MOLECULAR IMAGING IN RADIATION ONCOLOGY

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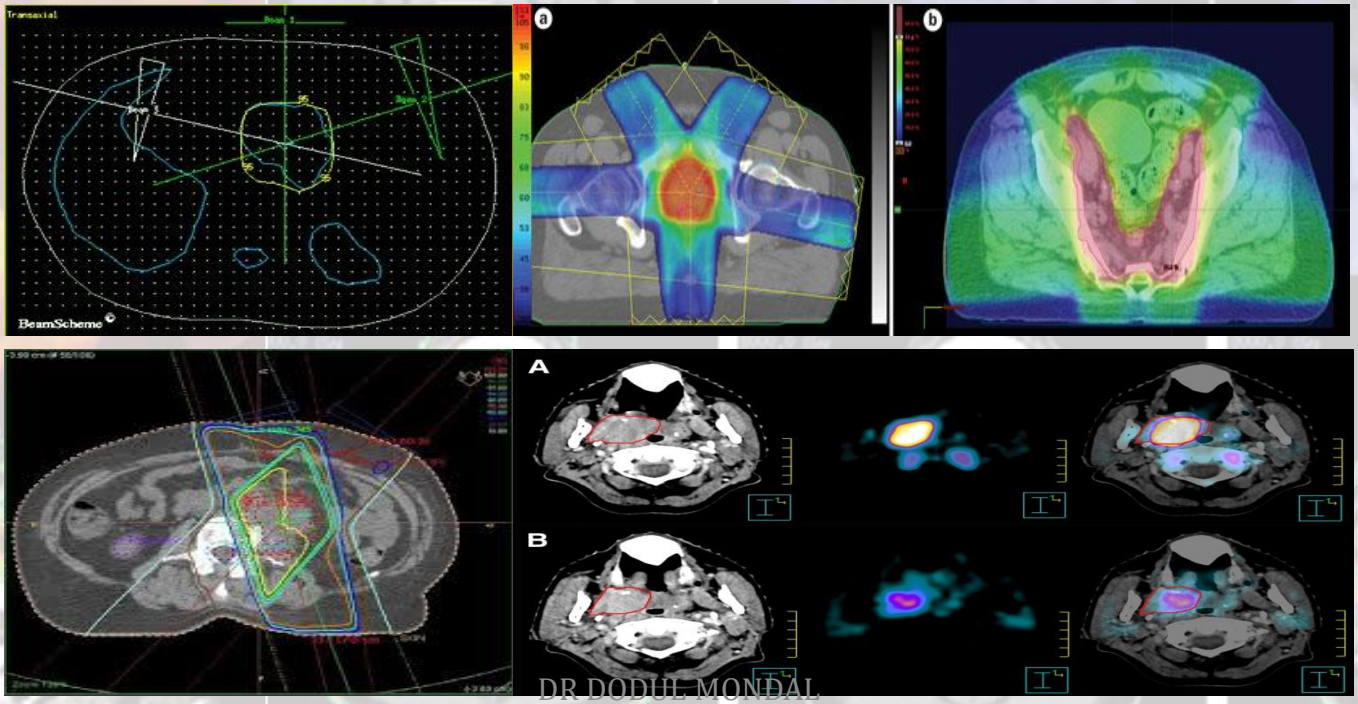
INTRODUCTION

Concept of radiotherapy planning has evolved from simple anatomy based planning to anatomic image based planning to highly precise modern day radiotherapy planning using more precise functional, molecular and genetic aspect of cancer

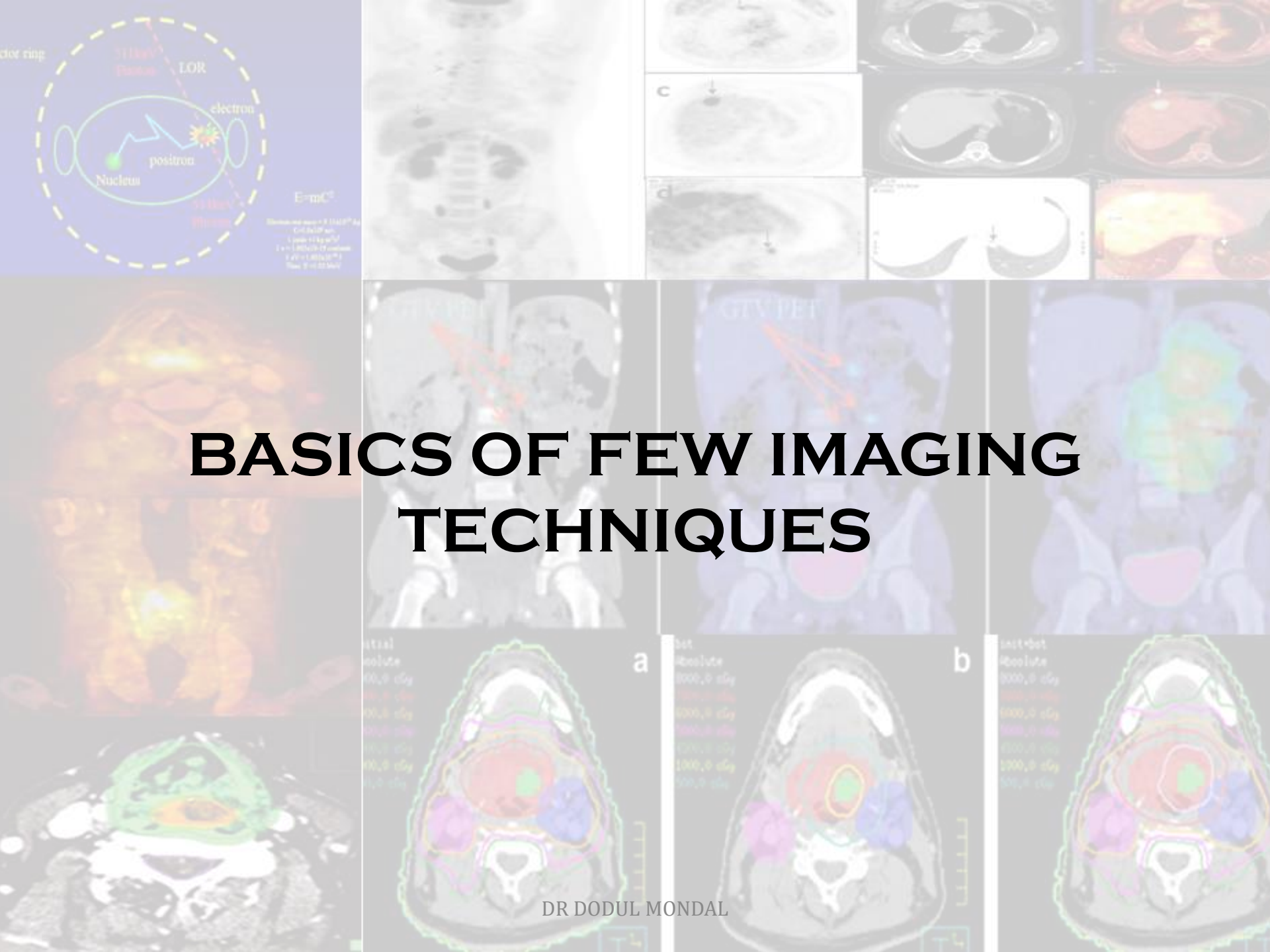


Molecular Imaging

- Originated from the concepts of radiopharmacology to better understand the fundamental molecular pathways inside organisms
- Non-invasive
- Enormous potential after the description of the human genome
- Images particular targets or pathways with specific probes or biomarkers
- Paradigm shift of cancer management: organ treatment to treatment specific molecular abnormality

Molecular imaging cont..

- Development of novel biomarkers and imaging of gene expression → earlier and more precise diagnosis, treatment
- Quantitative tests and greater degree of objectivity
- Principle of mass spectrometry



BASICS OF FEW IMAGING TECHNIQUES

IMPROVEMENTS IN IMAGING

- Spectacular advance in our knowledge of cancer at the molecular level
- Cross fertilization of multiple disciplines

Past: Anatomic

Present: Bilogic/Mechanistic

Wide spectrum of information

Hence "BIOLOGICAL"

- Metabolic
- Functional
- Biologic
- Functional

Others:
Molecular
Genotypic
Phenotypic

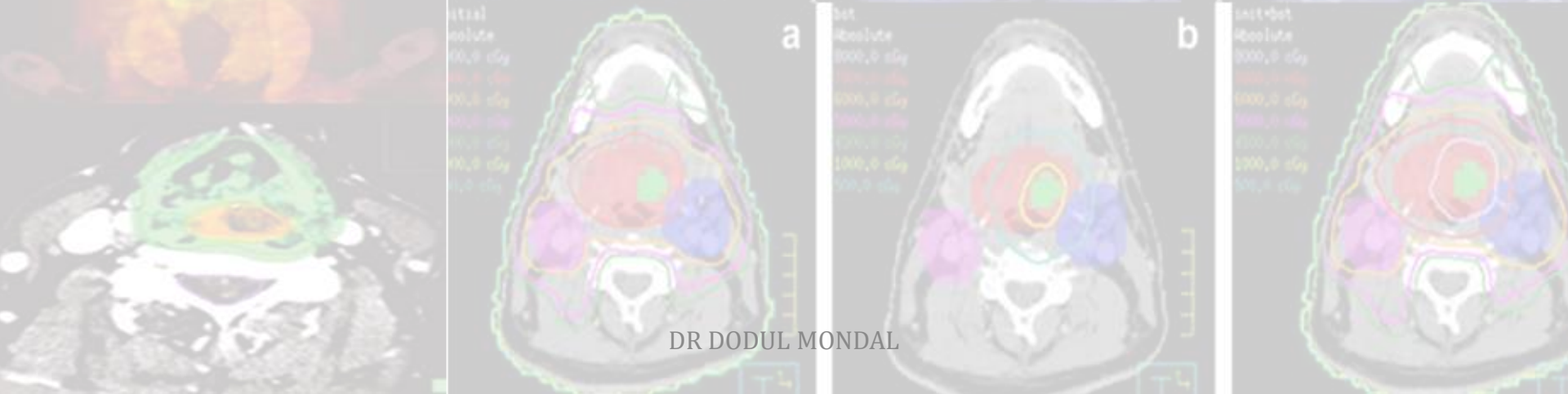
Computed tomography

- Tomos (slice) and Graphein (to write)
- EMI scan/CAT (Computed Axial Tomography) scan/ CT scan: First utilized in 1971 for brain scan by Sir Hounsefield.
- Two dimensional X-ray images taken around a single axis of rotation at multiple sections using multiple detectors→ Digital reconstruction → generate a three-dimensional image
- Essentially anatomic imaging
- Uses principle of photoelectric effect, however at high KV, Compton effect becomes predominant

Computed Tomography cont..

- Windowing - CT data manipulated demonstrate various bodily structures based on their ability to block X-ray

- Axial images reconstructed to get three dimensional images



Magnetic Resonance Imaging (MRI)

- Utilizes magnetic relaxation properties of cancer and non cancer tissues
- Provides information about resonance of populations of nuclei
- Their resonance is influenced by several physical and biological properties of interest
  - Local tissue chemical content
  - Temperature
  - Water diffusion
  - Blood flow
  - Tissue elasticity
- Provides anatomic, physiological, biochemical and molecular information

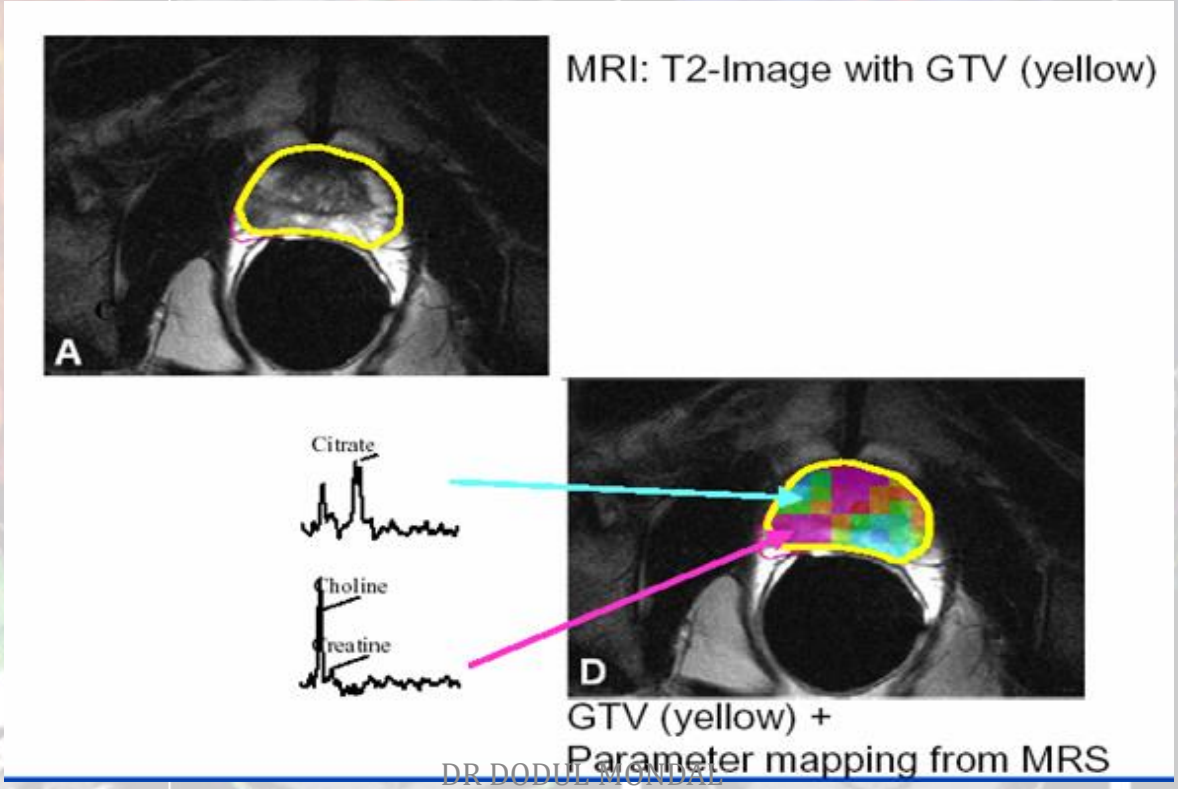
MAGNETIC RESONANCE SPECTROSCOPY

- MR spectrometer is in-built in all MRI machines.
- Routinely it ignores spectrum of resonances that come from a single voxel and clubs them together and hence we see a single signal either white or black or intermediate gray.
- With proper software and hardware modifications it can provide information within a region .
- Hence MRS is shown as a spectrum from a single voxel or else a grid of voxels.
- Spectra are collected from spinning nuclei
- Routinely from hydrogen nuclei (water is the most abundant molecule)

ROLE OF MRS

- Brain – can distinguish high grade gliomas from low grade gliomas
- Primary vs. metastatic lesion (pediatric tumors)
- Radiation necrosis vs. recurrence
- Serves as predictor of survival or progression.
- Choline to citrate ratio- prostate cancer, gliomas
- Results from enhanced phospholipid cell membrane turnover associated with tumor proliferation, increased cellularity and growth
  - Creatine, lactate- Adverse prognosis
  - Increased metastatic potential
  - Radio resistance

- NMR spectroscopy of 31P can provide information about energy status.
- Membrane precursor phosphocholine and phosphoethanolamine- changes in response to radio/chemotherapy- hence have early predictor of tumor response.



CONTRAST ENHANCED MRI

- MRI Contrast-
  - shorten T1(bright signal)
  - Shorten T2 (dark signal)
- Ferumoxtran-10- an iron based T2 agent that is collected in normal lymph nodes but excluded from metastatic nodes- shorten T2 signal (Not approved in India)
- Multihance- Hepatocyte specific T1 contrast agent (Approved in india): For characterizing hepatic tumors-Can differentiate between FNH and HCC
- Newer contrast agents- action specific- receptor specific

NEWER ADVANCES: PET-MR

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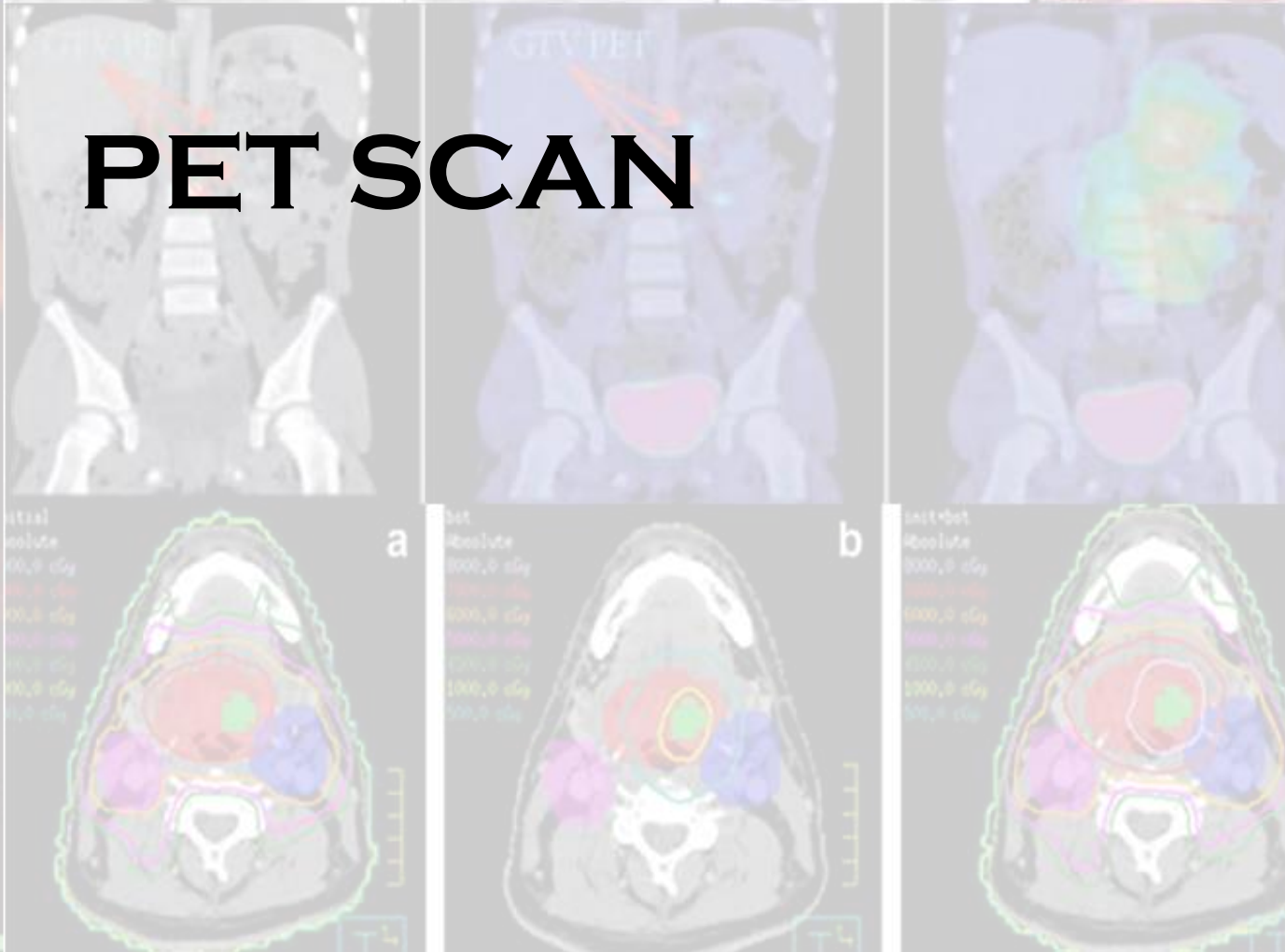
Review Article

PET/MR in oncology: an introduction with focus on MR and future perspectives for hybrid imaging

- Currently, no clinical indication for combined PET/MR has been established
- With PET/MR it might finally be possible, in the future, to gather the information necessary to perform radiotherapy with dose painting and to establish truly predictive imaging markers



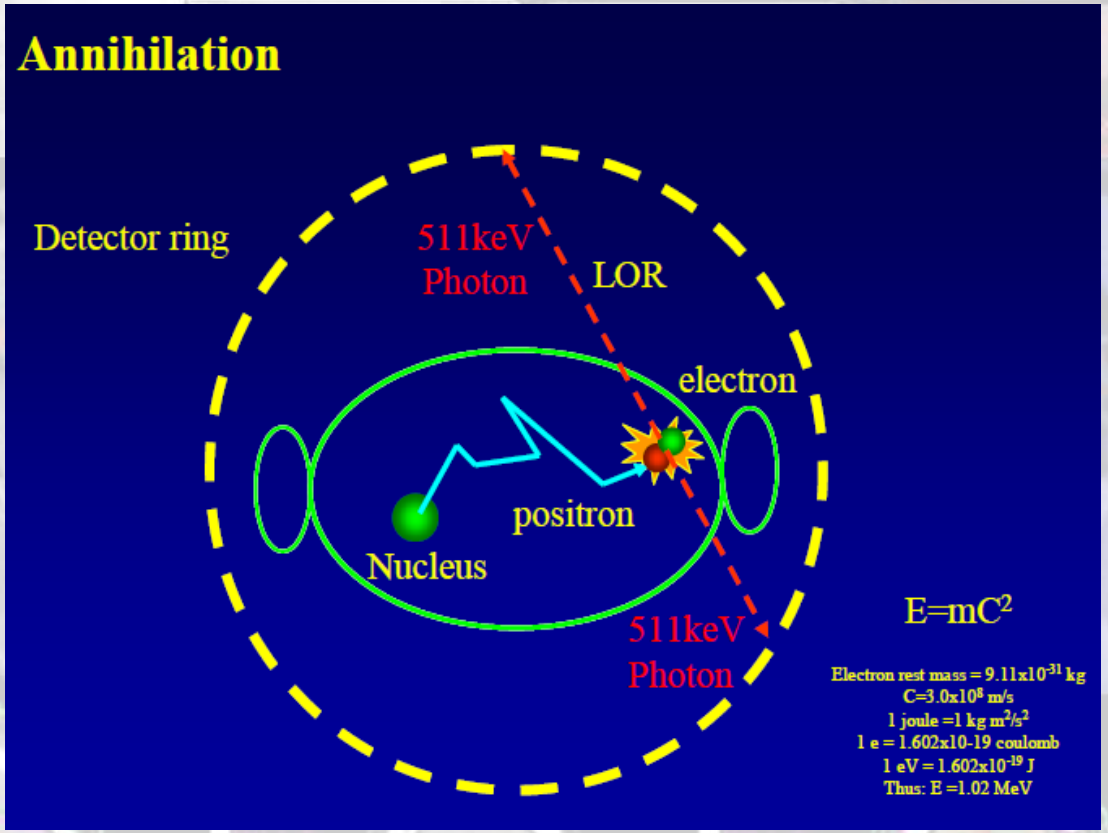
PET SCAN

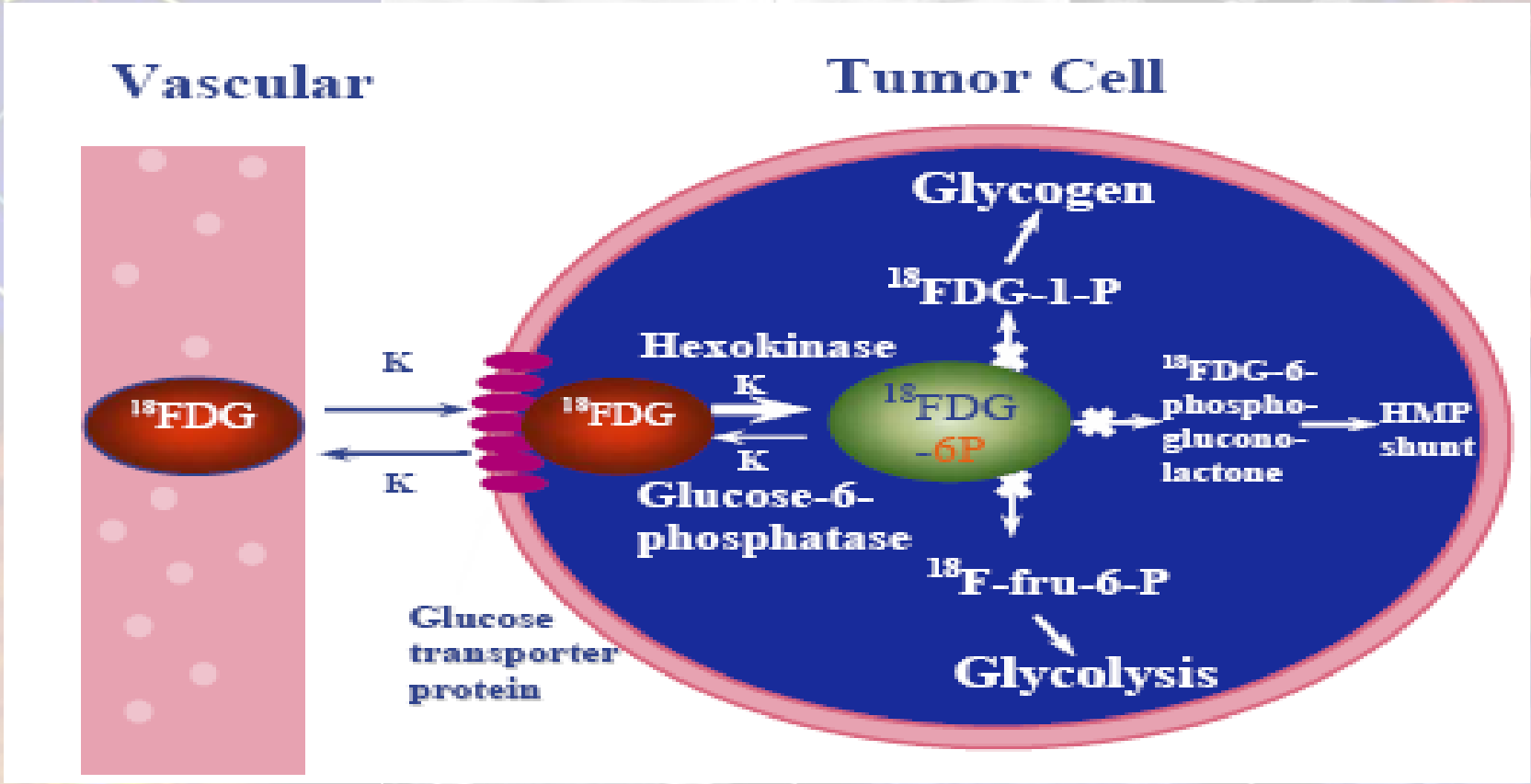
Positron Emission Tomography (PET)

- Functional imaging modality showing:
  - Blood flow
  - Glucose metabolism
  - Receptor density
- Basic Principle
  - Injection of a radioactive tracer to image chemical/biological processes.
  - Radioactive tracer decays by Positron Emission.
  - When the tracer is introduced into the body, it is site-specific uptake can be traced by means of the labelled atom

Positron Decay

- $p = n + \beta^{+} + \upsilon$
- A nucleus with too low a neutron-to-proton ratio converts a proton to a neutron, emitting a positron (β^{+}) and a neutrino (υ) to carry off the excess energy
- Photons emitted must have a specific energy(511 keV) and are always emitted in opposite direction.





- Dependent on the altered metabolic characteristics of tumor cells compared to its surroundings
- Uncontrolled proliferation- Hallmark
- Most widely used in oncologic practice is FDG- glucose analog

TRACERS FOR PET

PET radiotracer	Function	Disease
^{18}F-fluorodeoxyglucose (^{18}F-FDG)	Glucose metabolism	All tumors
^{11}C-methionine (^{11}C-MET)	Amino acid metabolism	Brain/H&N/breast/lung/GU
^{11}C-tyrosine (^{11}C-TYR)	Amino acid metabolism	Brain tumors
^{15}C-oxygen (^{15}C-O2)	Blood flow	Brain tumors
18[F]-fluoromisonidazole	Hypoxia	All tumors
^{15}C-carbon monoxide (^{15}C-O)	Blood volume	Brain tumors
Oxygen-15 ($^{15}O_2$)	Oxygen metabolism	Brain tumors
^{11}C-5-hydroxy tryptophan (^{11}C-5-HTP)	Serotonin levels	NE/GI
^{15}O-water ($H_2{}^{15}O$)	Blood flow	Thyroid tumors
^{11}C-L-dihydroxyphenylalanine (^{11}C-L-DOPA)	Dopamine levels	NE/pancreatic
^{18}F-fluoro-2′-deoxyuridine (^{18}F-FUdR)	Nucleic acid metabolism	Brain tumors

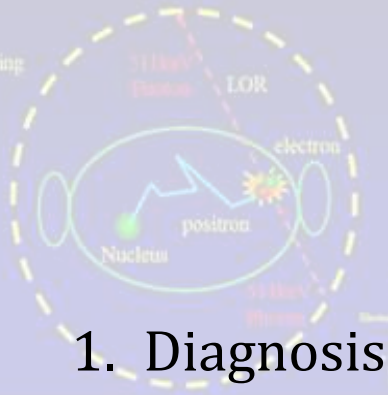
H&N = head & neck; GU = genitourinary; NE = neuroendocrine; GI = gastrointestinal.

PET IN RADIOTHERAPY PLANNING

- **BASIS FOR ROLE**

1. Distinguishes metabolically active tissue from scar.
2. Can detect functional/metabolic activity of cells
3. Quantification of metabolic activity of cells
4. Capability to detect signal intensity changes rather than lesion size.
5. Independent from anatomy and organ relationship. Hence is able to detect abnormal metabolic activity in tumor recurrence in patients post surgery and post RT where architecture is distorted.
6. Ability to assess different specific tissue functions due to functional specificity of developed pharmaceuticals.

ROLE OF PET



1. Diagnosis and staging.
2. Definition of extent of disease – staging and restaging
3. Identification and localization of disease foci in patients with unknown primary.
4. Assessment of response to therapy and its monitoring.
5. Identification of relapse and recurrence versus other imaging non-specific changes and increased tumor markers.
6. Biopsy site guide.
7. Predictor of response and survival based on SUV.
8. Most importantly, radiotherapy planning and guidance.

PET FOR RT PLANNING

- 30-40% of RT plans for cancer patients are changed when PET scan findings are featured into plan.
- Scanning for radiotherapy- simulation scans

1. Couch- flat table
2. Precise positioning
3. Precise immobilization
4. Laser used to guide marking
5. 3 fiducial markers: to establish reference slice; reference point – pseudoisocentre
6. From pseudoisocentre precise target is identified as necessary and true isocentre is defined with respect to it
7. Consistent and optimum spacing required

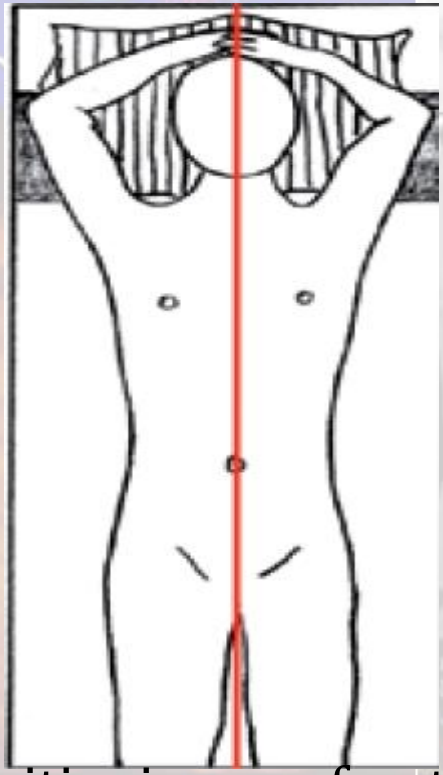
PET FOR RT PLANNING

8. Fasting for 4-6 hrs to enhance tracer uptake by tumor.
9. Refrain strenuous exercises 48 hrs before FDG administration- to avoid physiological uptake in recovering muscles.
10. Asked to wear warm clothing, particularly around shoulders and neck to avoid uptake in brown adipose tissue of neck and upper torso.
11. Discourage patients from moving or speaking during 60-90 min of FDG uptake.
12. Before scanning patients are asked to urinate.
13. Sedatives, anti-cholinergics, anti-emetics as required.

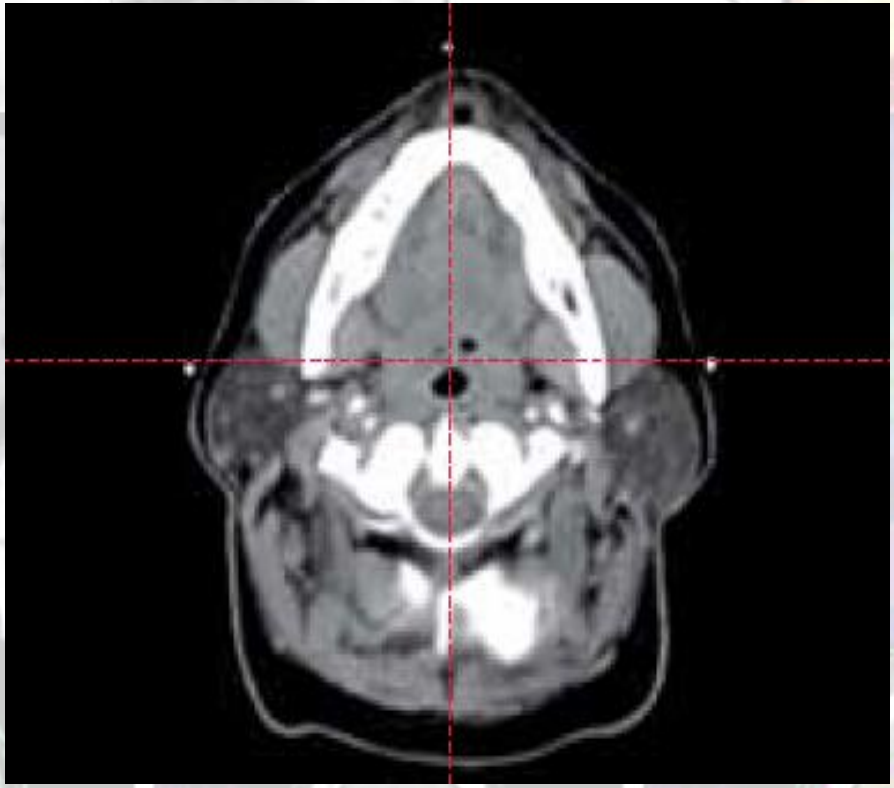
PET FOR RT PLANNING

15. Once data is acquired it is sent to RTP software.

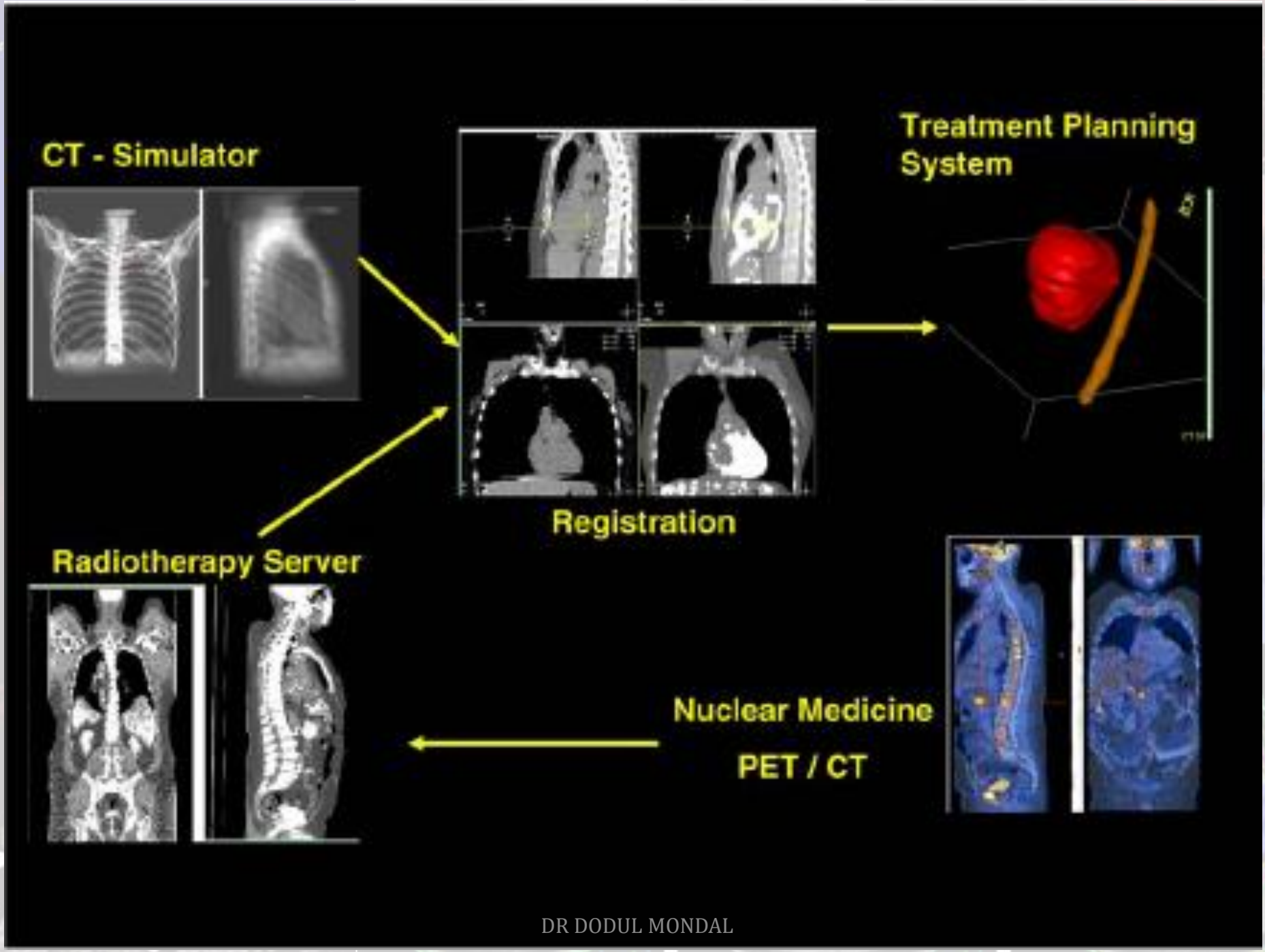
16. RTP software must validate the DICOM compatibility of CT or PET.



Positioning of the patient exactly in the middle of the longitudinal laser beam



Metal pins defining the isocentre


CT - Simulator
Treatment Planning System
Registration
Radiotherapy Server
Nuclear Medicine
PET / CT

	Impact on staging	Effect on radiotherapy
T stage	Upstaging (Larger extension of disease)	Enlargement of radiotherapy fields Change of indication from curative to palliative
	Downstaging (Less extension of disease)	Field reduction reducing normal tissue exposure, possible dose escalation Change of indication from palliative to curative
N stage	Upstaging (Detection of new site of lymph node)	Enlargement of radiotherapy fields to avoid geographical miss Change of indication from curative to palliative
	Downstaging(Omission of lymph node diagnosed as malignant on CT/MRI)	Field reduction reducing normal tissue exposure, possible dose escalation Change of indication from palliative to curative
M stage	Detection of metastasis	Change of indication from curative to palliative

Rational use of PET in radiation treatment planning depends on qualities of PET.

- ❑ Sensitivity
- ❑ Specificity
- ❑ Positive predictive value
- ❑ Negative predictive value
- ❑ Accuracy

PET Based Contouring

- CT positive but PET negative and vice versa?
- Who Needs To contour?
- Optimal PET volume for radiation therapy?

Optimal PET volume for radiation therapy?

- CT ⟶ Tumor margin sharp, PET ⟶ Fuzzy
- Philosophy should be "PET finds it CT defines it"
- Exceptions – PET defines tumor edge :
  - Neck/Pelvic mass that blends in with tumor surrounding soft tissue
  - Lung mass with accompanying atelectasis
- Manual segmentation
- Automatic segmentation based on SUV

Who Needs To contour?

- Radiation oncologist vs. Nuclear medicine expert
- Physiological variation and uptake:
  - post-surgery sites
  - irradiated sites
  - areas of inflammation
  - SUV variability – Patient LBW
  - activity of injected isotope
  - BSA
  - High background activity as in brain
- Collaboration with nuclear medicine expert
- As experience grows –requirement will be far less frequent

POSITIVE ON CT BUT NEGATIVE ON PET AND VICE VERSA?

1. No consensus – lack of experience and long-term data.
2. Any obvious tumor seen with CT that does not show FDG uptake within it should be still be included.
3. PET lesion to be included in GTV – it should either correspond to
   - Underlying CT abnormality
   - Lymph node
   - Convincing intensity within a common site for disease, that cannot be explained by a benign process or artifact

Role of PET in planning for NSCLC

- Accurate staging
- Selection of appropriate treatment- radical vs. palliative
- Monitor response to therapy
- Define local recurrence
- Aid for dose escalation-clearer def of GTV
- Determine sites of nodal involvement
- In patients with atelectatic lung reduce treatment fields.

GTV should be, in a majority of cases, equivalent to extent of hot spot depicted by PET complemented with information given by CT

Target volumes were reduced slightly more frequently, but volumes were also enlarged with no clear or consistent pattern among patients.

PET for Mediastinum:

Important when elective mediastinal radiation is not considered.

In the setting of neoadjuvant therapy.

Useful when nodal sites are marginal on CT scan

Dose Escalation

No data on its impact on survival

Important as a part of response adaptive therapy as a method of identifying the response of different populations of cancer cells to treatment. Hence allows treatment optimization-change in fractionation, concurrent chemo.

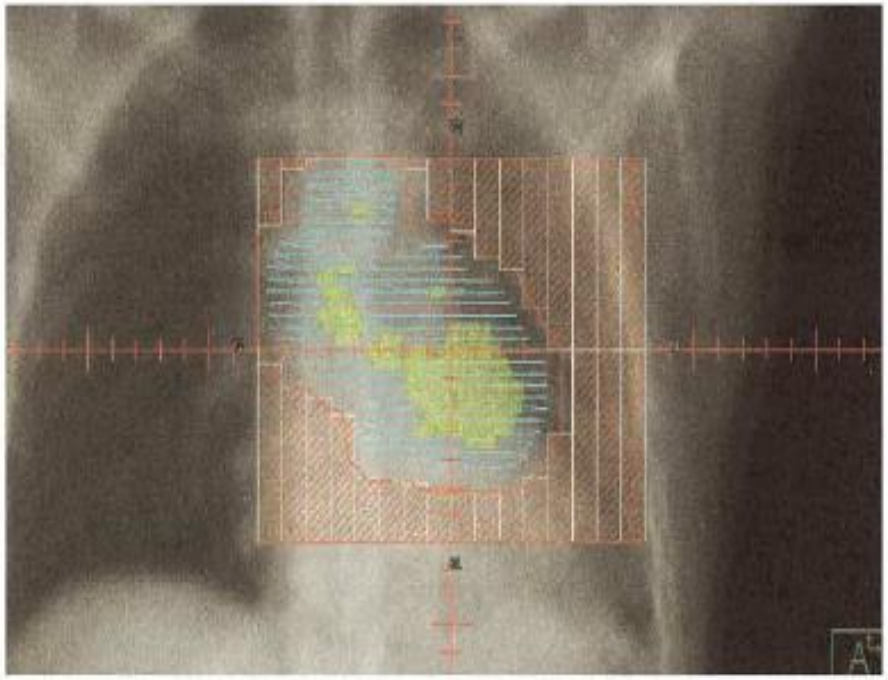
PET intensity as a marker of biological behavior

2yrsurvival SUV < 5- 91%;/ SUV<7 - 83%; / SUV < 10 –52%.

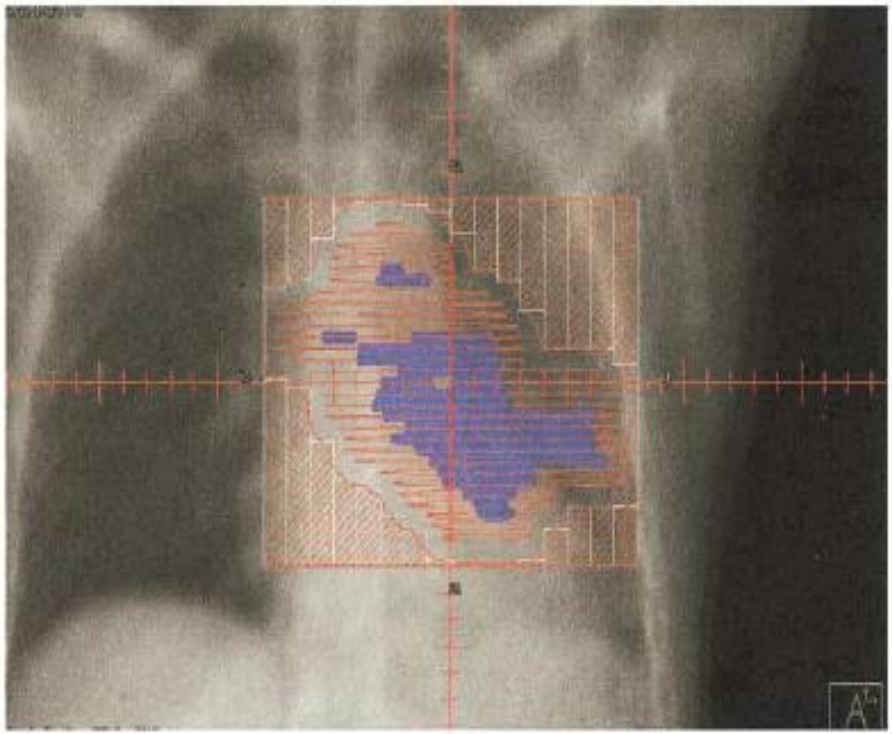
PET to stage after neoadjuvant therapy

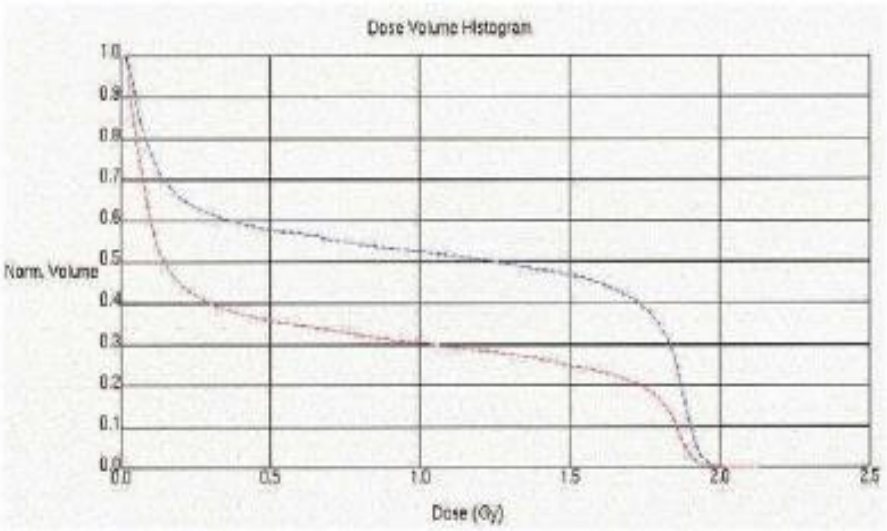
Early changes in PET to assess response to treatment

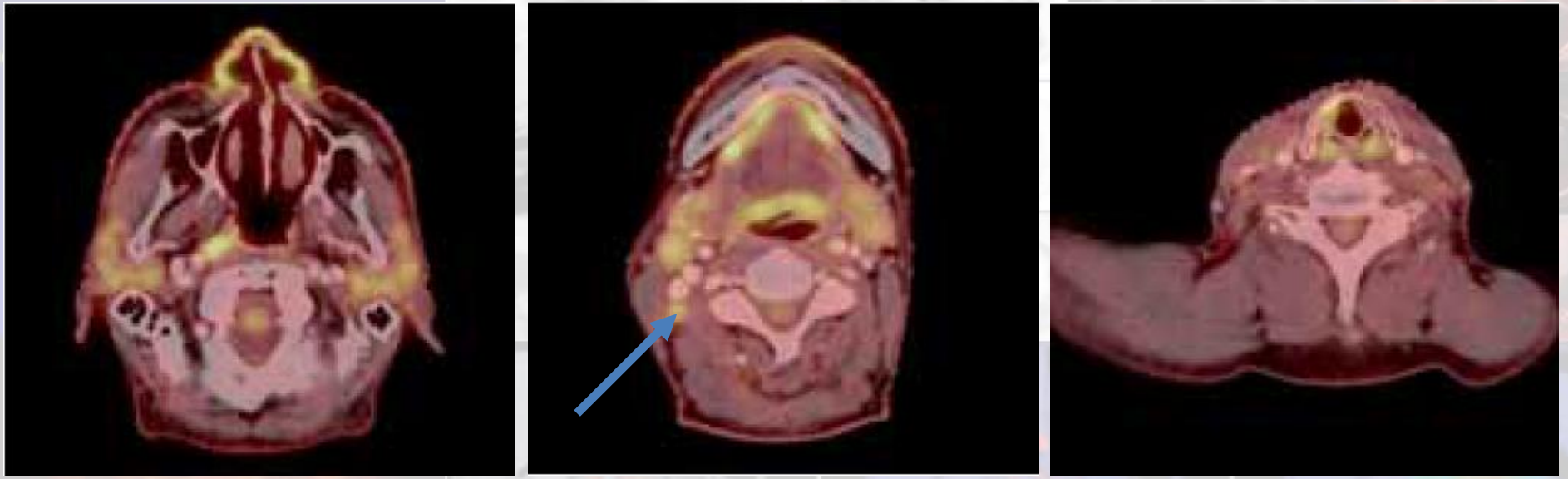
(a)



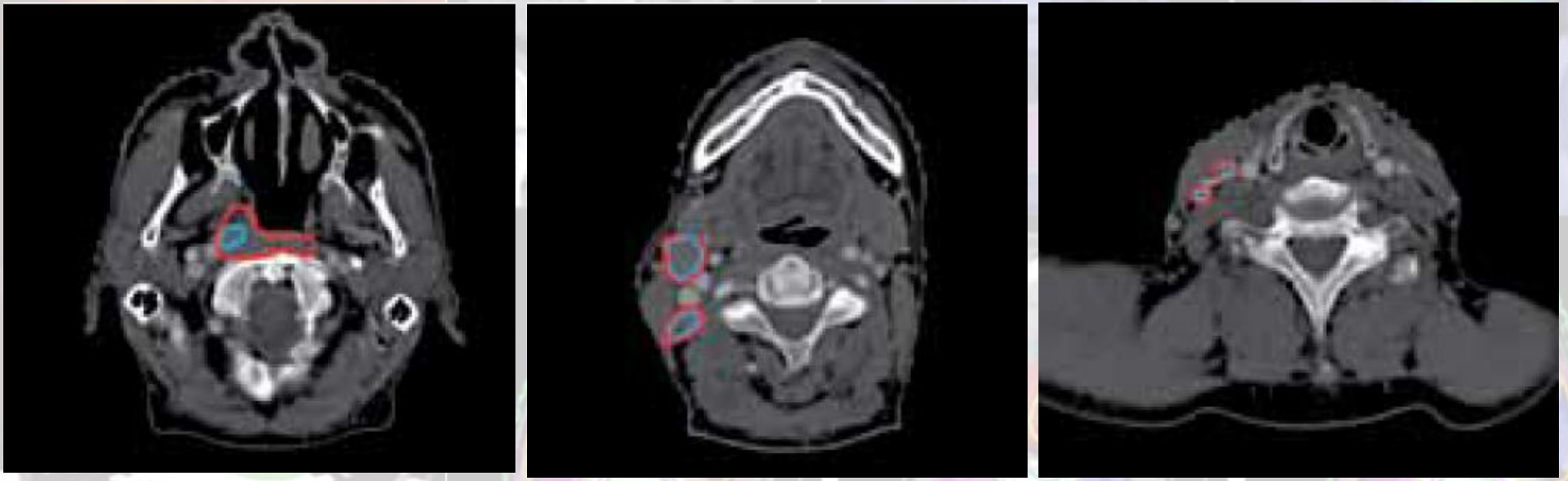
(c)



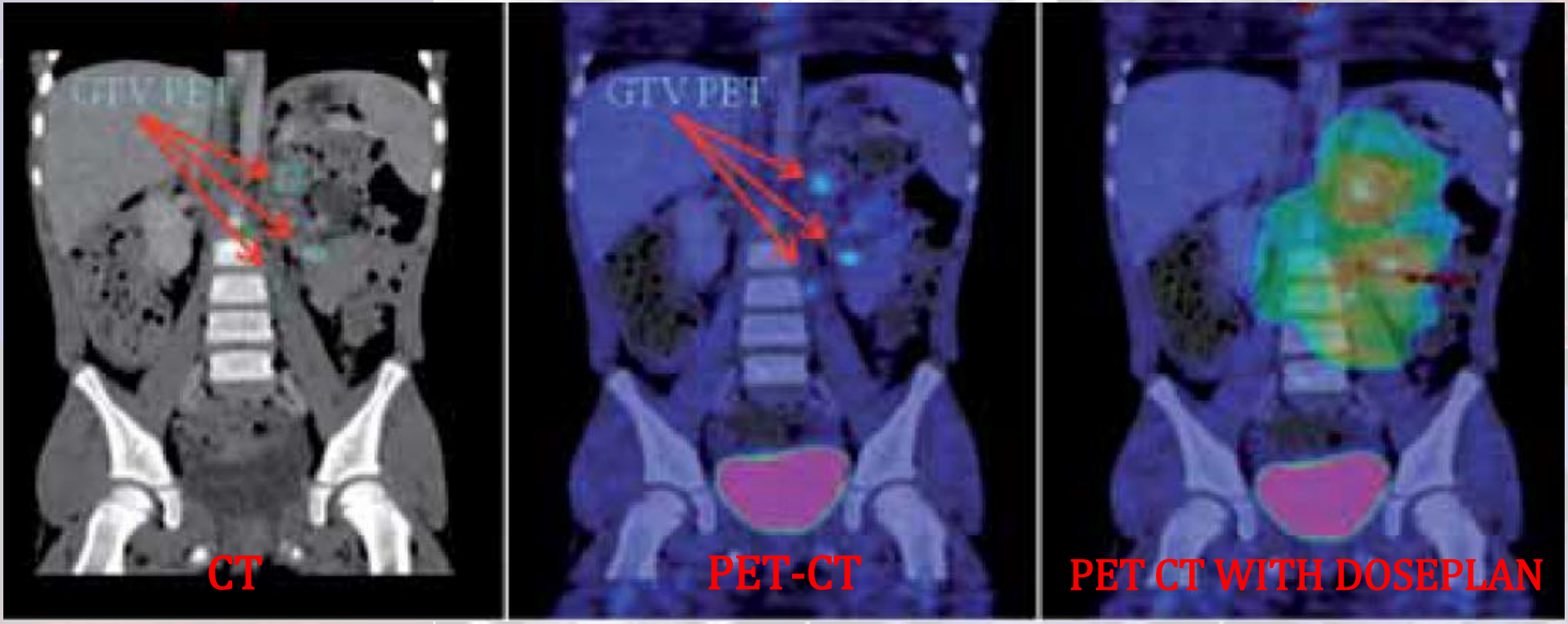

Dose Volume Histogram
Norm. Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
2.5
Dose (Gy)



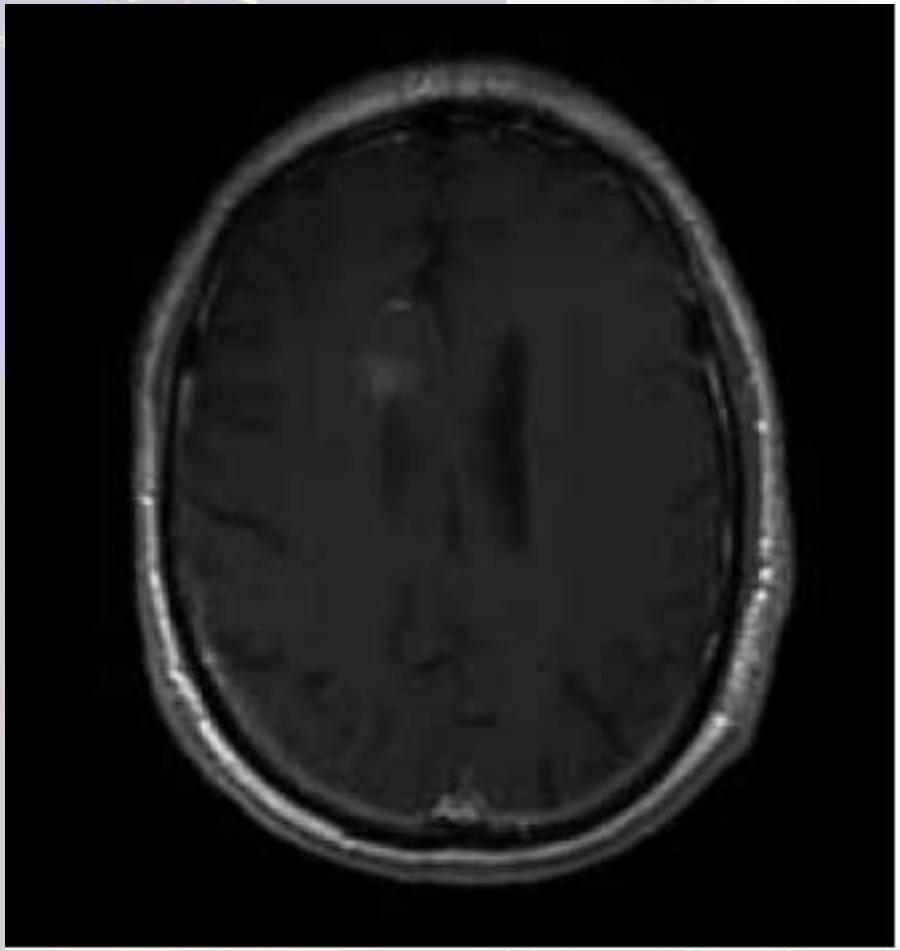
Transaxial fused PET/CT images of a patient with nasopharygeal cancer with lymph node metastases. Note the small lymph nodes of 4 mm defined by PET (Arrow)



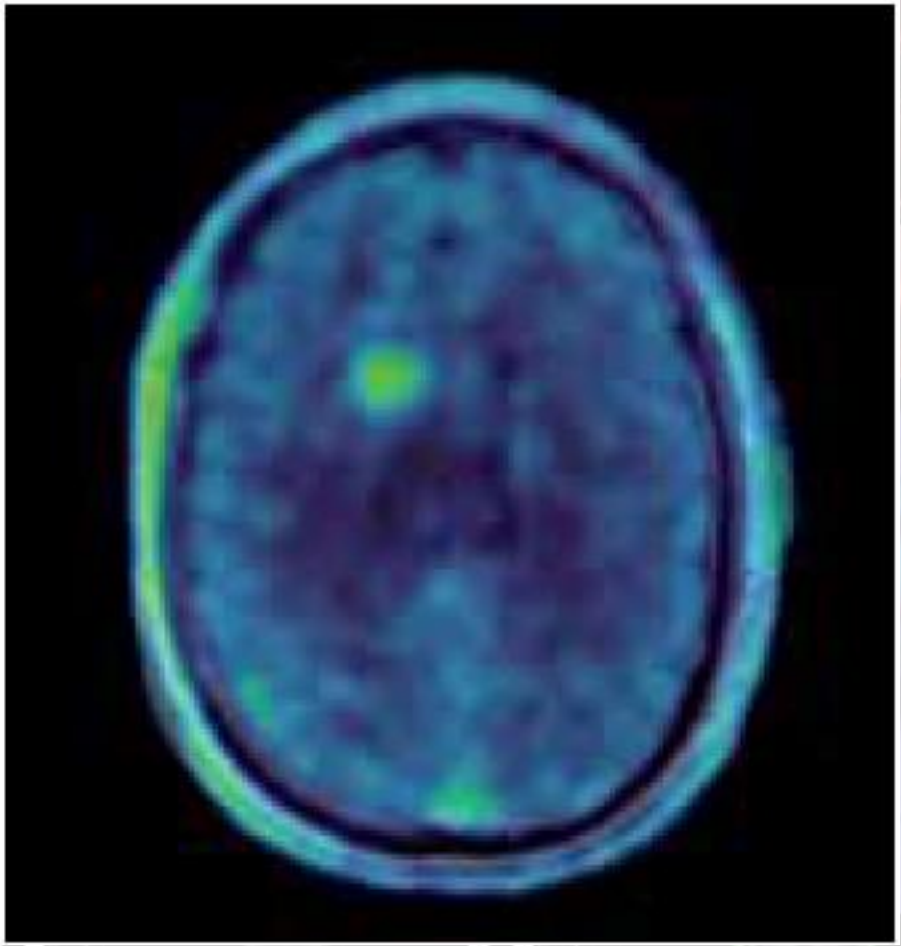
Transaxial CT images (same as above) showing the GTV delineated on PET/CT (GTV PET, blue lines) and the final GTV (red lines)



PET/CT-based radiotherapy planning of a paediatric tumour (sarcoma). The identification of the tumour is difficult on the CT scan (left), while PET shows a few FDG-avid regions in the abdomen (delineated using a blue curve). These regions, and a margin deemed sufficient, are included in the subsequent radiation therapy plan showing the dose distribution in temperature scale/colourwash (right)



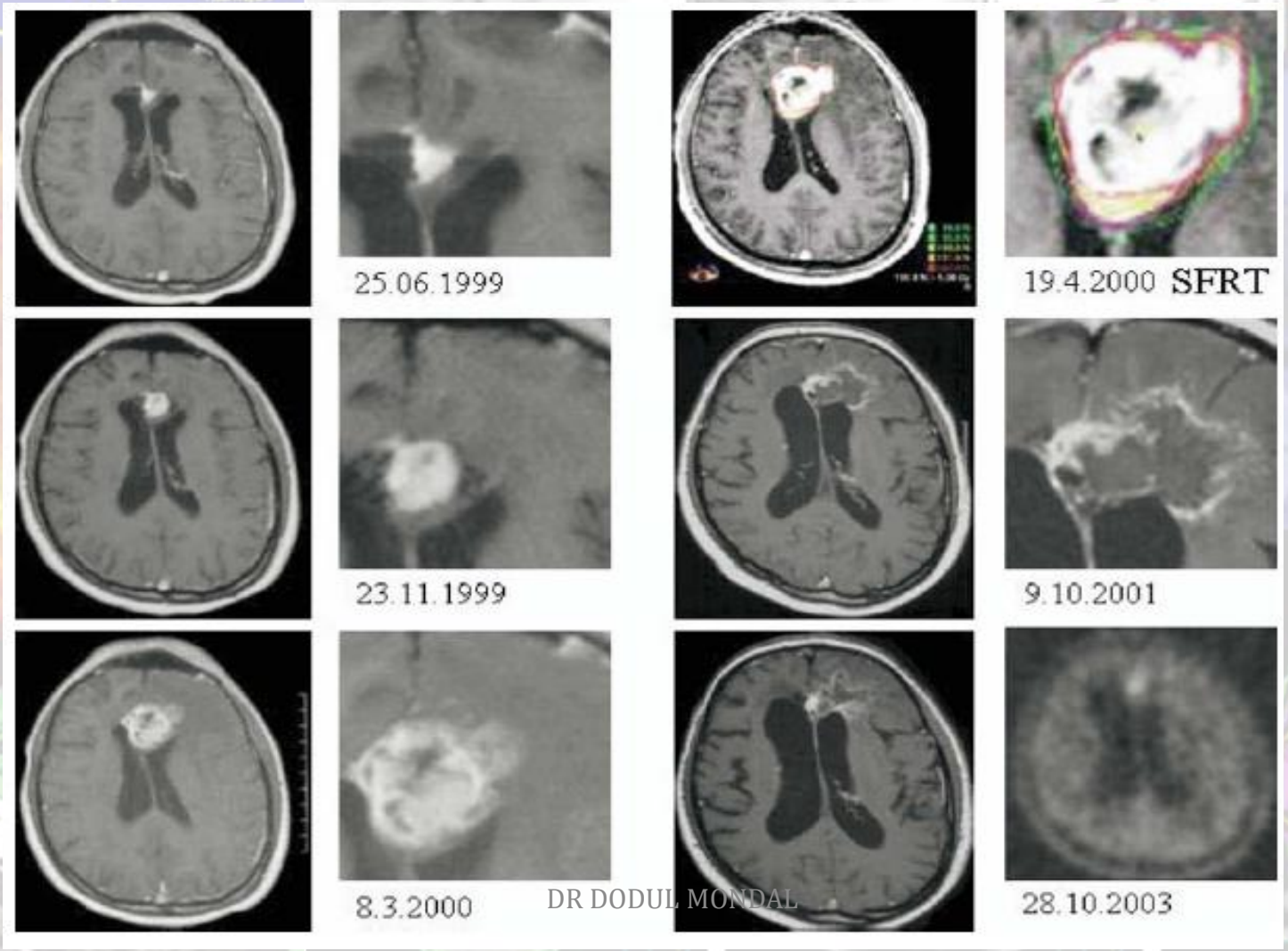
Pathological contrast enhancement in MRI imaging in a patient with suspected recurrence of glioblastoma multiforme



Fused images of FET-PET and MRI for better anatomical correlation

REIRRADIATION OF RECURRENT HIGH-GRADE GLIOMAS USING AMINO ACID PET (SPECT)/CT/MRI IMAGE FUSION TO DETERMINE GROSS TUMOR VOLUME FOR STEREOTACTIC FRACTIONATED RADIOTHERAPY

ANCA L. GROSU, M.D.,* WOLFGANG A. WEBER, M.D.,† MARTINA FRANZ,* SIBYLLE STÄRK, PH.D.,* MORAND PIERT, M.D.,† REINHARD THAMM, M.D.,* HARTMUT GUMPRECHT, M.D.,‡ MARKUS SCHWAIGER, M.D.,† MICHAEL MOLLS, M.D.,* AND CARSTEN NIEDER, M.D.*



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review

Clinical evidence on PET–CT for radiation therapy planning in cervix and endometrial cancers

Christine Haie-Meder *, Renaud Mazeron, Nicolas Magné

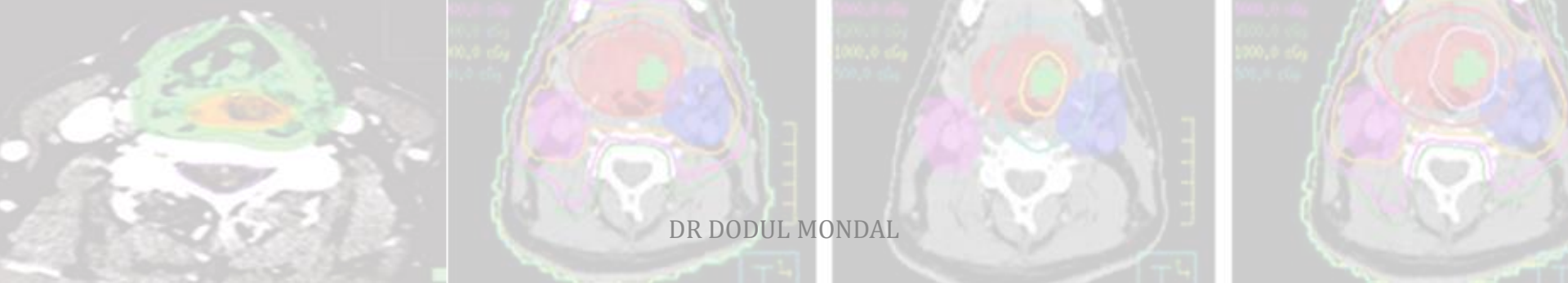
Brachytherapy Service, Institut Gustave Roussy, Villejuif, France

Conclusion

FDG PET appears to be an effective imaging technique in lymph node staging of locally advanced cervix carcinoma patients with negative CT findings. The results of PET–CT contribute to select the optimal treatment plan and to customize the radiotherapy planning by modifying radiation fields, and guide the brachytherapy planning. In endometrial cancer patients, this imaging modality may better select treatment strategies, especially in terms of lymphadenectomy. Preliminary published data on cervical cancer have indicated the prognostic value of post-therapeutic PET–CT assessment. Further evaluations in prospective clinical trials are required to assess the clinical benefit of this strategy.

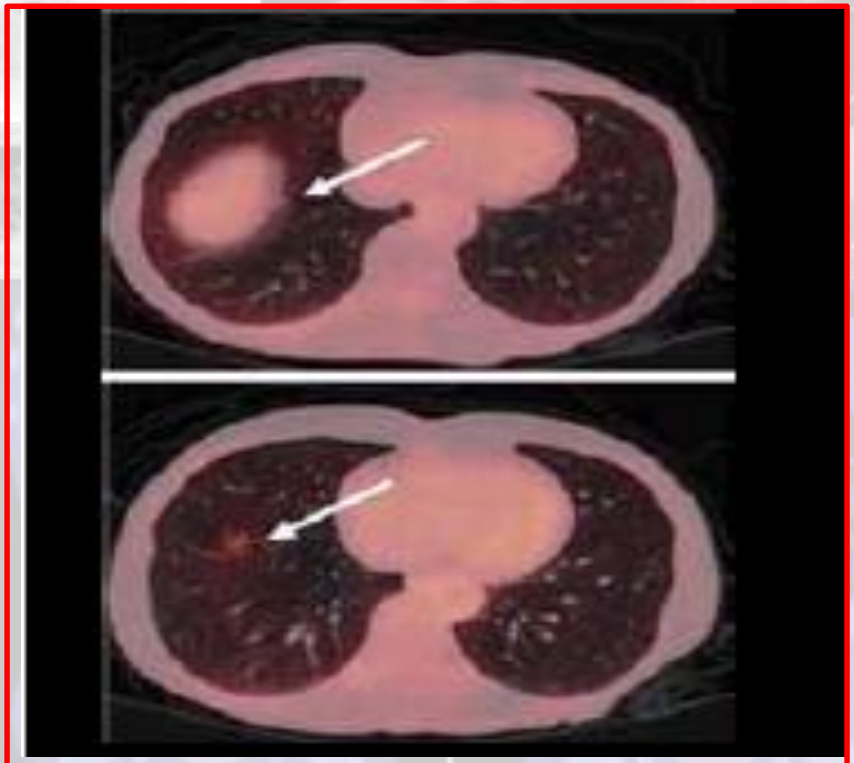
Future of PET-CT based planning: respiratory motion management

- PET-CT based respiratory motion management system available, but not widely used
- Two general philosophies of breathing adaptation:
  - Breath-hold PET scanning (eliminate motion by acquiring images in one single breathing phase (e.g. end-inspiration or end-expiration)
  - 4DPET(capture the tumour in all phases of the breathing cycle (similar to the 4DCT techniques)



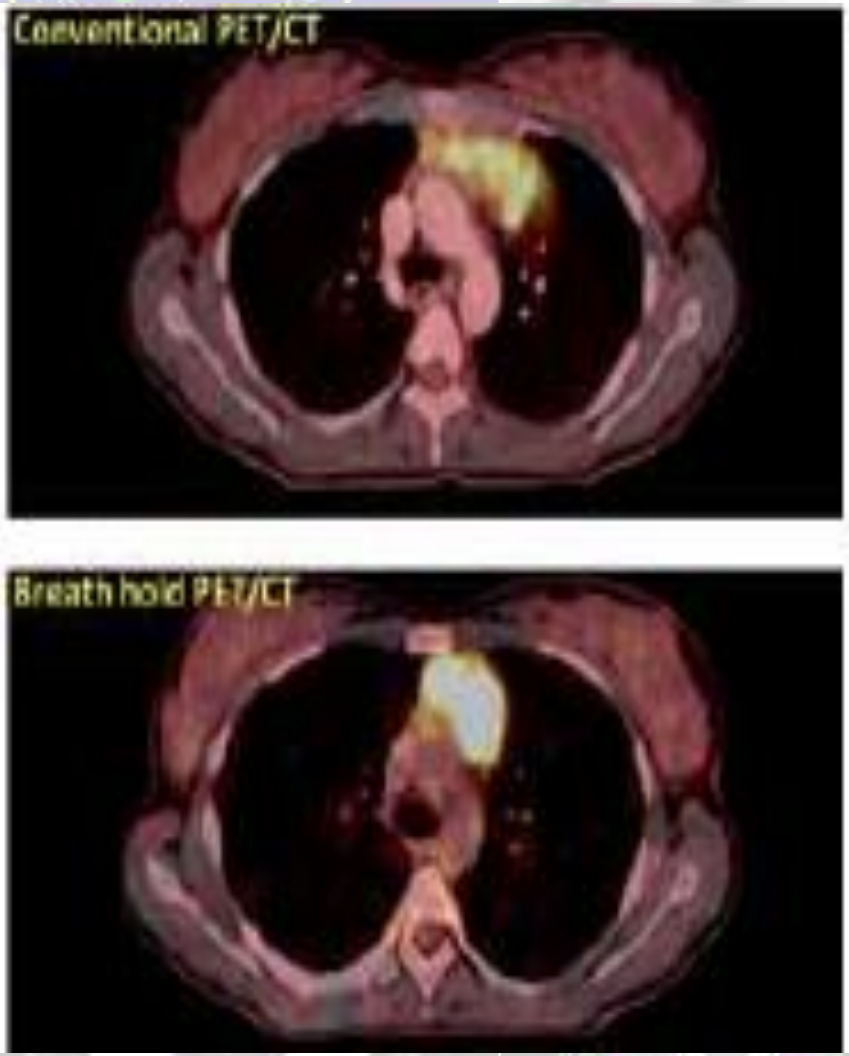
Breath-hold PET scanning

- Eliminate motion artefacts
- Patients asked to hold their breath
- Whole-body PET scan is not feasible in the breath-hold
- Often limited to a single field of view (e.g. over the thorax)
- Rest of the patient's anatomy is imaged in normal respiration.
- Respiratory guidance (such as visual and/or audio coaching)
- Images are free (or almost free) of motion artefacts and minimises the probability of a mismatch between PET and CT



Mismatch between CT and PETimages during a hybrid PET/CT examination. The CT lesion can be seen close to the liver (top image), while the PET-positive focus appears to have moved in the cranial direction

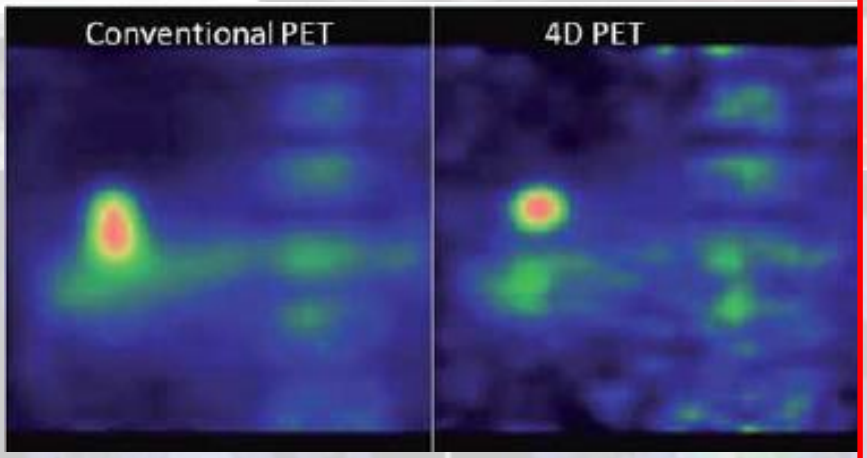
Breath-hold PET scanning



Transverse reconstructions of conventional (normal breathing) PET/CT followed by a single field of view, deep inspiration breath-hold PET/CT in a Hodgkin lymphoma patient. Note the changes in tumour appearance (more defined, homogeneous uptake in the breath-hold image)

4DPET

- Uses adapted version of the cardiac gating mode available on PET/CT
- SUV max, SUVmean and tumour volume can be recovered in spite of considerable tumour motion (over 2 cm)
- 4DPET recovers the true SUV of the tumour even in the presence of breathing motion
- Few caveats:
  - Examination time is prolonged (about 20 min for a single bed position)
  - May need to increase the activity injected (for example, by 30%
- Similar to 4DCT, 4DPET depends on a regular breathing patternto reduce artefacts



The same lung tumour imaged with conventional PET and 4D PET. Notice how the uptake area appears blurred owing to breathing artefacts in the conventional image

PET-CT based planning: Is Everything good?

ELSEVIER

Radiotherapy and Oncology

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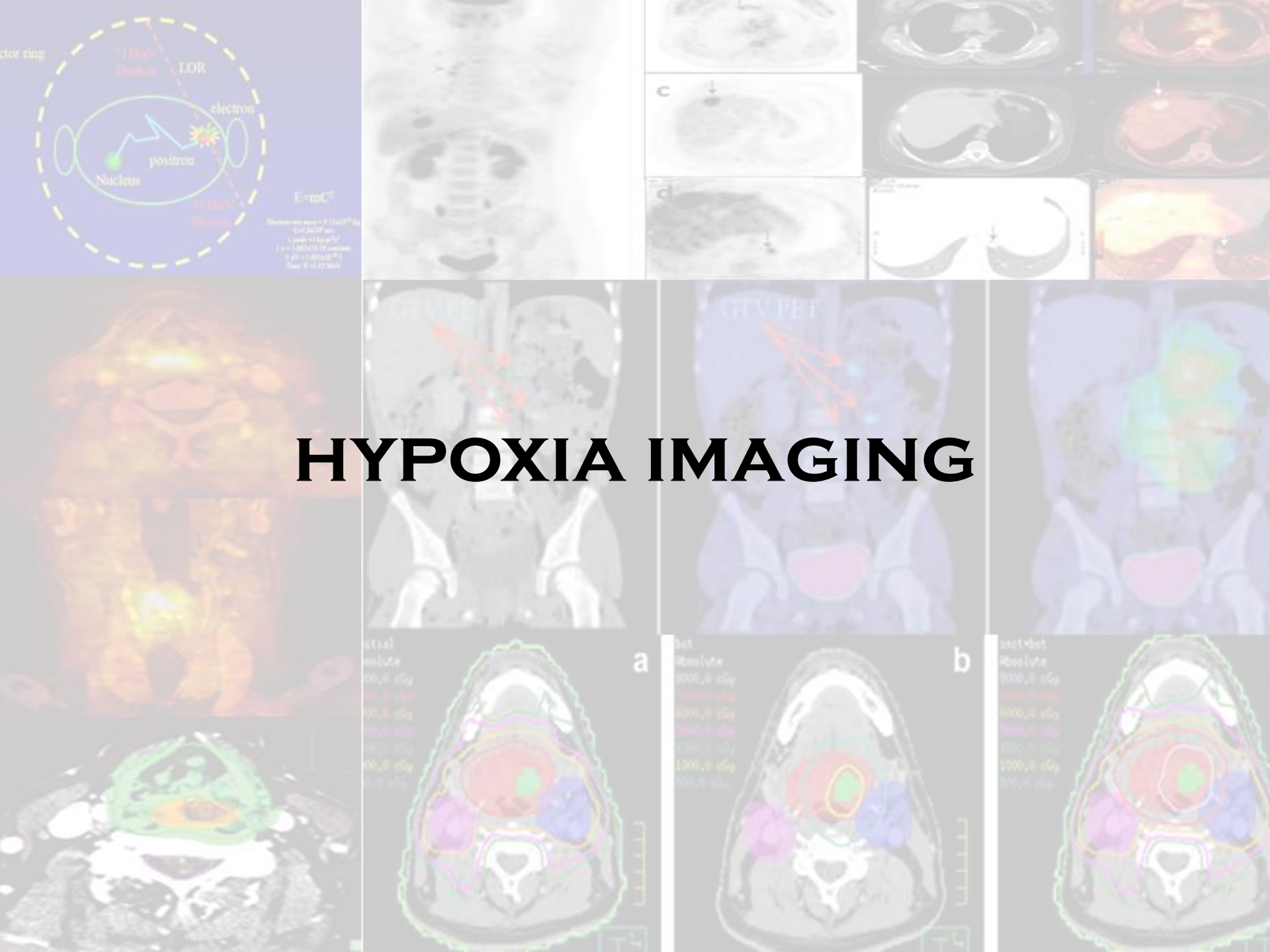
Systematic review

A systematic review on the role of FDG-PET/CT in tumour delineation and radiotherapy planning in patients with esophageal cancer

Christina T. Muijs [a,*], Jannet C. Beukema [a], Jan Pruim [b], Veronique E. Mul [a], Henk Groen [c], John Th. Plukker [d], Johannes A. Langendijk [a]

Conclusion: Since the literature is very limited standard implementation of FDG-PET/CT into the tumour delineation process for radiation treatment seems unjustified and needs further clinical validation first.



HYPOXIA IMAGING

HYPOXIA IMAGING

- Tumour hypoxia has been shown to strongly affect individual outcome of radiotherapy (RT) treatment
- Reduced tumour perfusion shown to correlate with therapy failure
- Most clinical data for head and neck cancer (HNC) and gynecological cancers
- Higher local control rates might be reached, especially for head-and-neck cancer (HNC) patients, by individually adapting the dose to hypoxic tumour regions (Dose Painting)

Why hypoxia in tumors?

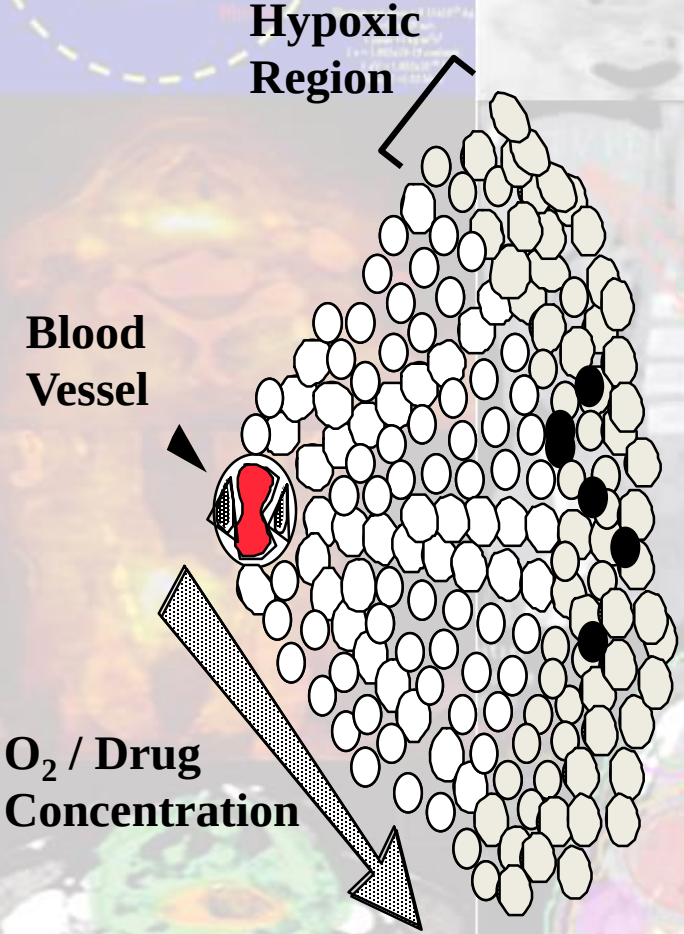
Reasons for hypoxia in tumors

- High O_2 consumption rate.
- Low vascular density.
- Inefficient orientation of blood vessels.
- Intense variations in red blood cell flux, resulting in regions of cycling hypoxia.
- A limited arteriolar supply→ low vascular pO2 in regions distant from the arteriolar source (longitudinal O2 gradient).
- Stiffening of hypoxic red blood cells
- Increased blood viscosity.

Sluggish blood flow

- Large-diameter shunts that divert blood away from the tumor bed regions of low pO2.

Biology of Tumor Hypoxia

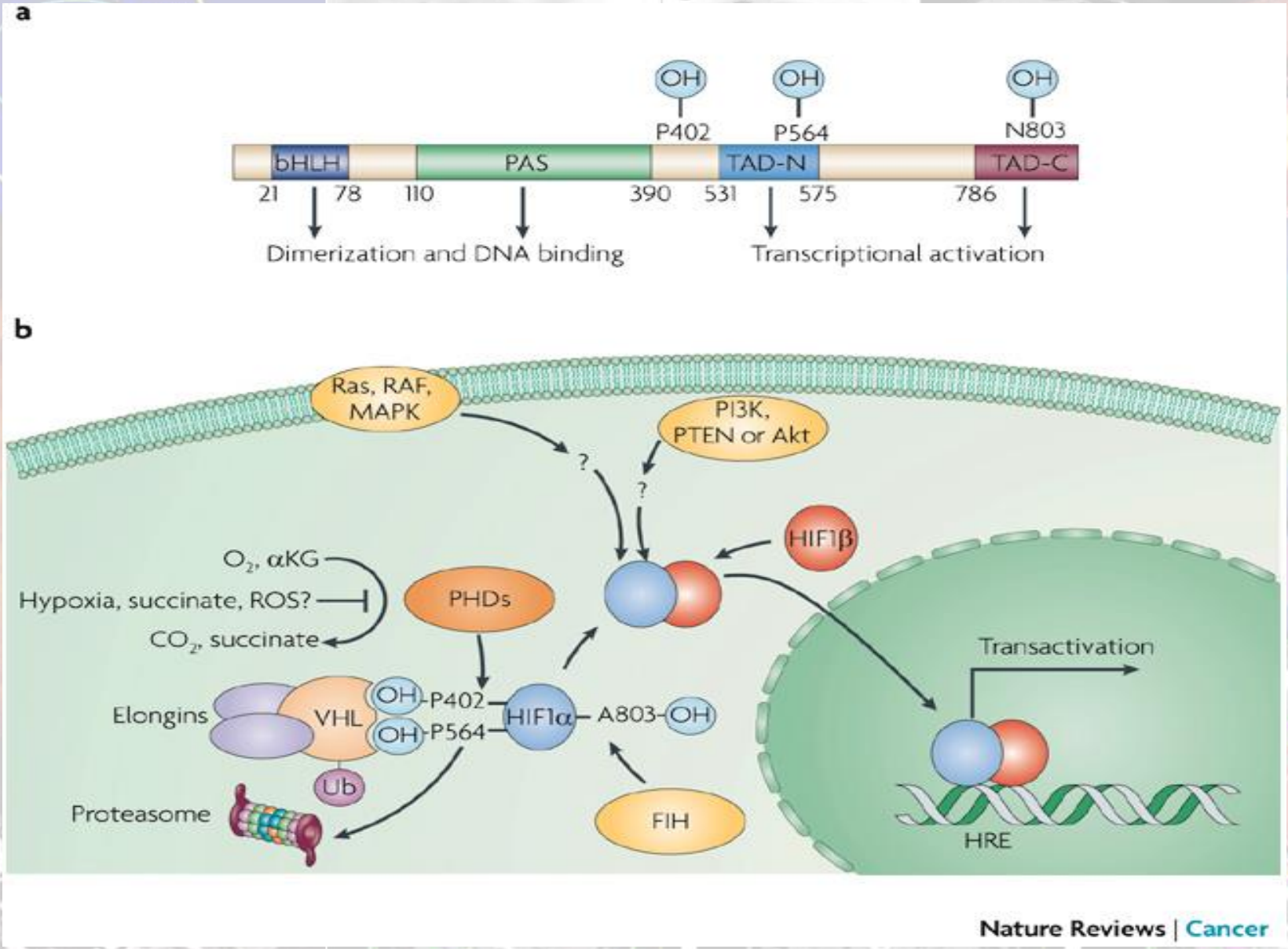


- Gene/Protein Regulation
- Selection of Apoptosis Resistance
- Increased Genomic Instability
- Chemo/Radio-therapy Resistance
- Increased Glycolysis
- Increased Angiogenesis

Hypoxia: Poor clinical outcomes

- Enhanced resistance to chemotherapy and radiotherapy
- Selection of apoptosis-resistant clones (p53)
- Facilitation of tumor invasion and metastasis
- Increased expression of drug-resistance genes
- Reduced expression of DNA-repair genes
- Increased genomic instability

Molecular pathways in hypoxic cells



Denko, N.C., Nature Reviews Cancer 8, 705-713 (September 2008)

Hypoxia PET Tracer

- Commonest non-invasive hypoxia imaging performed with PET
- Commonest tracer: **[18F]-fluoromisonidazole (FMISO)**
- Others:
  - [18F]-fluoroazomycin (FAZA)
  - Cu-ATSM
  - EF3
  - EF5 [32]
- FMISO, FAZA, Cu-ATSM validated in clinical studies

^{18}F-MISO PET scan

- Late 1980's
- Misonidazole first proposed by Chapman for hypoxic imaging
- Misonidazole covalently binds to viable hypoxic tumor cells preferentially; higher concentrations in areas of hypoxia
- Radiolabelled fluoromisonidazole as an imaging agent for tumor hypoxia 1st by Rasey et al in 1989

Int J Radiat Oncol Biol Phys. 1989 NoSurgicav;17(5):985-91.

- Tried in human tumors, esp H&N, Lung, bladder
- Single pretreatment evaluation adequate to predict hypoxic areas ,even in fractionated courses of treatment
- FDG-PET cannot reliably detect hypoxic areas from normoxic ones, F-MISO correlates better

FDG--a marker of tumor hypoxia? A comparison with [18F]fluoromisonidazole and pO2-polarography in metastatic head and neck cancer.Zimny M. et al. Department of Nuclear Medicine, University Hospital Aachen, Aachen, Germany

Acta Oncologica, 2010; 49: 934–940

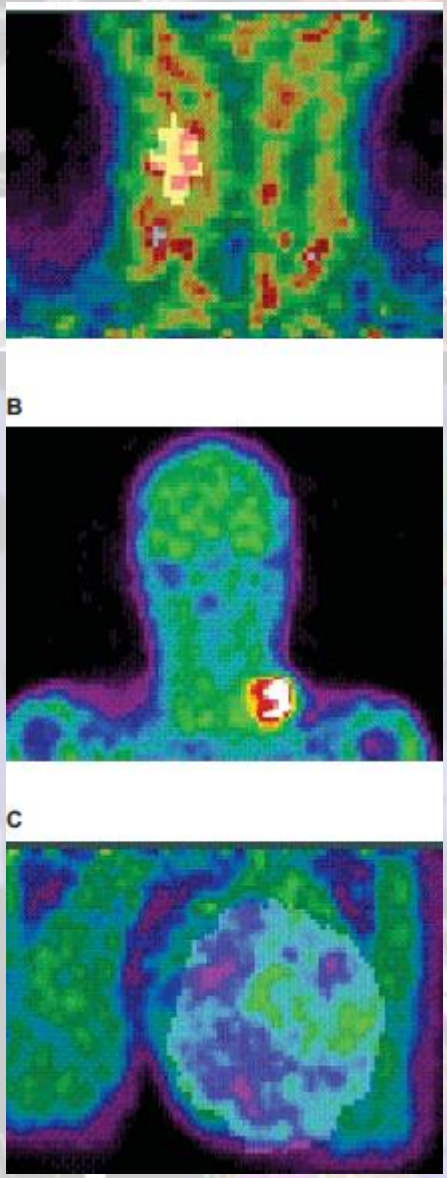
informa
healthcare

ORIGINAL ARTICLE

Identifying hypoxia in human tumors: A correlation study between ^{18}F-FMISO PET and the Eppendorf oxygen-sensitive electrode

LISE SAKSØ MORTENSEN[1*], SIMON BUUS[1*], MARIANNE NORDSMARK[1], LISE BENTZEN[1], OLE LAJORD MUNK[2], SUSANNE KEIDING[2] & JENS OVERGAARD[1]

[1]*Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark and*
[2]*PET Center, Aarhus University Hospital, Aarhus, Denmark*



- Conflicting evidence regarding whether F-MISO PET correlates to the actual tumor hypoxia as measured by needle electrodes.
- And the prognostic significance of MISO-PET?
- Next approach - to define hypoxic areas of the tumor in order to escalate doses to part of the tumor

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journal homepage: www.thegreenjournal.com

Review

Implementation of hypoxia imaging into treatment planning and delivery ☆

Daniela Thorwarth [a,*], Markus Alber [b]

[a] Section for Biomedical Physics, University Hospital for Radiation Oncology, Eberhard-Karls-University Tübingen, Germany; [b] University Hospital for Radiation Oncology, Ludwig-Maximilians-University Munich, Germany

Purpose: To review the current status of implementation of functional hypoxia imaging in radiotherapy (RT) planning and treatment delivery.

Methods: Before biological imaging techniques such as positron emission tomography (PET) or magnetic resonance (MR) can be used for individual RT adaptation, three main requirements have to be fulfilled. First, tissue parameters have to be derived from the imaging data that correlate with individual therapy outcome. Then, the spatial and temporal stability of hypoxia PET images needs to be established. Finally, the dose painting (DP) concepts have to be practically feasible to be used as a basis for clinical trials.

Results: A number of recent clinical studies could show the correlation of hypoxia PET imaging with different tracers and RT outcome. Most of the studies revealed a correlation between mean or maximum values and parameters assessed from the PET avid volume and treatment success, only few investigations used quantitative imaging. Multiparametric imaging seems to be very valuable. Recently, the spatial and temporal stability of hypoxia PET attracted attention. Temporal changes in the distribution of functional tumour properties were reported. Furthermore, technical feasibility of DP by contours (DPC) as well as DP by numbers (DPBN) was shown by several investigators. The challenge is now to design clinical studies in order to prove the impact of DP treatments on individual therapy success.

Conclusion: A patient-specific adaptation of RT based on functional hypoxia imaging with PET is possible and promising. Conceptual feasibility could be shown for DPBN whereas to date, only DPC seems to be plausible and feasible in a clinical context.

 Radiotherapy and Oncology 97 (2010) 172–175

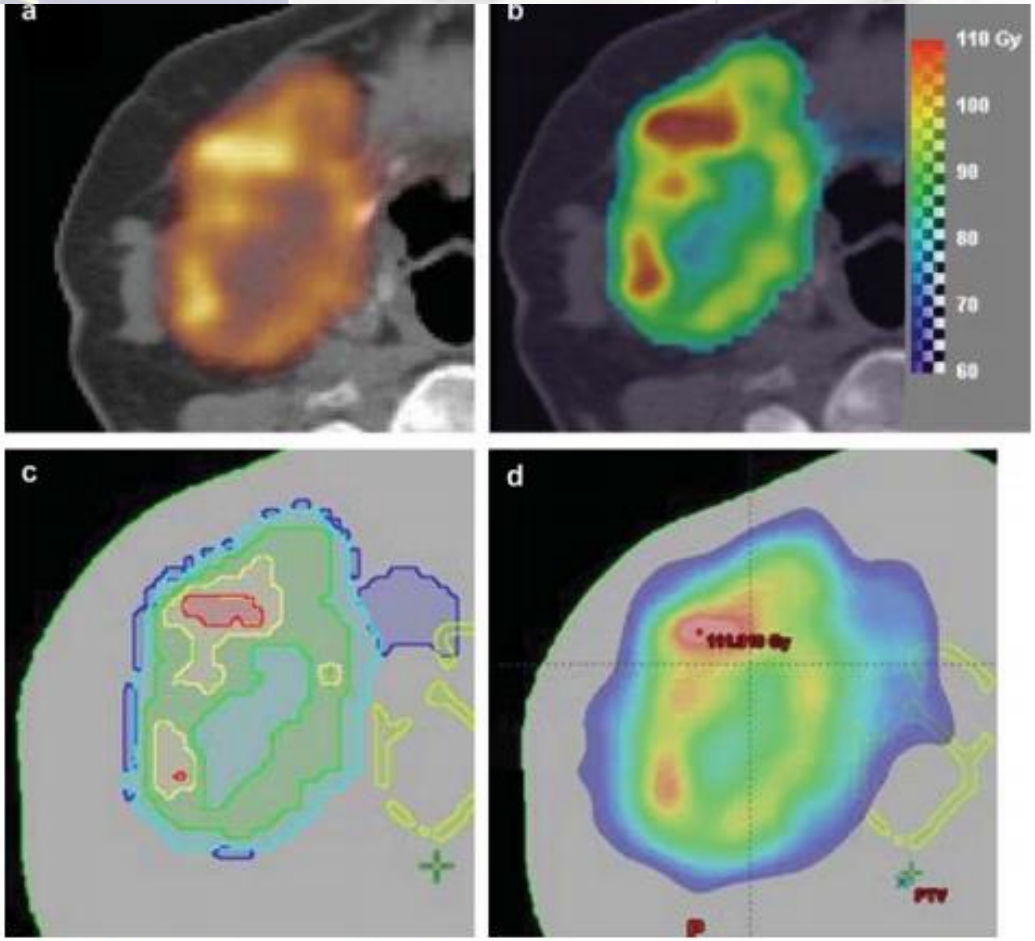

Figure 1. (a) The Cu-ATSM PET image for the patient, (b) the dose prescription map, (c) the substructures corresponding to five dose prescription levels, (d) an example of the optimised dose.

Dose painting by contours(DPC) is feasible while Dose painting by numbers (DPBN) is only theoretically possible as of now

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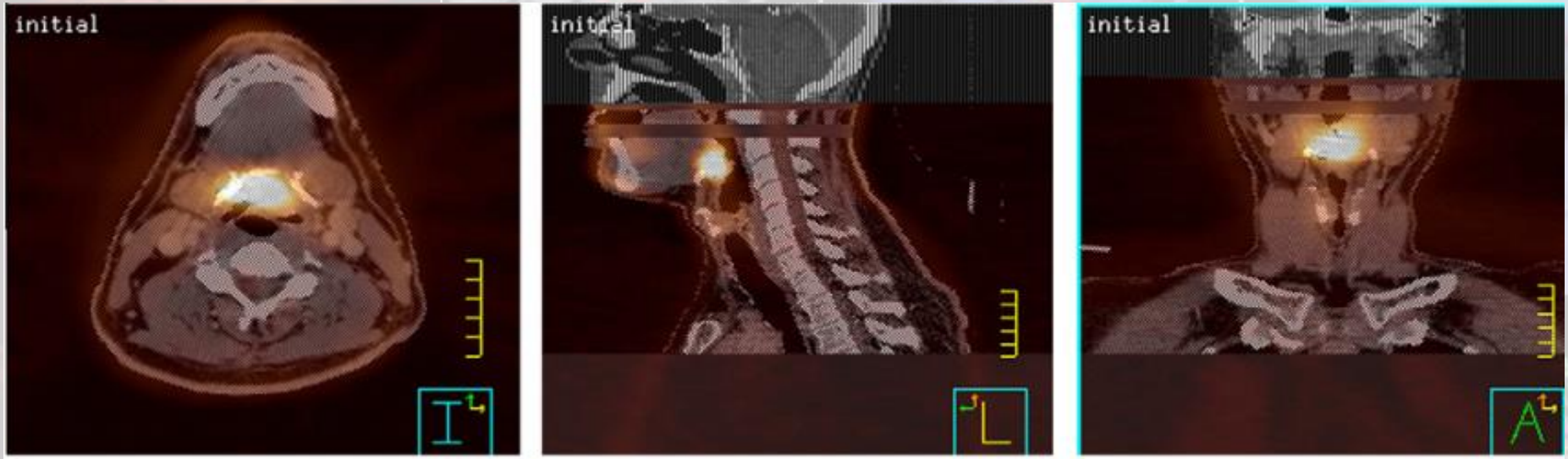
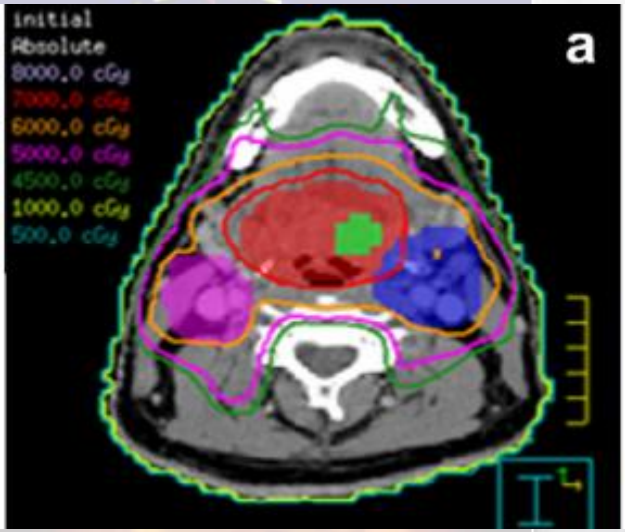
Hypoxic PET in treatment planning

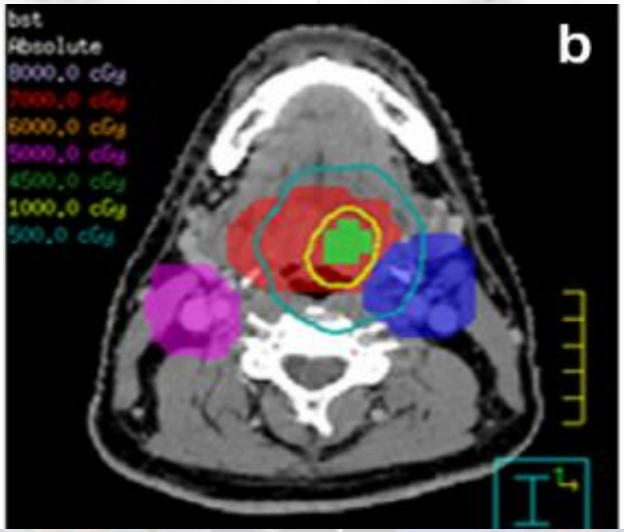
Hypoxia imaging with [F-18] FMISO-PET in head and neck cancer: Potential for guiding intensity modulated radiation therapy in overcoming hypoxia-induced treatment resistance

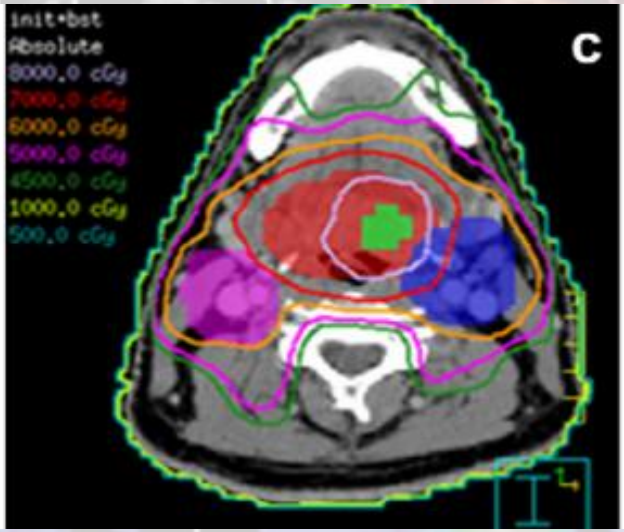
Kristi Hendrickson [a], Mark Phillips [a], Wade Smith [b], Lanell Peterson [c], Kenneth Krohn [a,c], Joseph Rajendran [a,c,*]



Co-registered CT and FMISO-PET images in transaxial, sagittal, and coronal projections for BOT example patient







Isodose display on axial slices for SIB IMRT plan showing conformal 70-Gy dose around primary PTV (red) and 60-Gy dose around affected nodes (pink and blue). Hypoxic GTV (green) is covered by 80-Gy isodose. Parotid glands (orange and lilac) are avoided by high isodose lines

Conclusion: FMISO-PET will prove useful for selecting patients for the most appropriate treatment. Its applications include:

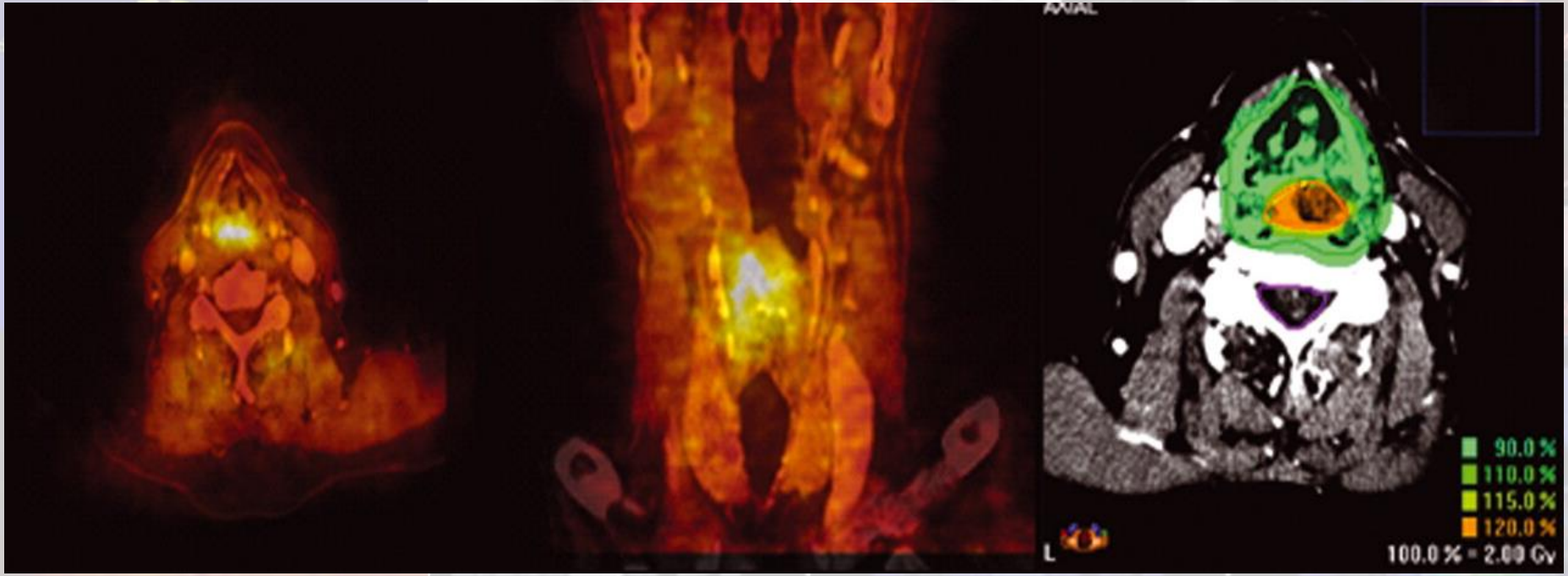
(1) Identification and localization of significant hypoxia

(2) Delineation of hypoxic sub-volumes within the GTV for boost radiation

(3) Selection of appropriate systemic agents to complement the boost therapy

FAZA

- 18 F-labeled PET hypoxia-tracer ^{18}F azomycin arabinoside (FAZA)
- Superior pharmacokinetics than F-MISO: faster clearance from normal tissues
- Significantly higher tumor to background (TB) ratio than F-MISO PET= better resolution



Integrated ^{18}F-azomycin arabinoside (FAZA)-PET/CT in a patient with larynx squamous cell carcinoma. The PET/CT image fusion ((a) axial; (b) coronal; (c) intensity-modulated radiotherapy dose painting). The hypoxic area (biological target volume) is treated with 2.4 Gy/fraction; the gross tumour volume, based on radiological and clinical data is treated with 2 Gy/fraction

Int. J. Radiation Oncology Biol. Phys., Vol. 49, No. 4, pp. 1171–1182, 2001

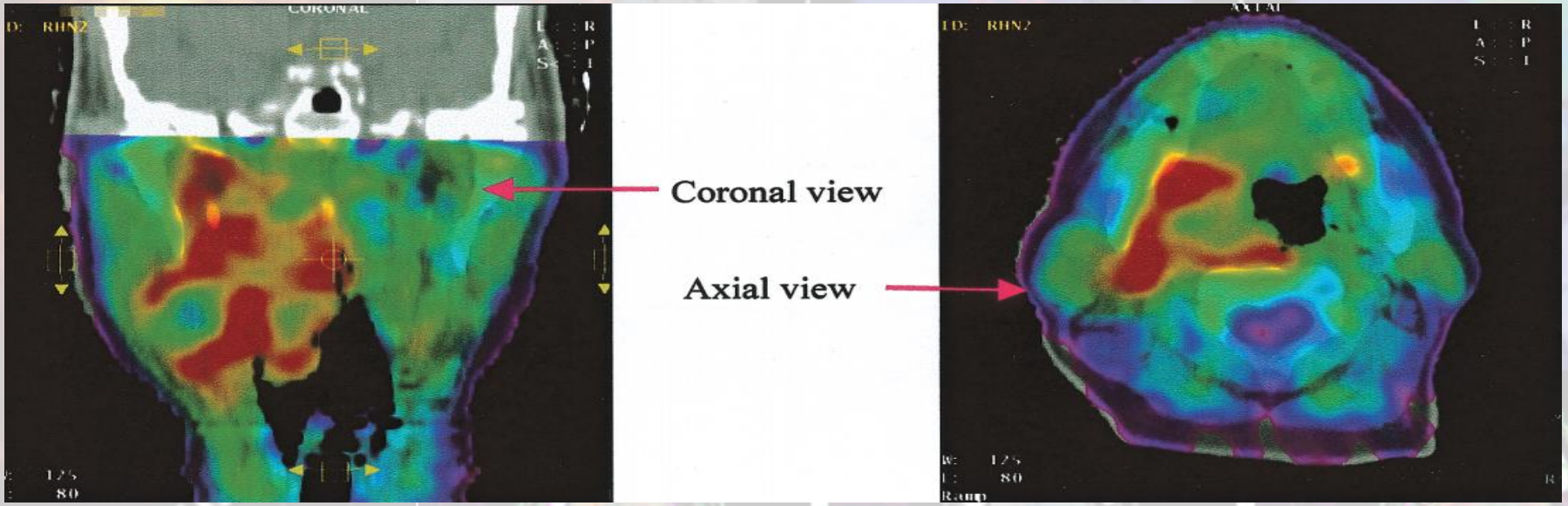
0360-3016/01/$–see front matter

PII S0360-3016(00)01433-4

PHYSICS CONTRIBUTION

A NOVEL APPROACH TO OVERCOME HYPOXIC TUMOR RESISTANCE: Cu-ATSM-GUIDED INTENSITY-MODULATED RADIATION THERAPY

K. S. Clifford Chao, M.D.,* Walter R. Bosch, Ph.D.,* Sasa Mutic, M.S.,*
Jason S. Lewis, Ph.D.,† Farrokh Dehdashti, M.D.,‡ Mark A. Mintun, M.D.,†‡
James F. Dempsey, Ph.D.,* Carlos A. Perez, M.D.,* James A. Purdy, Ph.D.,* and
Michael J. Welch, Ph.D.†



Color-washed images illustrated regions of heterogeneous 60Cu-ATSM intensity within the gross tumor representing the presence of tumor hypoxia.

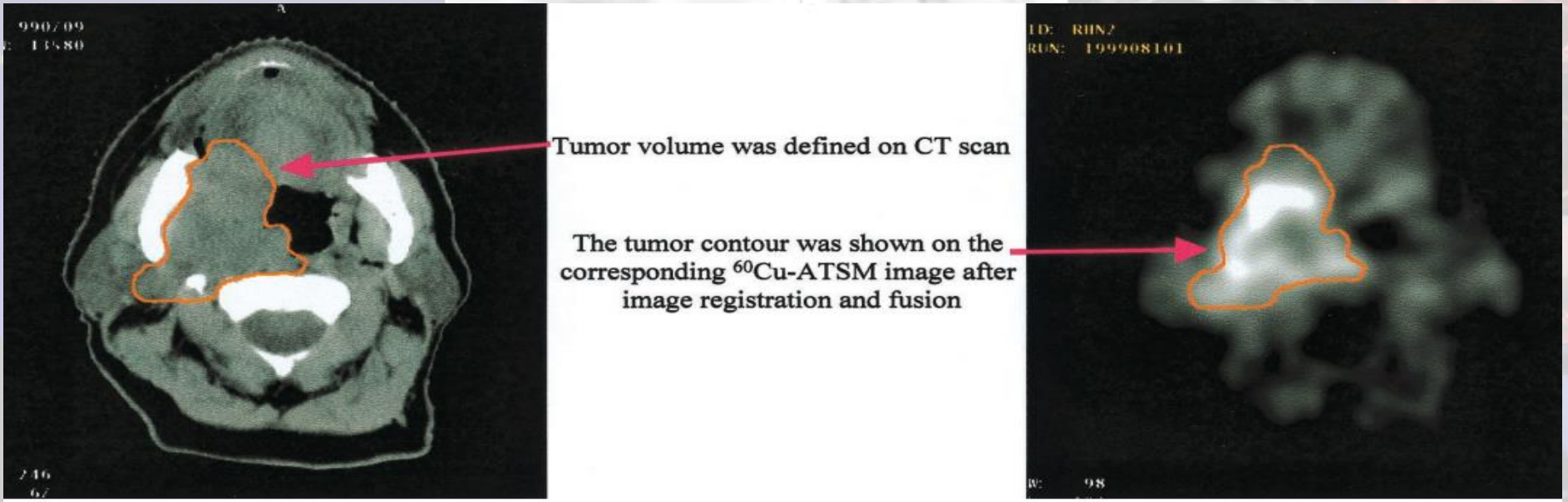


Fig. 7. Delineation of the gross tumor volume and its ATSM-avid fraction by CT-PET imaging fusion.

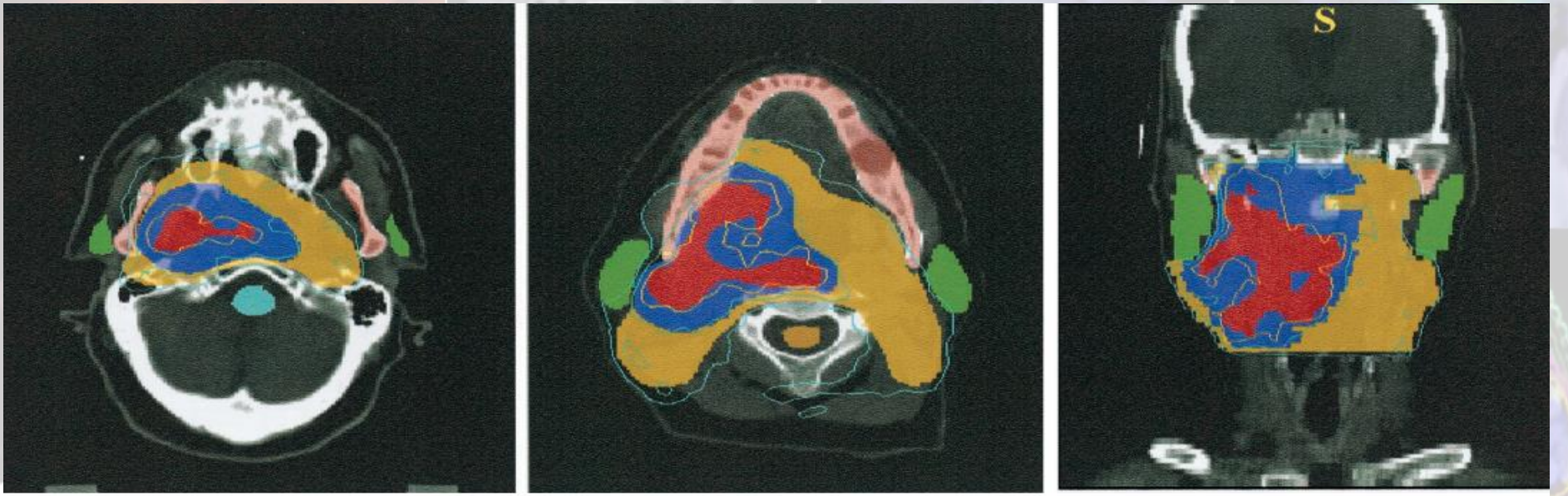


Fig. 8. Dose distribution (blue iso-dose line-50 Gy, green isodose line-70 Gy, yellow isodose line-80 Gy) of Cu-ATSM-guided intensity-modulated radiation therapy.

Fractionation and Hypoxia

- Fractionated course of radiotherapy is more effective in a given hypoxic tumor than a single fraction
- Minimum time between 2 fractions of radiotherapy should be 4 hours
- Hyperfractionation/ accelerated radiotherapy also tackles the issue of accelerated repopulation of tumor cells, esp in H&N cancer where most of the studies of hypoxic modification have also been carried out
- Delivering hypofractionated radiation to the hypoxic component may give better outcome

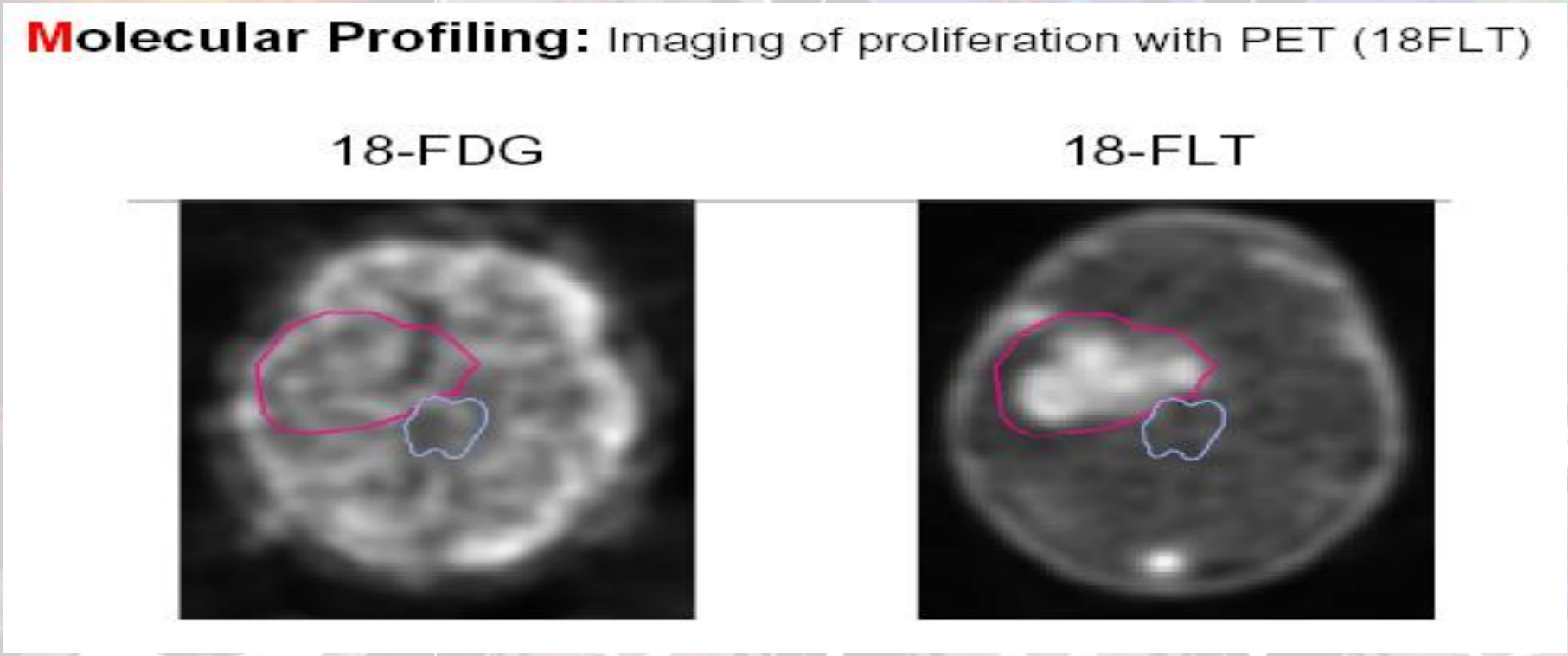
Hypoxia imaging: Unresolved issues

- Hypoxia-a dynamic phenomenon within tumor
- Limited spatial resolution
- Influence of changes in the oxygenation status before and during treatment?
- Dose levels required to effectively eliminate these radioresistant subpopulations?

OTHER MOLECULAR IMAGING

Tumor Proliferation

- Radiolabelled deoxy-uridines: rapid degradation of these compounds in vivo
- FLT- 18F-3'deoxy 3'flourothymidine.- 2 studies have shown significant correlation with Ki-67 labeling index



Other targets

EGFR

Cyclin D

- Molecular risk profiling
- Search for fingerprinting of malignant phenotypes, sensitive to a specific type of modified RT(accelerated /hyperfractionated).

Many new Theragnostic imaging modalities are likely to be identified.

Theragnostic imaging for radiation oncology is use of molecular and biological imaging to prescribe the distribution of radiation in four dimensions- 3 dimensions of space plus time.

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Molecular radiobiology

Radiolabeled anti-EGFR-antibody improves local tumor control after external beam radiotherapy and offers theragnostic potential

Lydia Koi [a,b], Ralf Bergmann [c], Kerstin Brüchner [a,b,d], Jens Pietzsch [c,e], Hans-Jürgen Pietzsch [c,e], Mechthild Krause [a,b,d,f], Jörg Steinbach [c,e], Daniel Zips [a,b,g,1], Michael Baumann [a,b,d,f,*,1]

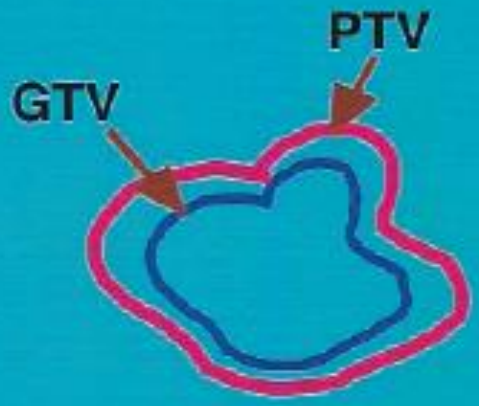
Results: TCD50 after EBRT was significantly decreased by EGFR-targeted RIT in FaDu (RT responder) but not in UT-SCC-5 (RT nonresponder).

Conclusion: EGFR-targeted EBRIT can improve permanent local tumor control compared to EBRT alone. PET imaging of bioavailability of labeled cetuximab appears to be a suitable predictor for response to EBRIT.

BIOLOGICAL TARGET VOLUME/ BIOLOGICAL EYE VIEW

- Dose uniformity within PTV in external beam-matter of tradition and convention.
- IMRT-Non uniform dose, Dose painting/sculpting…but how?
- Answer is: Biological imaging
- Biological tumor volume – Derived from biological images and their use may guide customized dose delivery to various parts of treatment volume.

Biological Target Volume?



- PET
- F-miso

Hypoxia

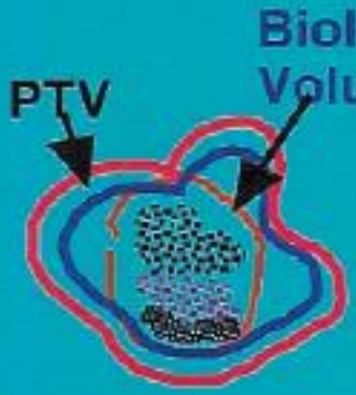
- MRI/MRS
- choline/citrate

Tumor burden

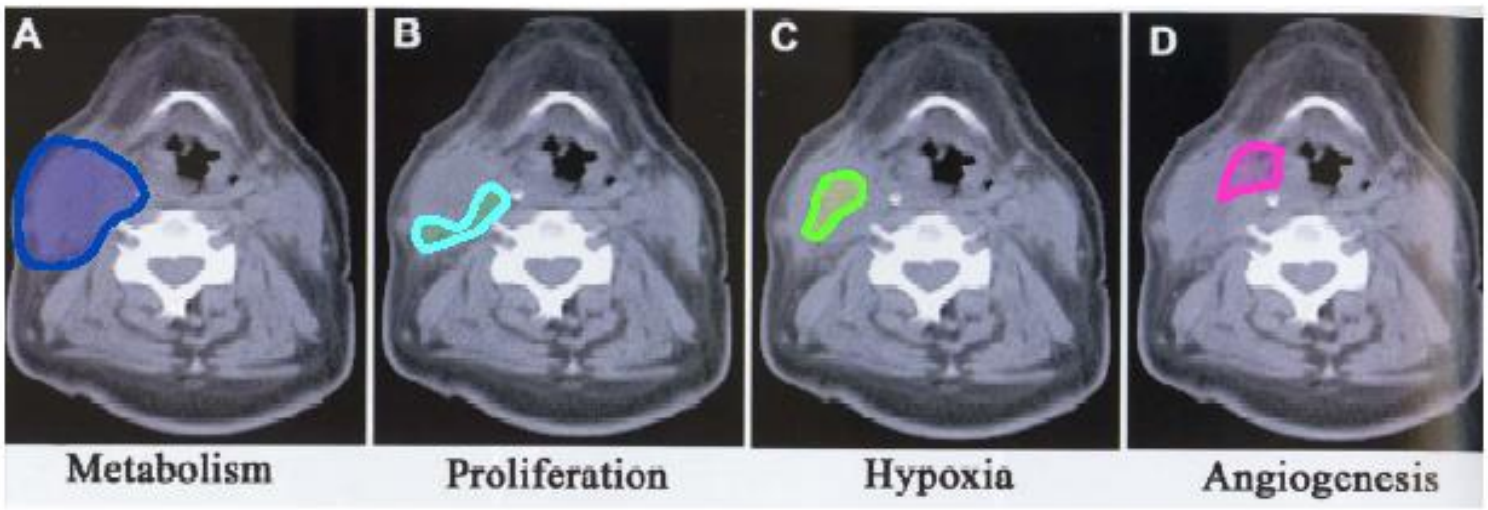
- PET
- IUDR

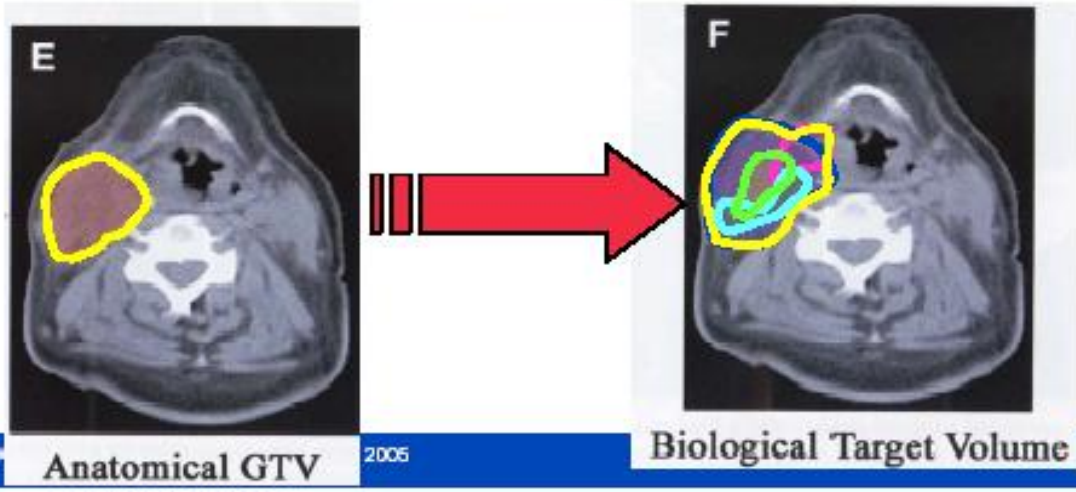
Tumor growth

Biological Eye View



The concept of a „biological target volume“





Bioluminescence

- Bioluminescence is the production and emission of light by a living organism
- Bioluminescence is emitted when chemical energy is converted to light

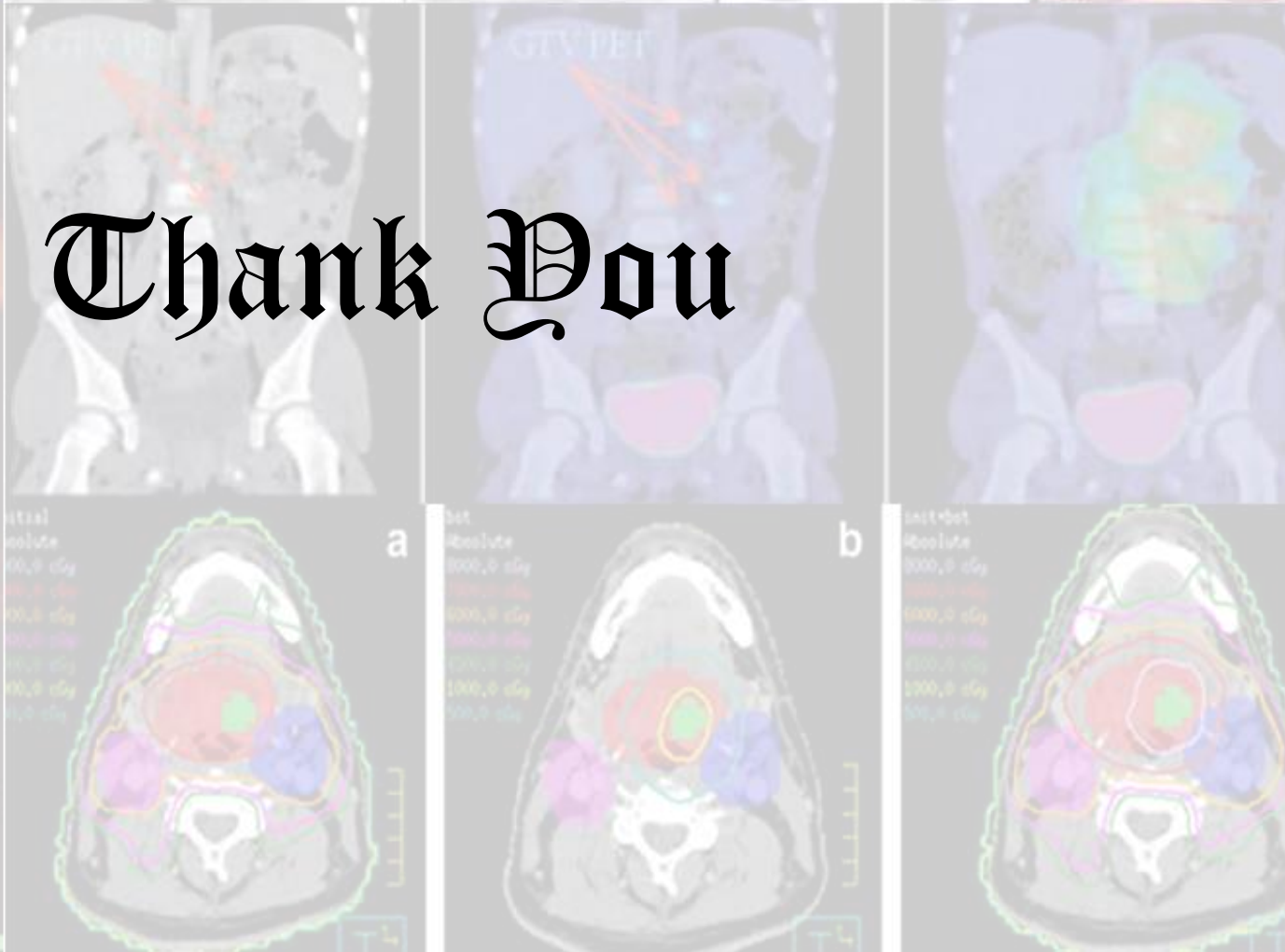
Bioluminescent Imaging of HPV-Positive Oral Tumor Growth and Its Response to Image-Guided Radiotherapy

Rong Zhong, Matt Pytynia, Charles Pelizzari, and Michael Spiotto

- In presence of activated Cre recombinase, luciferase activity, and by proxy, HPV oncogenes were induced to 11-fold higher levels.
- Tamoxifen treatment resulted in oral tumor development with increased bioluminescent activity
- Decreased bioluminescence after treatment with rapamycin or image-guided radiotherapy
- Novel system enables to rapidly visualize HPV-positive tumor growth and new interventions using clinically relevant drugs and radiotherapy techniques

CONCLUSION

- Molecular imaging-a powerful tool in cancer management
- PET scan is most widely accepted and utilized
- Anatomic imaging and molecular imaging- complementary to each other
- Molecular imaging-perhaps the future of radiation oncology decision making and planning



Thank You