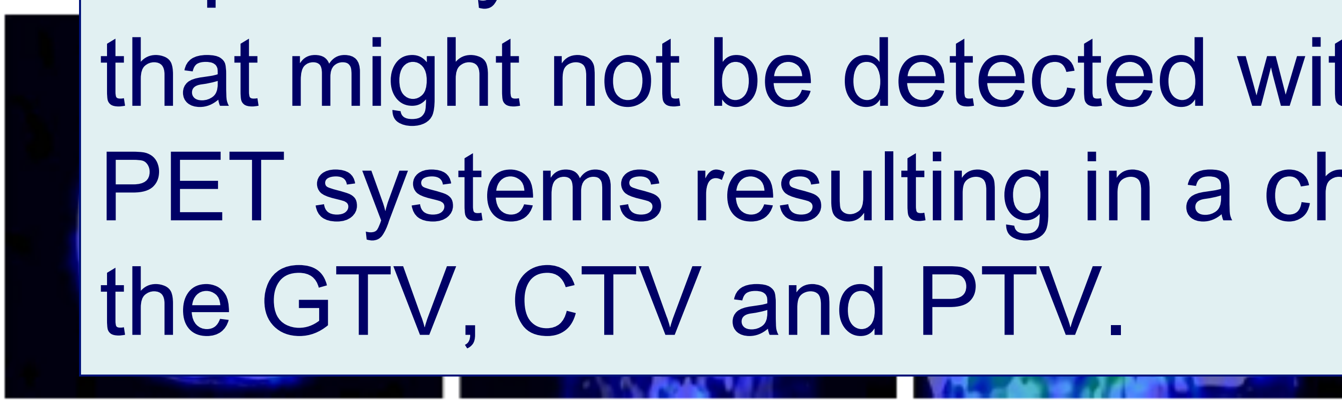
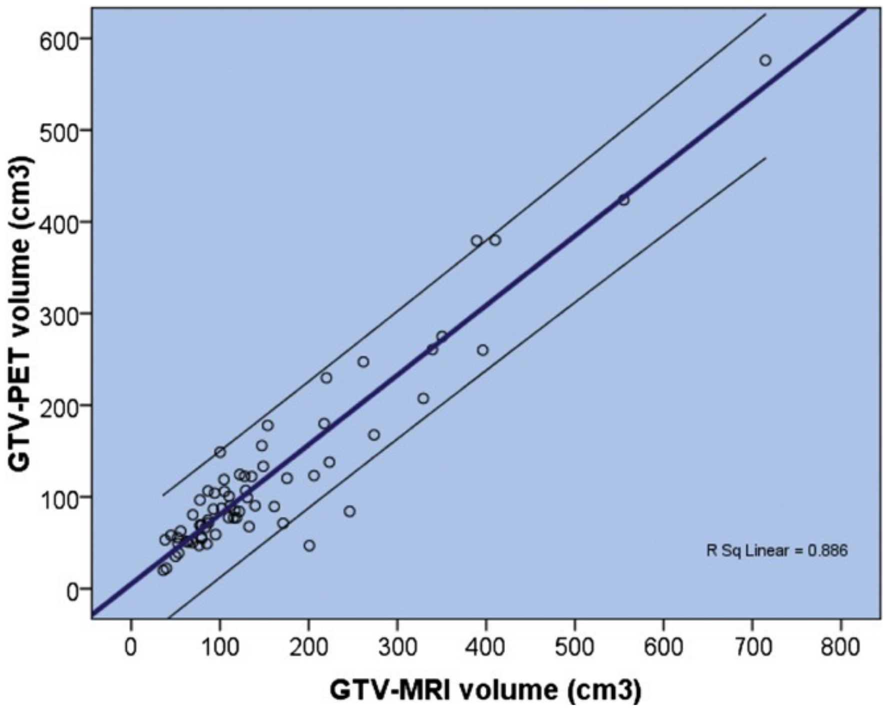
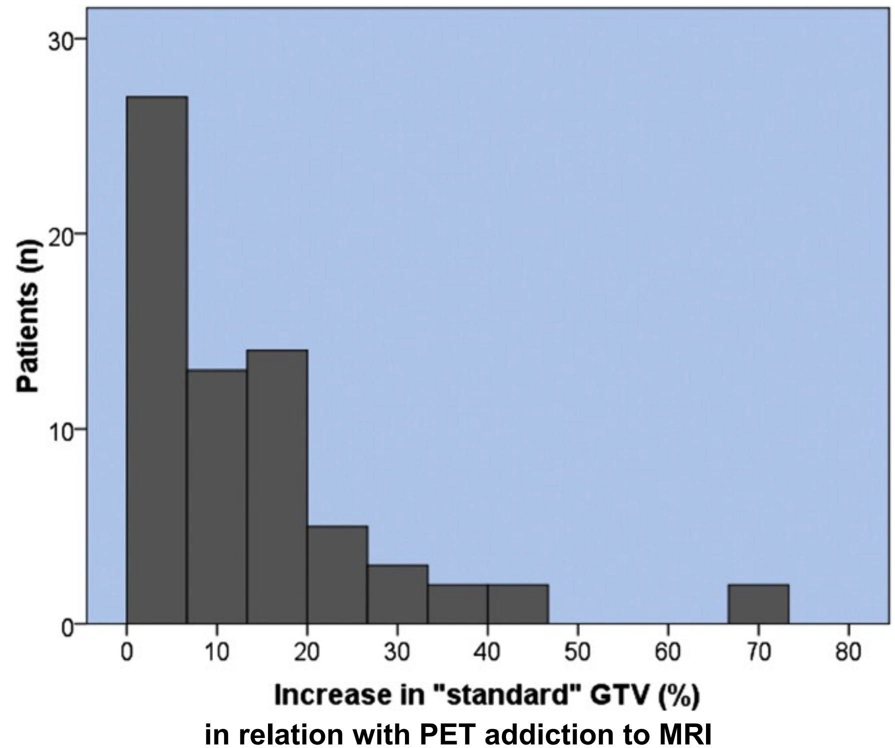


MRI and PET/CT in Rectal Cancer





Braendengen, IJROBP, 2011

3 – Dose / fractionation Painting

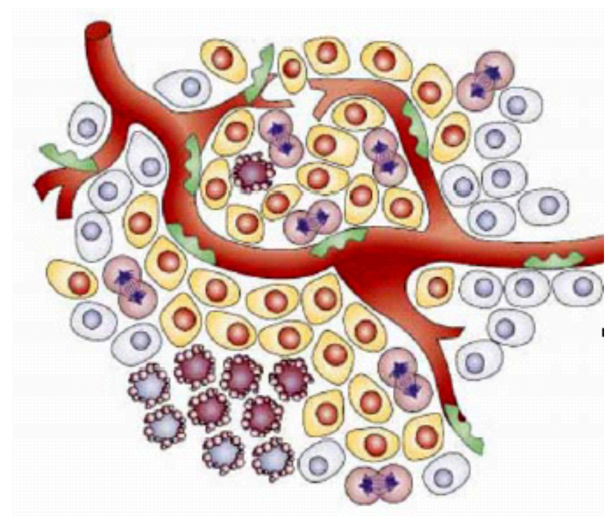
Tumor tissue is heterogeneous and different volumes may need different dose / fractionation / (dose rate? LET/RBE?):

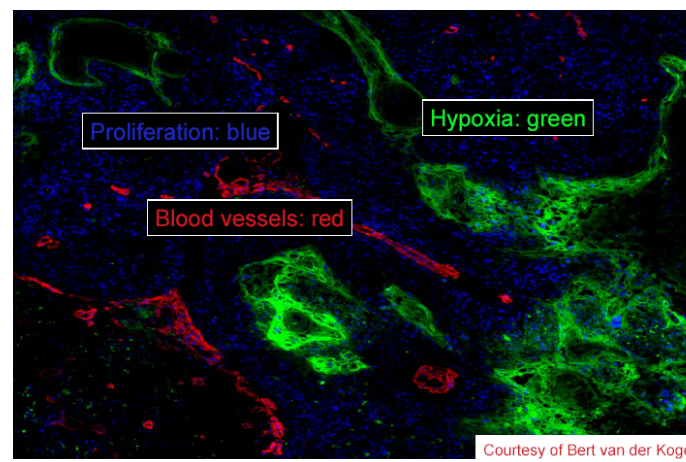
- Different oxygenation (hypoxic volumes)

- Different proliferation

- Neoangiogenesis

- Presence of different concentration of tumor stem cells





Courtesy of Bert van der Kogel

Dose Painting in Radiotherapy for Head and Neck Squamous Cell Carcinoma: Value of Repeated Functional Imaging with ^{18}F-FDG PET, ^{18}F-Fluoromisonidazole PET, Diffusion-Weighted MRI, and Dynamic Contrast-Enhanced MRI

Dirix P et al, J Nucl Med, 2009

Week	pre-RT	1	2	3	4	5	6	...	9	...	14

- Good correlation between CT and T2- MRI, T1- MRI

negatively with DFS

- MRI during treatment demonstrates clear shrinkage of the tumor volume emphasizing the need for truly adaptive RT

- DWMRI showed that lesions in which locoregional recurrence developed had significantly lower apparent diffusion coefficients on scans during wk 4 of RT and at 3 wk after treatment.

- all ***locoregional failures*** occurred within the initial 18F-FDG–avid volume. This finding suggests that the GTVFDG within the GTVCT

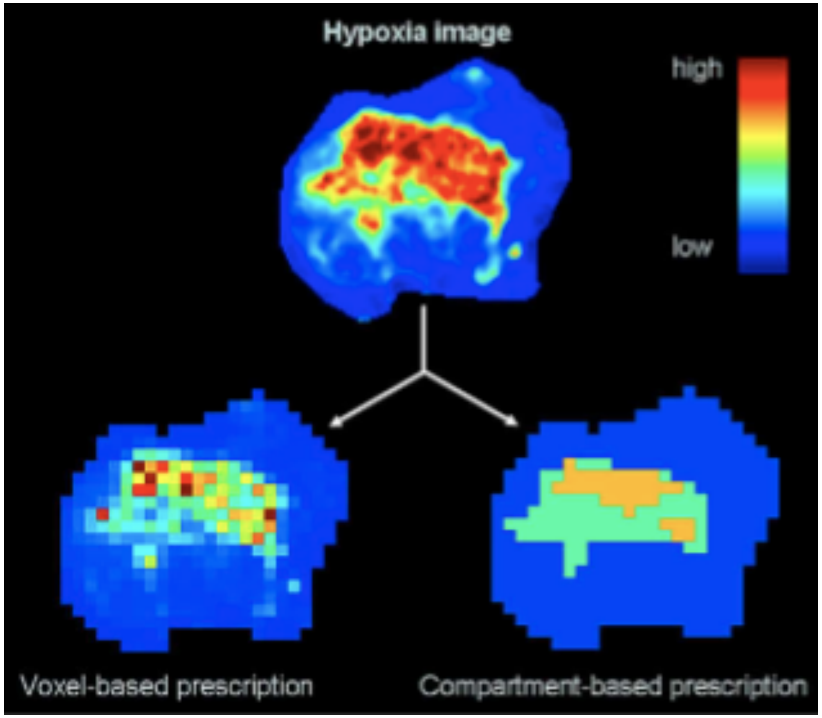
- Hypothetically, DWMRI could be used as a noninvasive tool to select pts who have a high risk of locoregional control and would benefit from treatment intensification

- DWMRI showed that lesions in which locoregional recurrence developed had significantly lower apparent diffusion coefficients on scans ***during wk 4 of RT*** and at ***3 wk after*** treatment.

- Hypothetically, DWMRI could be used as a noninvasive tool to select pts who have a high risk of locoregional control and would benefit from treatment intensification

suspect on 18F-FDG PET at 8 wks after treatment (D). (E) Residual disease was confirmed.

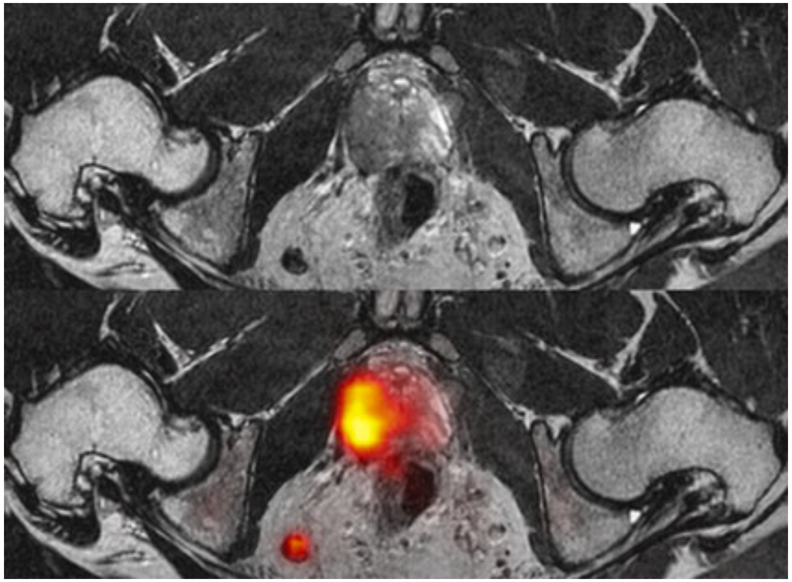
Molecular imaging-based dose painting:
dose painting by volumes (DPBV)
dose painting by numbers (DPBN)



- DPBN requires a very precise co-registration

Choline PET based dose-painting in prostate cancer – Modelling of dose effects

- **Parameters:**
  - **sensitivity:** **64 - 81**
  - **whole prostate dose:** **74 – 78 Gy**
  - **SIB dose** **90 Gy**
  - **TCP definition γ50:** **1.4 - 2.2**
  - **$\alpha[Gy^{-1}]$:** **0.03 – 0.08**
  - **α/β:** **1.5 – 8.3**



- **TCP increase: from 6.0 to 22.2**

(Niyazi, Radiat Oncol, 2010)

Prostate Cancer
MR-Spectroscopy in tumor volume definition

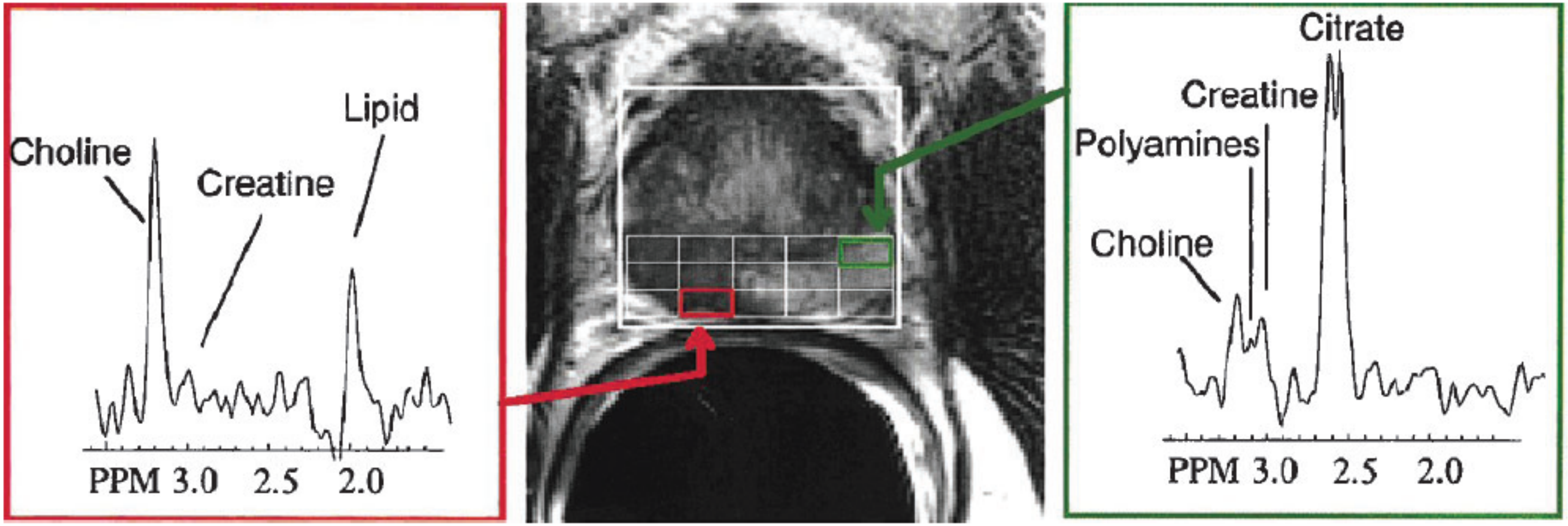


Figure 4. Centre: T_2 weighted transverse image of prostate with tumour in right mid-gland, overlain with grid of voxels from which spectra were acquired. Left: Spectrum acquired from region of tumour, illustrating dramatically elevated choline and absence of citrate and polyamines. Right: Spectrum from healthy peripheral zone tissue with high citrate and presence of polyamines. (Reproduced with permission from J Kurhanewicz et al [46]).

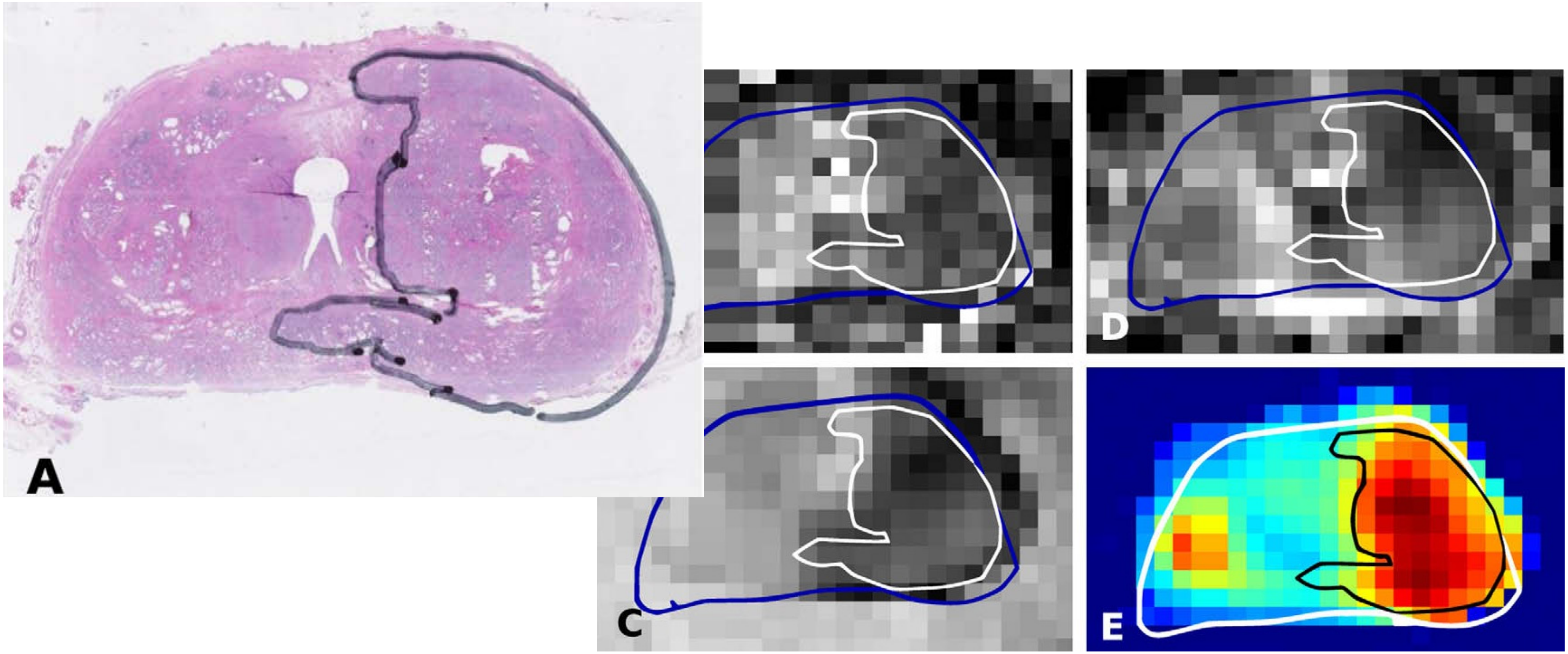
Correlation between MRS - and biopsy - and MRS + and biopsy +

Kurhanewicz J, Radiology 198:795:805; 1996

MRS: voxel (8-10 mm3); < spatial resolution with respect to CT and MRI

Pirzkall A, New Technologies in Radiation Oncology; Springer 2006

DW-MRI and DCE-MRI in prostate cancer



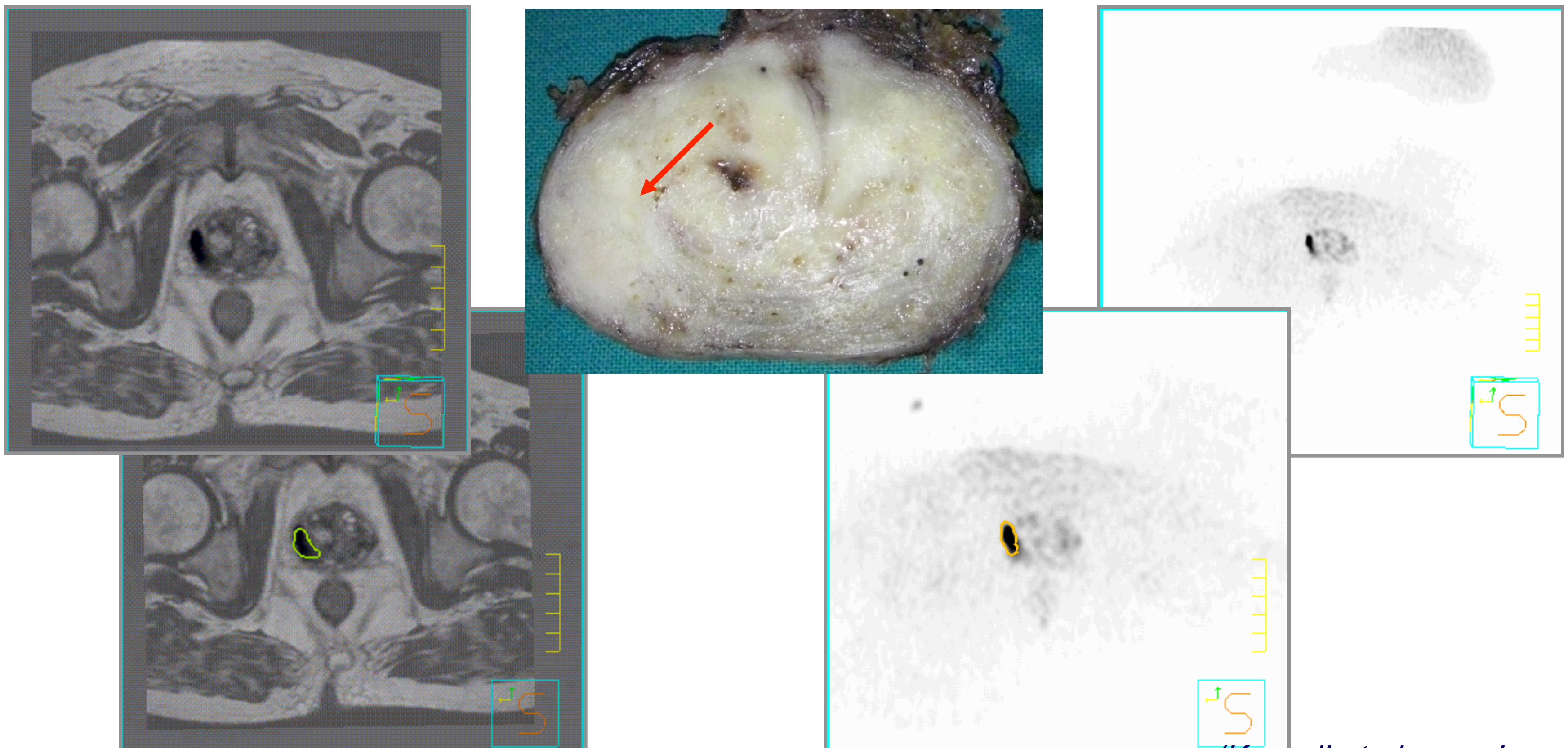
Reasonable tumor coverage of about 85% and larger was found when applying a margin of 5 mm to the MR based tumor delineations.

(Groenendaal et al. R&O, 2010)

Correlation of T2-MRI and DW-MRI with pathology in prostate cancer

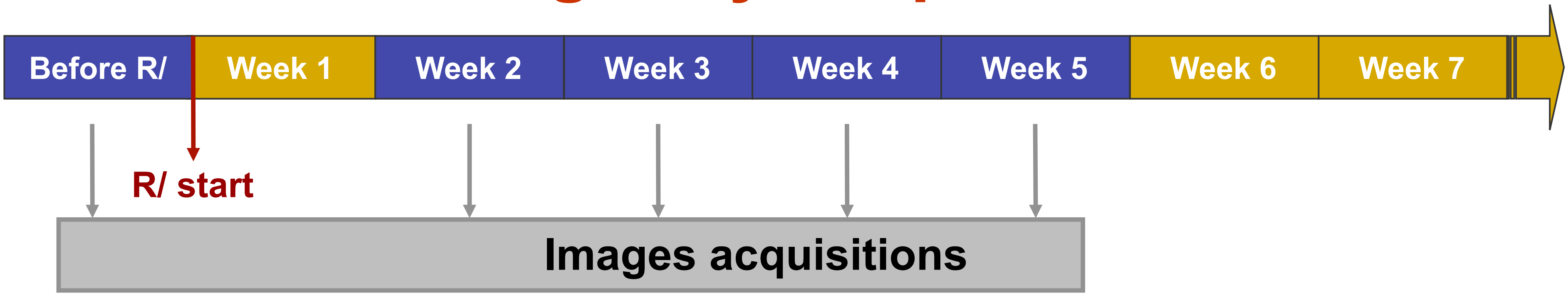
Case CG

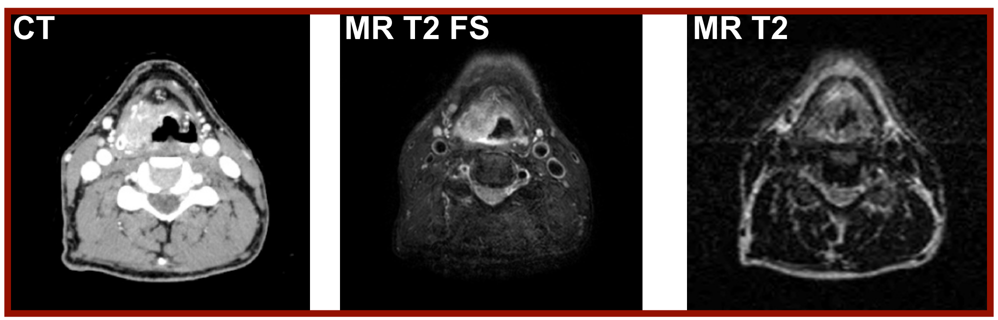
pathology	T2-MRI	DW-MRI
1	1.41 cc	1.69 cc



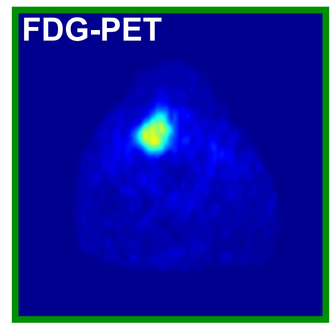
(Krengli et al, ongoing study)

4 – Early response evaluation and biologically adaptive RT

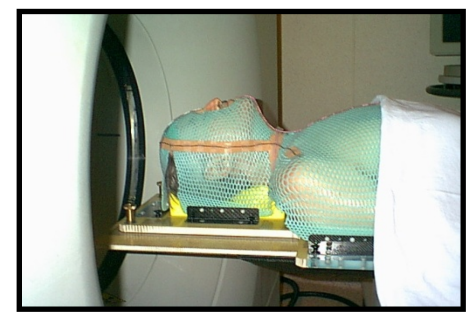




Anatomic imaging



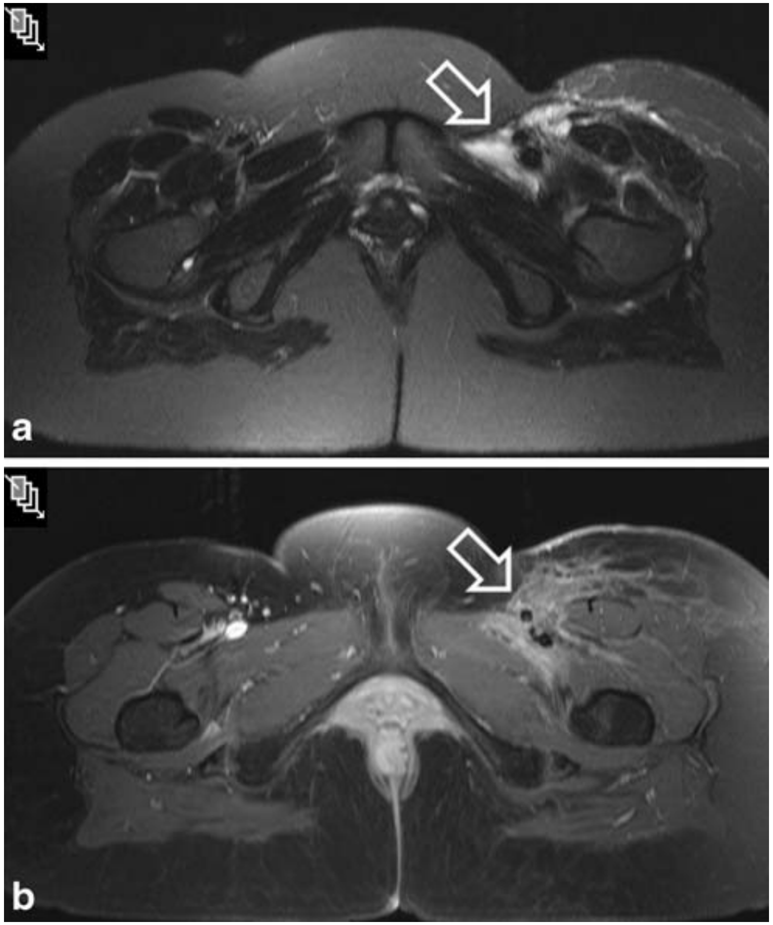
Dynamic FDG-PET



- 10 patients with stage III-IV pharyngo-laryngeal SCC treated by CT-RT
- Images acquired before R/ and during RT after means doses of 14, 25, 35 and 45 Gy.

(Gregoire, 2009)

5 - Response assessment



Postoperative status in patient with lymph node metastases in the left groin from malignant histocytoma of the left sole of the foot.

T2 (a) and c-e T1 (b) MRI demonstrate edema and scar tissue with contrast uptake which is difficult to distinguish from residual disease. Inclusion of PET data may be of benefit in this clinical question

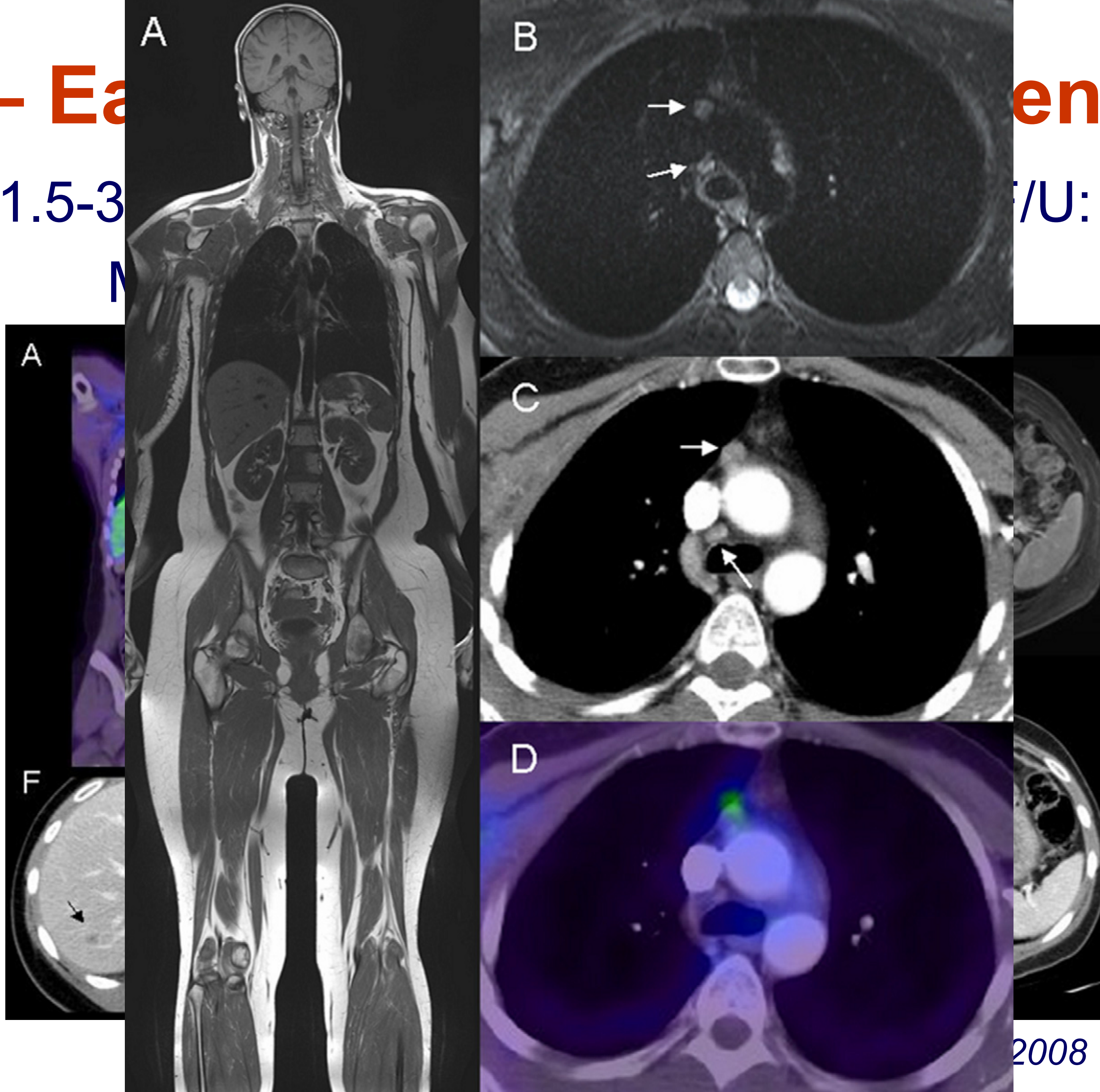
Antoch G, Eur J Nucl Med Mol Imaging, 2009

- MRI useful in neoadjuvant setting (resectability especially in soft tissue)

6 – Ea ence

1.5-3 F/U:

M

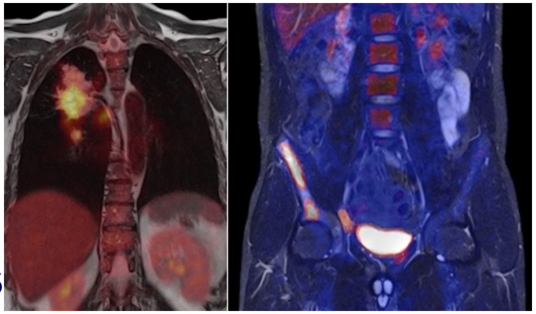


2008

Critical Issues for the use of MRI/PET in RT

- Attenuation correction factors for PET/MR data
- Limitations: lung (CT is still the standard procedure), metal implants, pacemakers, claustrophobia
- Image distortion at the periphery of the field
- Time of acquisition: workflow and risk of patient movements
- Diameter of gantry
- Cost

Future of MRI/PET for RT?



Common aspects with other oncological branches

- Fast and precise diagnosis and staging procedures (high resolution PET)
- Useful for response assessment and early detection of tumor recurrence

Specific aspects related to RT

- Target identification with biological characterization of multiple features of the tumor resulting in optimal information for dose painting and adaptive radiotherapy
- RT planning on MRI based on proton density ?

General aspects

- It is an ideal technology for investigational purposes and large scale studies are needed to demonstrate the clinical benefits of PET/MRI compared with the other imaging modalities first of all PET/CT.
- Training of specialists with specif ic skill in combined CT/MRI/PET/SPECT imaging is needed.