Bio-molecular basis & challenges of PET/CT in radiation treatment planning

Garrett CL Ho, MD
Hong Kong Sanatorium & Hospital

Bergonie and Tribondeau (1906)

*Haber AH, Rothstein BE. Radiosensitivity and rate of cell division: "**law of Bergonie and Tribondeau**". Science 1969;163:1338-1339*

Radiosensitivity ⟷ Cytokinetics

- Less mature
- Predifferentiated
- Well-nourished
- High mitotic rate
- High metabolic rate

- Young generation
- Cellular differentiation
- Vascular supply, O_2 tension
- Mitotic phase
- Biochemistry

Bergonie and Tribondeau (1906)

Haber AH, Rothstein BE. Radiosensitivity and rate of cell division: "law of Bergonie and Tribondeau". Science 1969;163:1338-1339

Radiosensitivity ⟷ Cytokinetics

- Less mature
- Predifferentiated
- Well-nourished
- High mitotic rate
- High metabolic rate

PET parameters
(PERCIST, Kinetics)

Tumor metabolism
Receptor expression

RT on Overall Survival (OS)

- Highly associated with the ability to offer local regional control (LRC) and to minimize the degree of treatment-induced side-effects
- High degree of precision
- To achieve the best chance of tumor control, aim at giving a curative dose maximal tolerance

Art of RT Science

- Define the boundary of the radiation portal coverage and distribution of the radiation flux density
- Conventional tool for calculation of tumor boundary & volume is CT/MR
- Difficulties in assessing or monitoring the biological changes of the tumor during therapy

Pappas EP et al. Technology in Cancer Research & Treatment 2017, Vol. 16(6) 1120–1129

PET/CT in Radiation Therapy

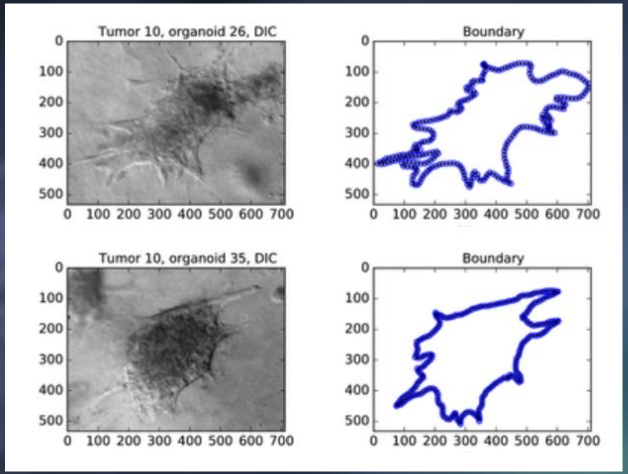
- Modification of management: 63%
  - Cancelled RT: 17%
  - Curative to palliative: 20%
  - RT dose change: 30%
  - Target volume change: 40%

(Dizendorf E, et al., Zurich
Kessler ML, et al., U Michigan)

PET/CT for RT Planning

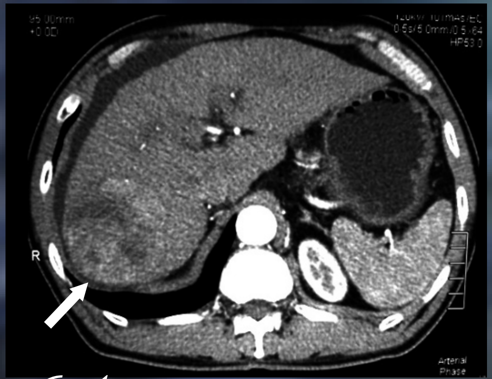
- Specific functional tracer
- Probe actual biochemical derangement
- Quantify the rate of abnormal biochemical processes
- metabolic index (SUV or Km)
- Metabolic volume
- Degree of cellular differentiation

metabolic rate constant

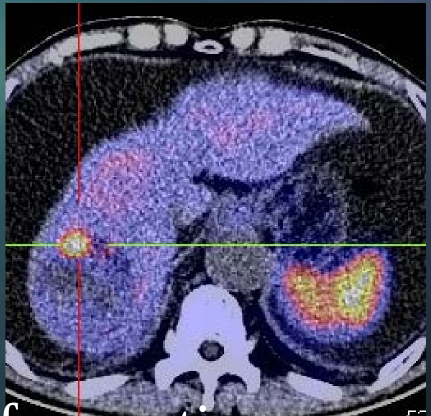


Independent of the availability of a well-defined physical boundary

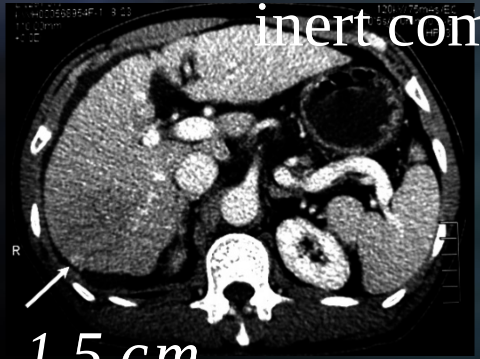
A biological boundary is more relevant to represent the outward spreading tumor activity



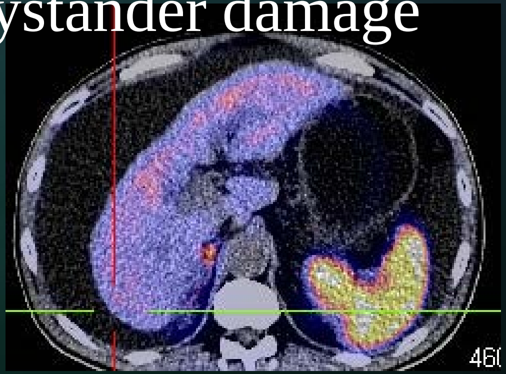
6.4 cm

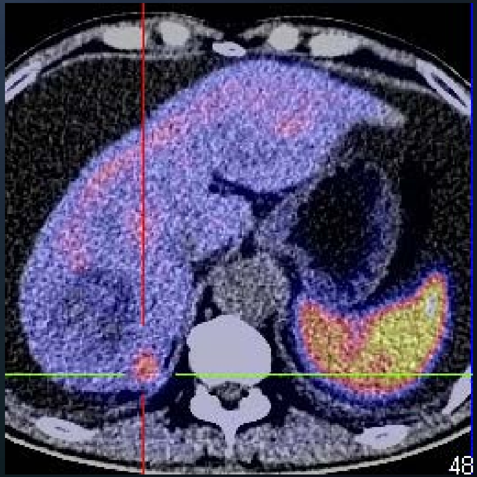


avoiding the inclusion of necrotic areas, inert components and bystander damage



1.5 cm





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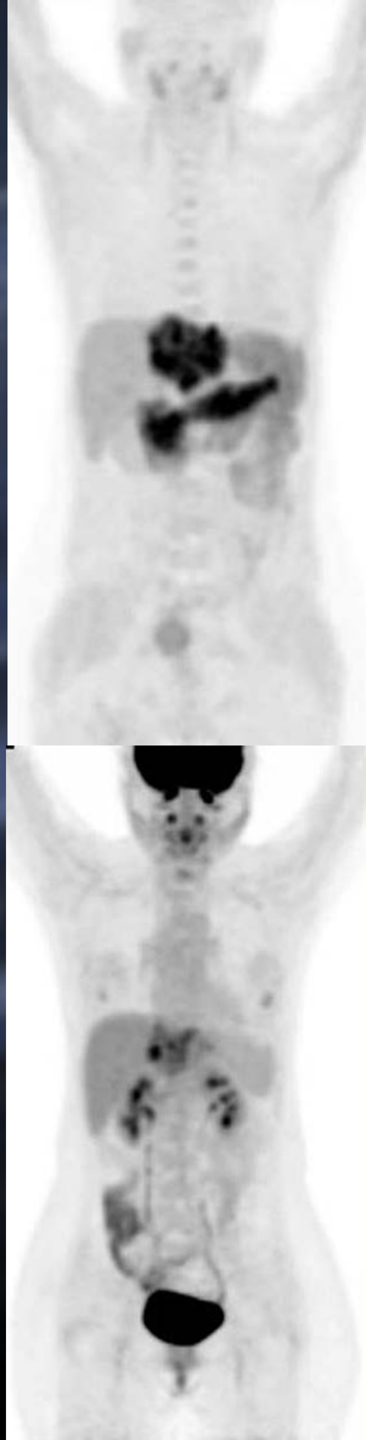
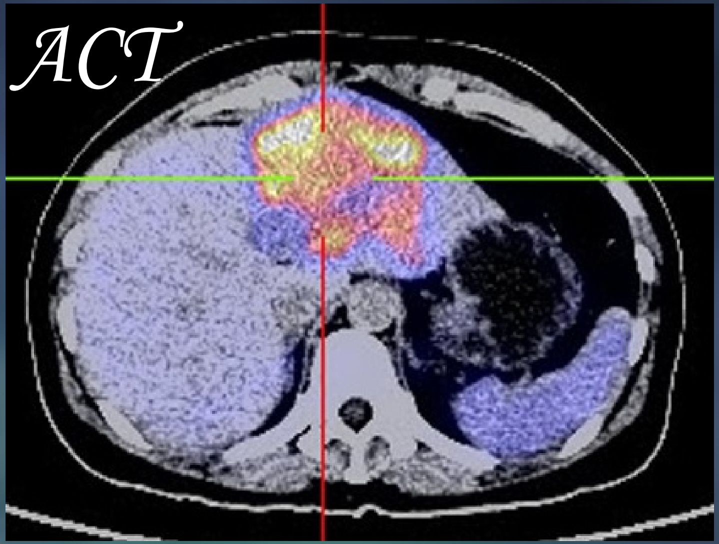
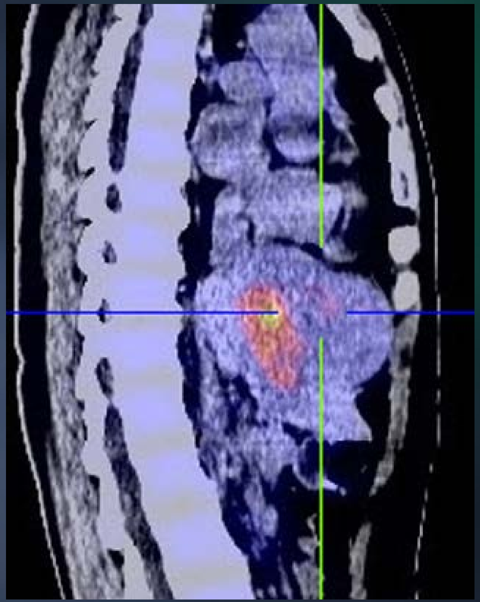
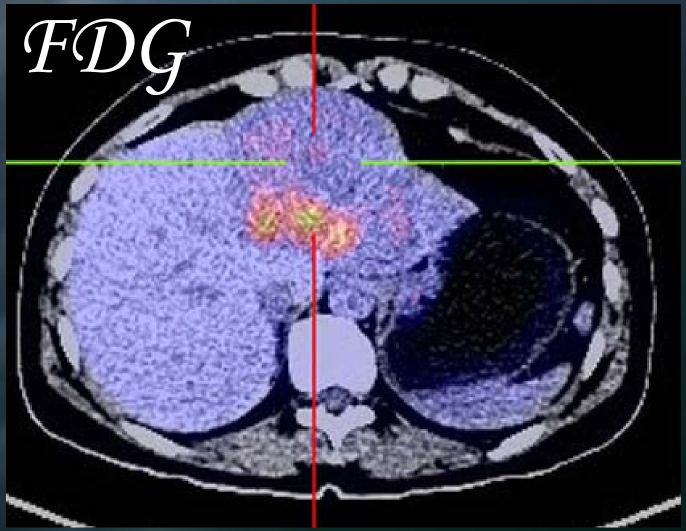
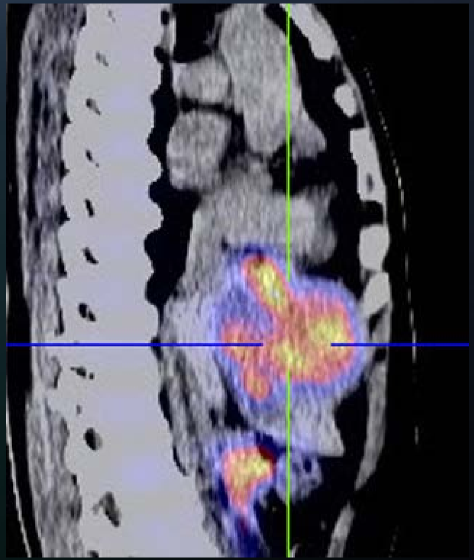






Tracer-specific tumor metabolism





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Quantification

MTB = Metabolic Tumor Burden

$$= \sum_{v_i=1}^{n} [\text{meta activity x meta volume}]_{v_i}$$

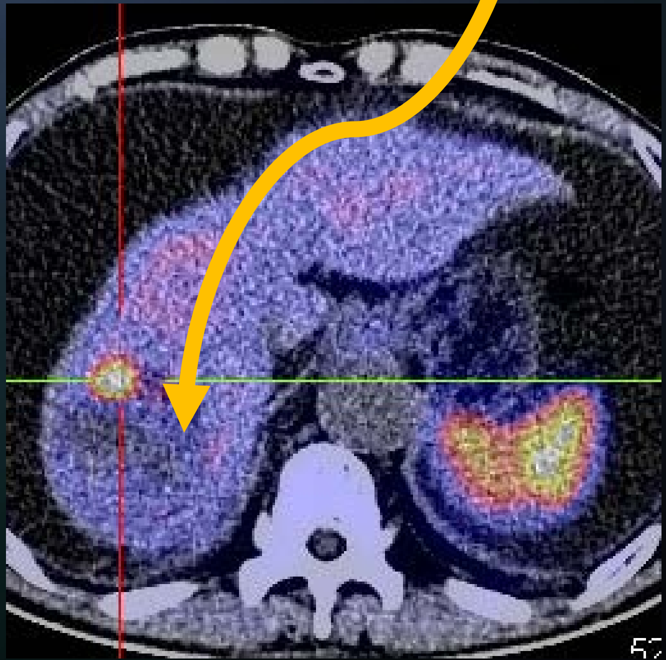
avoiding the inclusion of necrotic areas, inert components and bystander damage

= True Tumor Burden

"Metabolic growth center"

$\neq$ Geometric center

RT dose escalation & beam direction



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Cellular Hypoxia

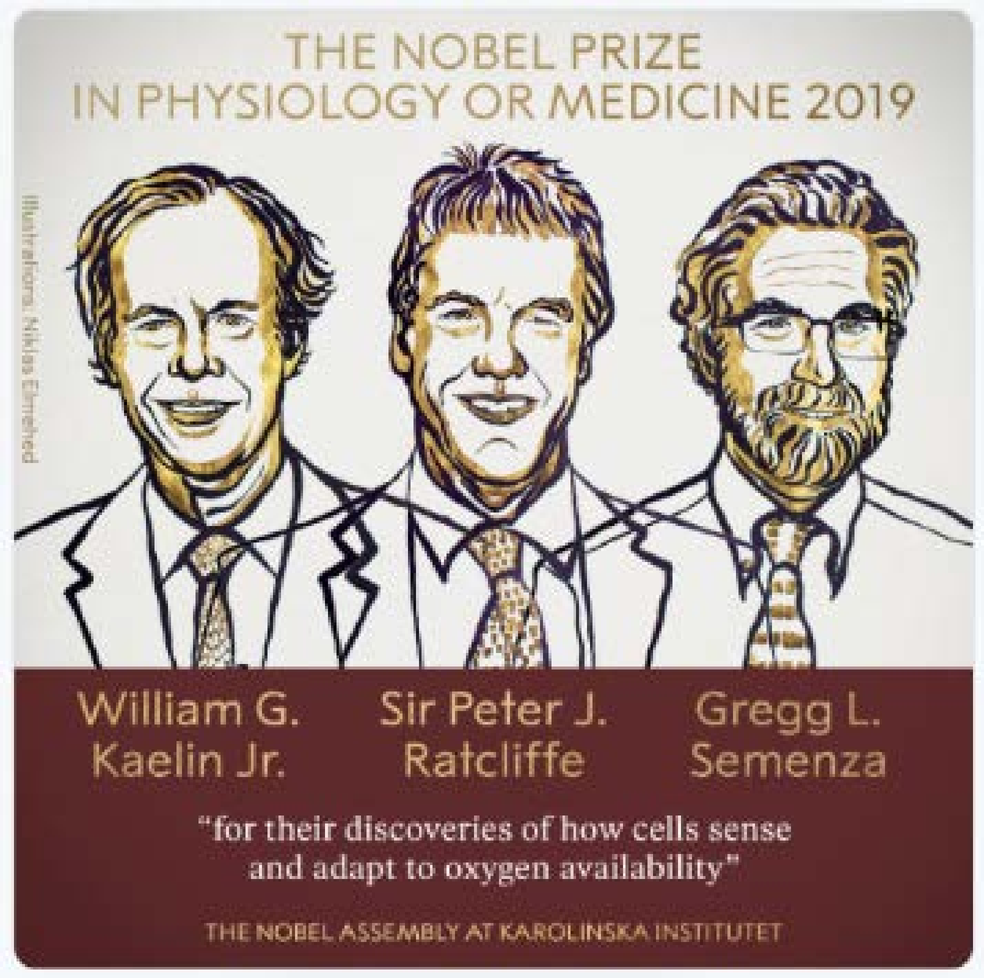
- <5-10 mmHg O_2 tension
- Delivery-to-consumption mismatch
- Sign of poor tumor response to treatment
- Negative prognostic indicator
- Association with aggressive tumor phenotype
- Therapeutic resistance

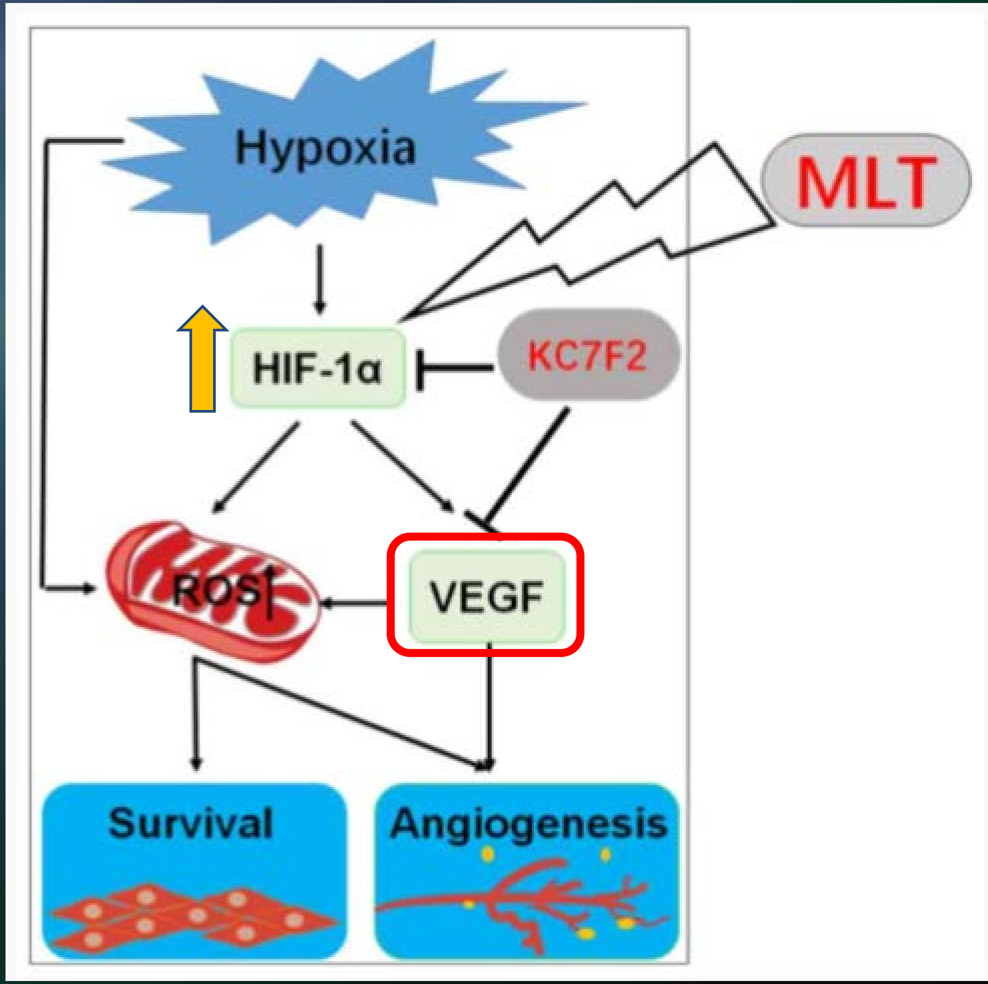
Types of Cellular Hypoxia

1. Impaired blood supply
2. Impaired diffusion
3. Impaired O2 carrier capacity

1. Ischemic hypoxia
2. Chronic tissue hypoxia
3. Anemic hypoxia

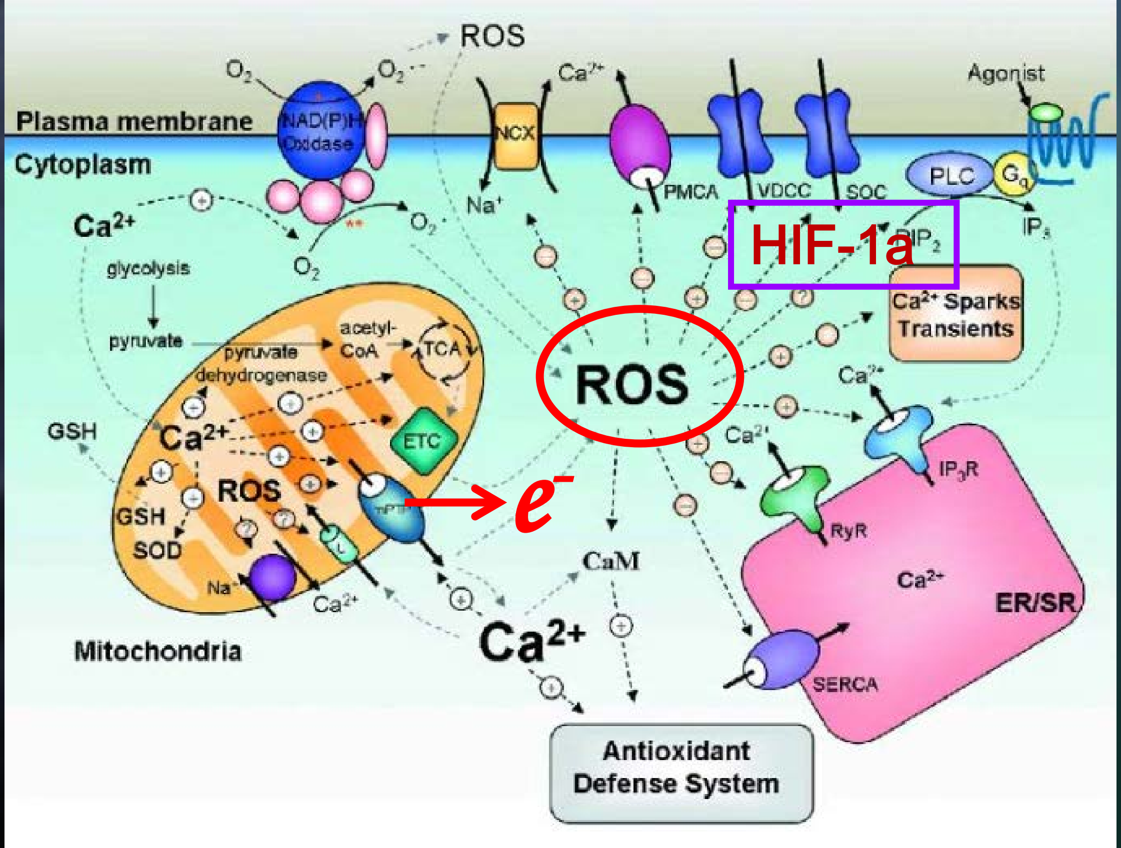
Hypoxia induces HIF-1α & angiogenesis





Cheng J et al. Melatonin restricts the viability and angiogenesis of vascular endothelial cells by suppressing HIF-1α/ROS/VEGF. Int J Mol Med 43: 945-955, 2019

Hypoxia leads to mitochondrial oxidative stress and ROS



$2e^- + O_2 \rightarrow 2\,O^-$

$O^- + H_2O \rightarrow H_2O_2^-$

$O^- + O_2 \rightarrow O_3^-$

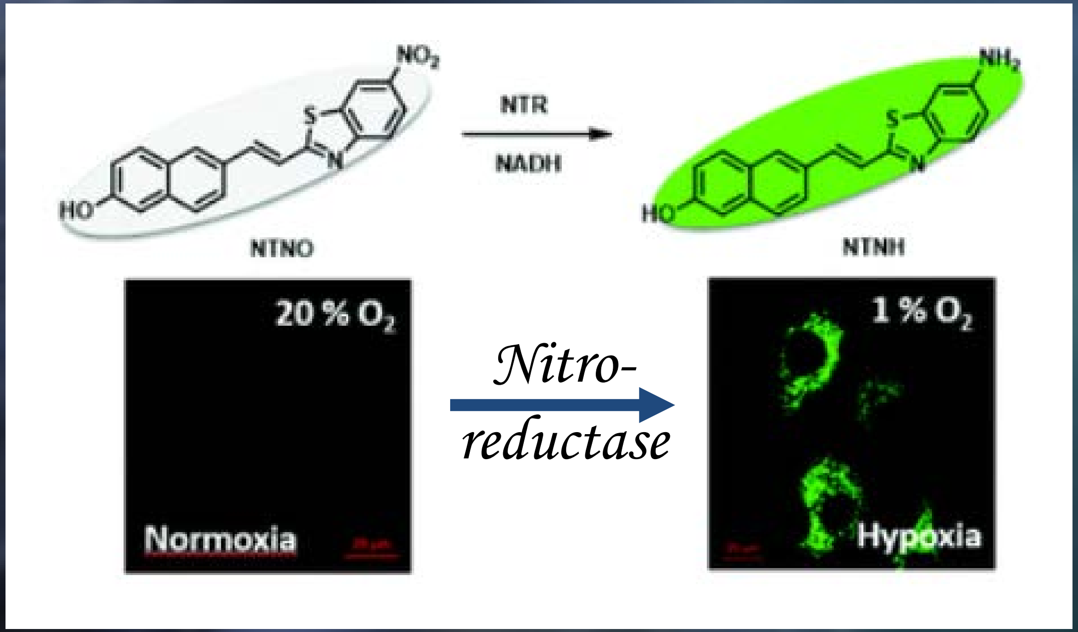
ROS

$\uparrow\uparrow$ *Oxidoreductase*

$H_2O_2^- \longrightarrow H_2O + OH^-$

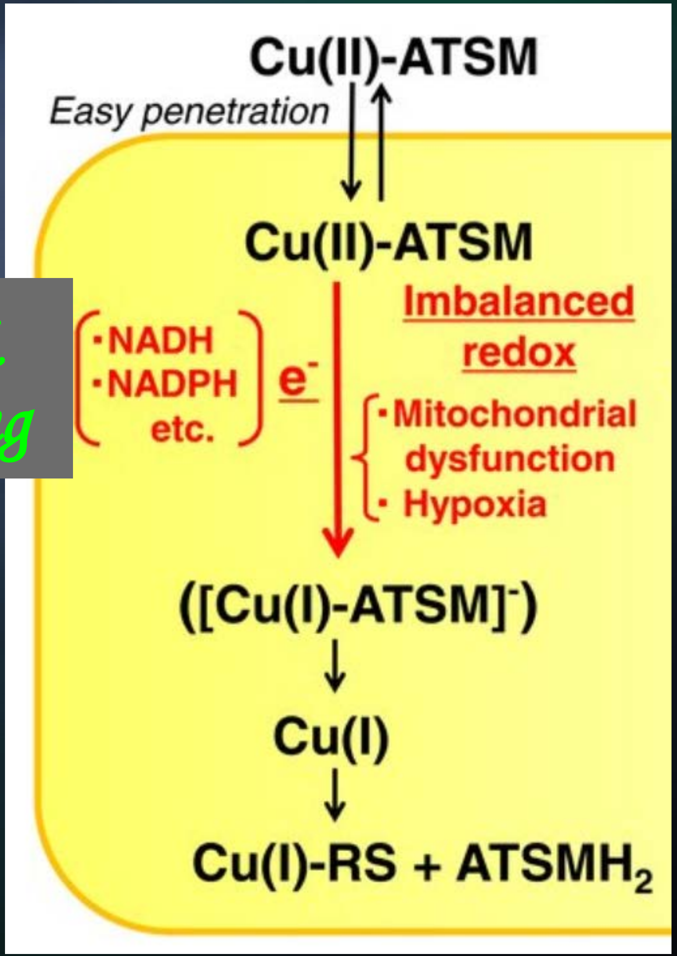
NADH → NAD$^+$

Hypoxic imaging - ^{64}Cu-ATSM



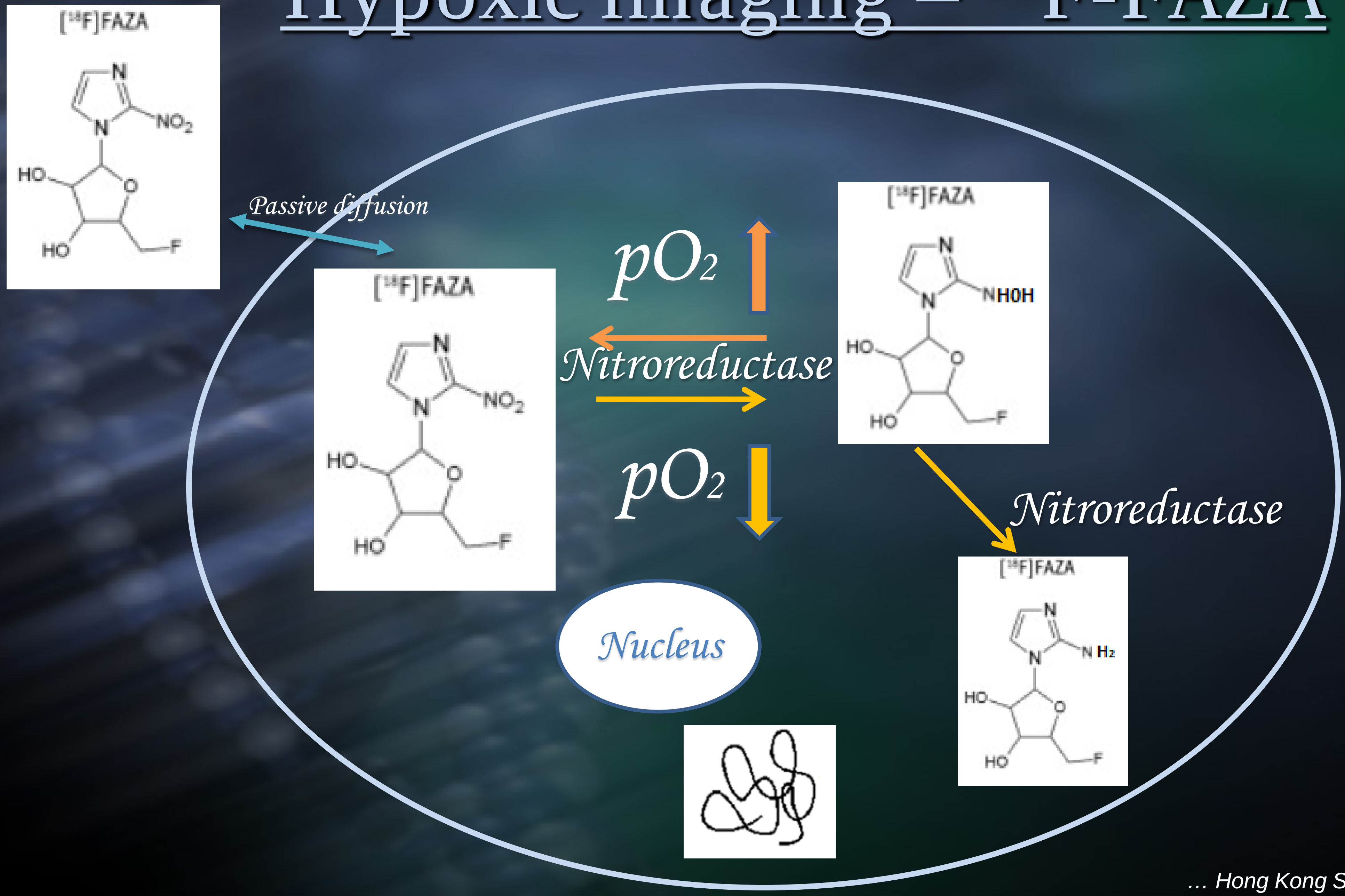
Nitro-reductase

Redox Trapping



Oxidoreductase Family ⟷ *Nitroreductase Member*

Hypoxic imaging – ^{18}F-FAZA



NIH Public Access
Author Manuscript
Clin Cancer Res. Author manuscript; available in PMC 2016 January 15.

Published in final edited form as:
Clin Cancer Res. 2015 January 15; 21(2): 335–346. doi:10.1158/1078-0432.CCR-14-0217.

Available at HKSH

^{18}F-FAZA PET imaging response tracks the reoxygenation of tumors in mice upon treatment with the mitochondrial complex I inhibitor BAY 87-2243

Edwin Chang[1], **Hongguang Liu**[1], **Kerstin Unterschemmann**[2], **Peter Ellinghaus**[2], **Shuanglong Liu**[1], **Volker Gekeler**[3], **Zhen Cheng**[1], **Dietmar Berndorff**[3], and **Sanjiv S Gambhir**[1]

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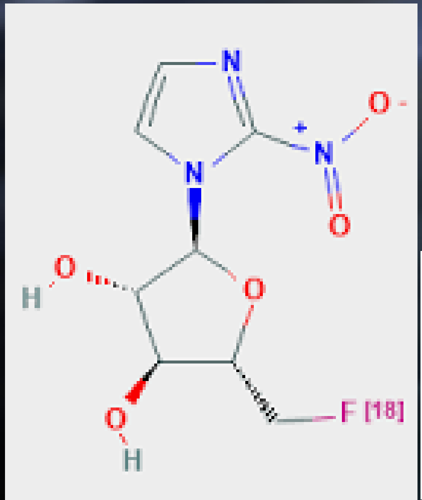
[3]Bayer Pharma AG, Global Drug Discovery, Berlin, Germany

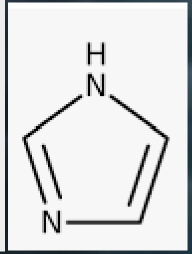
Clinical Significance of Hypoxic imaging

- To identify radioresistant tumor areas
- To benefit from hypoxia-targeted therapy
- Escalation of radiation dose to the hypoxic area
- To overcome the radiation-resistant clones or
- Use of radiation sensitizers

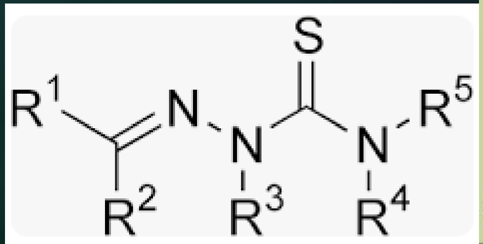
^{18}F-FAZA

Ubiquitous scavenger nitroreductase

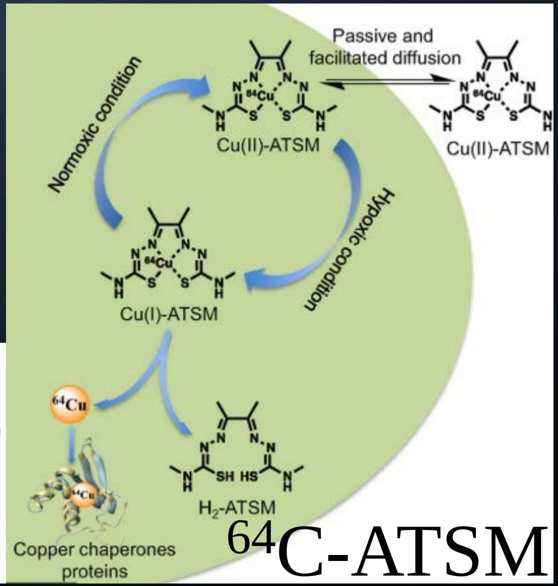




imidazole



thiosemicarbazone



^{64}C-ATSM

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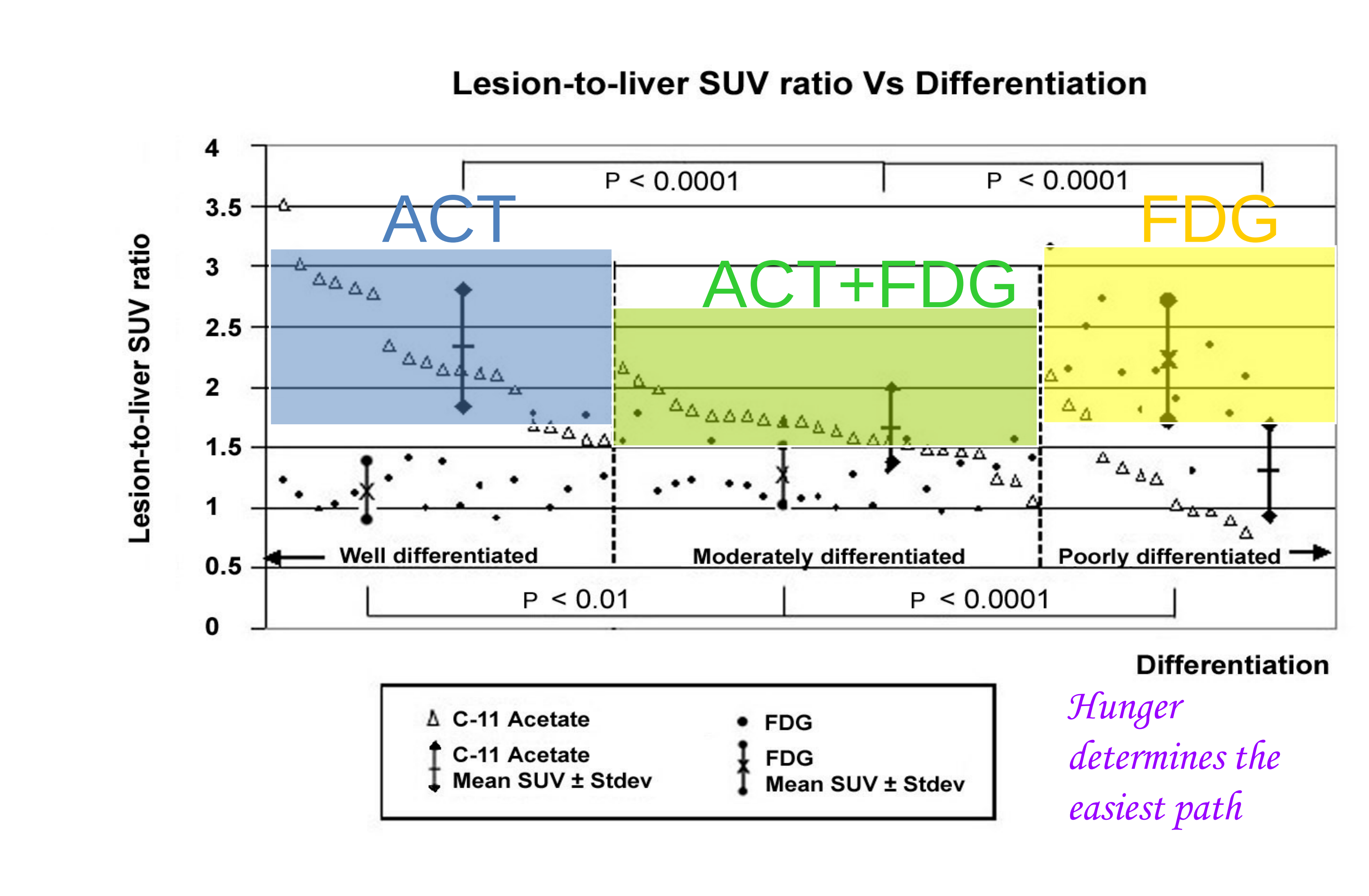
Tracer-specific biochemistry relates to radiosensitivity

- ^{18}F-FDG
- ^{11}C-acetate
- ^{18}F-PSMA-1007
- ^{68}Ga-PSMA-11
- ^{11}C-methionine
- ^{18}F-FET
- ^{18}F-DOPA
- ^{18}F-FLT
- ^{11}C-choline/^{18}F-choline

- Warburg's glycolysis
- Acetyl-CoA metabolism
- Upregulation in receptor density & activity
- Amino acid utilization for peptide, neuro-transmitter synthesis
- DNA proliferation
- Membrane synthesis

PET tracers as biomarkers of HCC cellular differentiation



Hunger determines the easiest path

(Ho CL et al. J Nucl Med 2003; 44:213-21)

^{90}Y-GMRE HCC Study

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:2110–2121
https://doi.org/10.1007/s00259-018-4064-6

ORIGINAL ARTICLE

CrossMark

Radioembolization with ^{90}Y glass microspheres for hepatocellular carcinoma: significance of pretreatment ^{11}C-acetate and ^{18}F-FDG PET/CT and posttreatment ^{90}Y PET/CT in individualized dose prescription

Chi Lai Ho[1] · Sirong Chen[1,2] · Shing Kee Cheung[1] · Yim Lung Leung[1] · Kam Chau Cheng[1] · Ka Nin Wong[1] · Yuet Hung Wong[1] · Thomas Wai Tong Leung[3]

Received: 7 March 2018 / Accepted: 27 May 2018 / Published online: 11 June 2018

Abstract

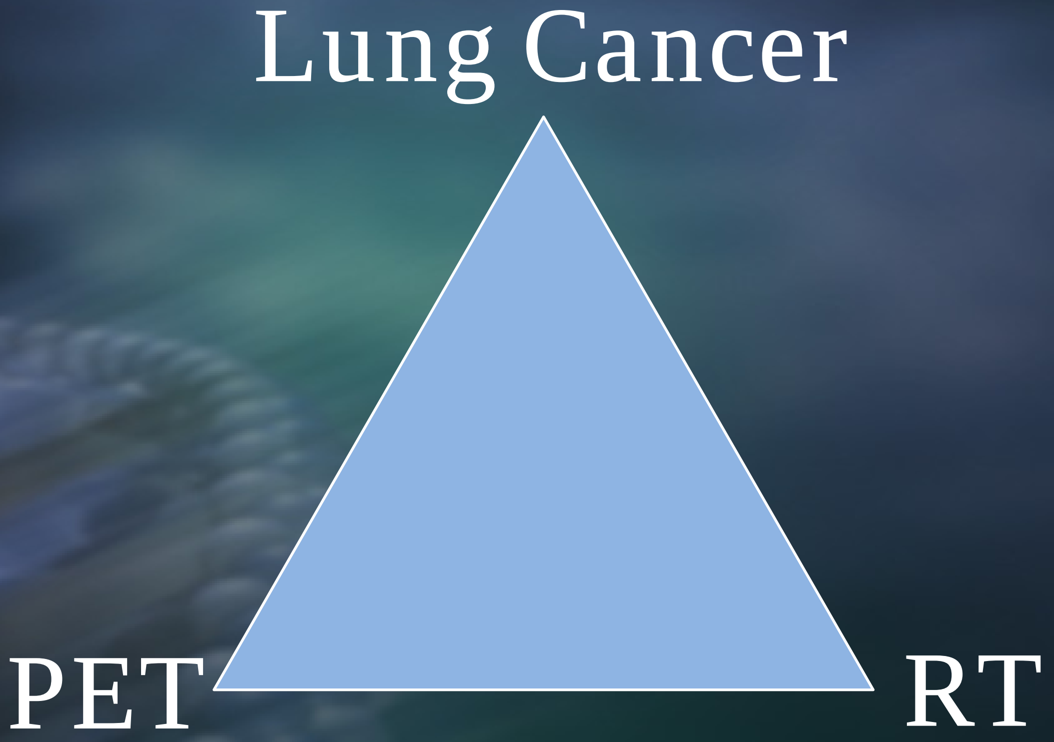
Purpose The aim of this study was to establish an algorithm for the prescription of ^{90}Y glass microsphere radioembolization (^{90}Y-GMRE) of HCC in individual patients based on the relationship between tumour dose (TD) and response validated by ^{90}Y PET/CT dosimetry and dual-tracer PET/CT metabolic parameters.

Methods The study group comprised 62 HCC patients prospectively recruited for ^{90}Y-GMRE who underwent pretreatment dual-tracer (^{11}C-acetate and ^{18}F-FDG) PET/CT as surrogate markers of HCC cellular differentiation. Pretreatment tumour-to-nontumour ratio on ^{99m}Tc-MAA SPECT/CT (T/NT$_{MAA}$) was correlated with posttreatment ^{90}Y PET/CT T/NT$_{90Y}$ after quantification validation. The TD–response relationship for HCC of different tracer groups was assessed on follow-up PET/CT 2 months after treatment.

Cut-off TD for ^{90}Y-GMRE

(Achieving good response)

Group	Cut-off tumour dose (Gy)	Sensitivity (%)	Specificity (%)	AUC
Overall ($n = 62$)	170	70.3 (26/37)	76 (19/25)	0.755
^{11}C-Acetate ($n = 29$)	152	90.5 (19/21)	87.5 (7/8)	0.857
Mixed ($n = 17$)	174	91.7 (11/12)	80 (4/5)	0.75
^{18}F-FDG ($n = 16$)	262	75 (3/4)	91.7 (11/12)	0.792

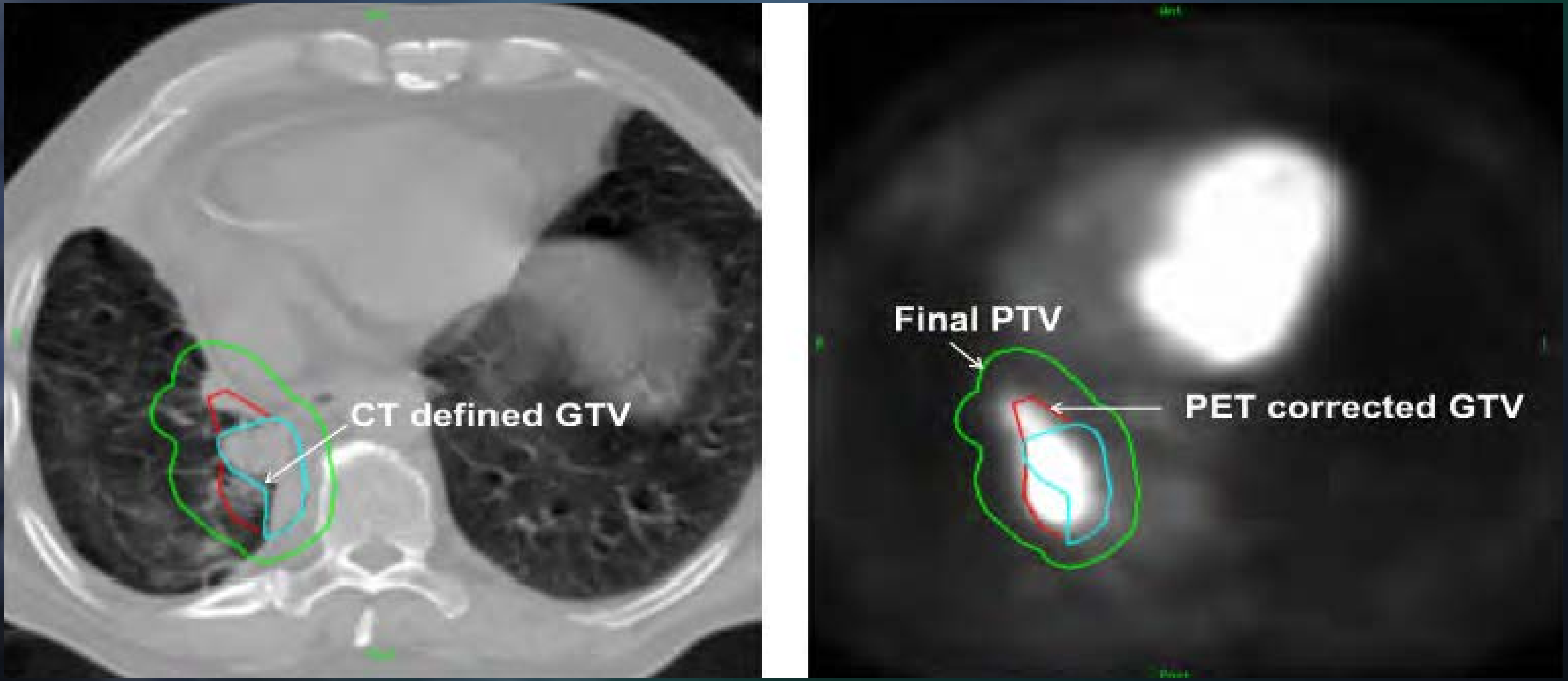

Lung Cancer
PET
RT

Lung Cancer

- PET-based GTV $\neq$ CT-based GTV
  - by exclusion of post-obstructive atelectasis, infectious infiltrates and necrotic tissue
- 20-40% patients significant change in GTV definition
- 20-50% patients had stage alterations
- ⇩PTV ➔ ⇩dose to esophagus
- 2014 IAEA Consensus report: "curative-intent RT" is defined by PET-based GTV

Radiother Oncol 2015 Jul;116(1):27-34

Lung Cancer



Lancet Oncology 2020 on PET-based RT Planning

Imaging-based target volume reduction in chemoradiotherapy for locally advanced non-small-cell lung cancer (PET-Plan): a multicentre, open-label, randomised, controlled trial

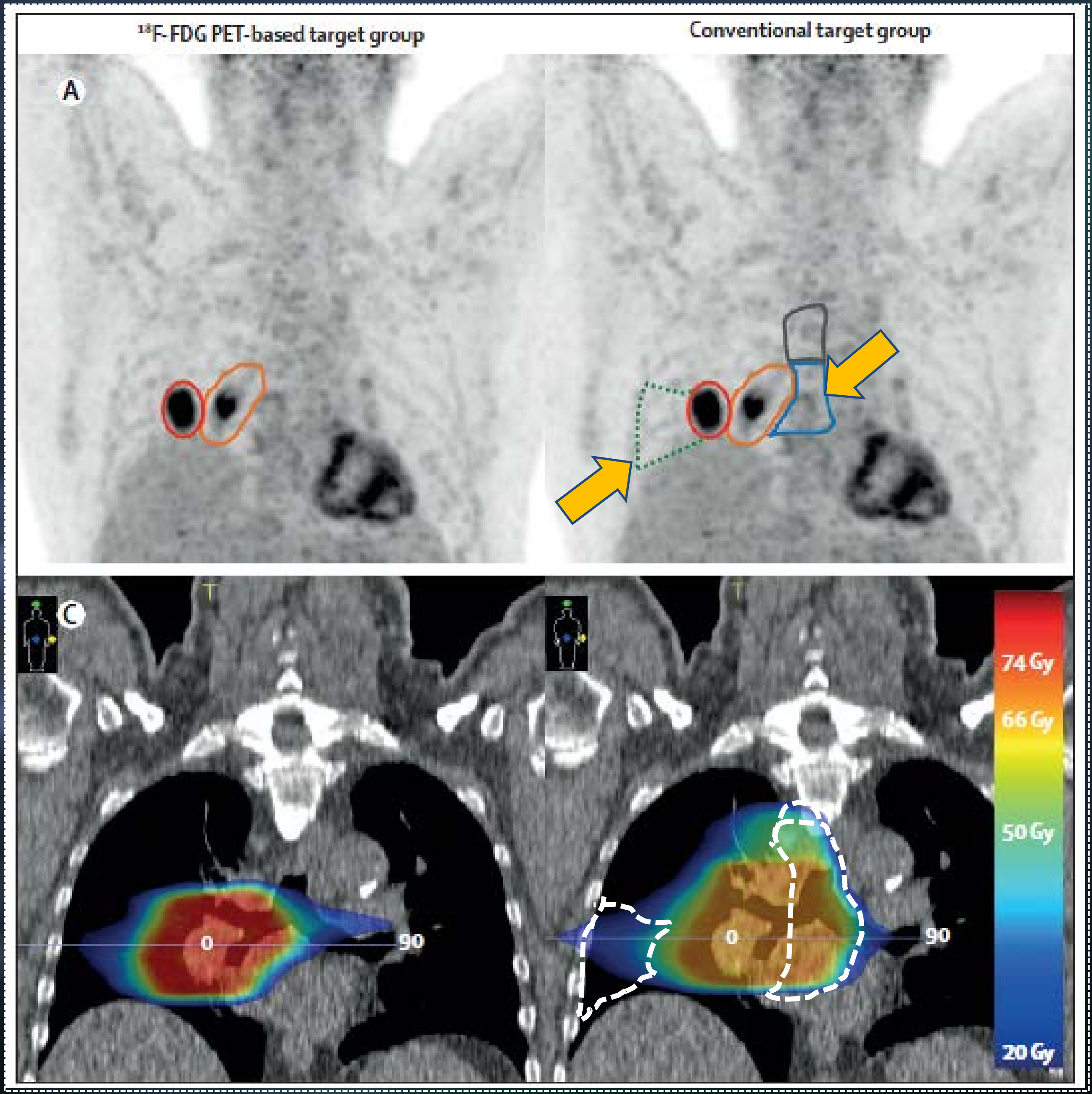
Ursula Nestle, Tanja Schimek-Jasch, Stephanie Kremp, Andrea Schaefer-Schuler, Michael Mix, Andreas Küsters, Marco Tosch, Thomas Hehr, Susanne Martina Eschmann, Yves-Pierre Bultel, Peter Hass, Jochen Fleckenstein, Alexander Thieme, Marcus Stockinger, Karin Dieckmann, Matthias Miederer, Gabriele Holl, H Christian Rischke, Eleni Gkika, Sonja Adebahr, Jochem König, Anca-Ligia Grosu, for the PET-Plan study group

Summary

Background With increasingly precise radiotherapy and advanced medical imaging, the concept of radiotherapy target volume planning might be redefined with the aim of improving outcomes. We aimed to investigate whether target volume reduction is feasible and effective compared with conventional planning in the context of radical chemoradiotherapy for patients with locally advanced non-small-cell lung cancer.

RT Planning for Lung Cancer

- Multicenter, randomized, controlled trial
- Stage II-III NSCLC
- 2 arms comparison:
  - conventional PTV (n=84)
  - PET-based PTV (n=88)
- Results:
  - PET-based arm was NOT inferior to the conventional arm



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Brain, H&N cancer

PET

RT

Brain Tumors

- RANO (Response Assessment in Neuro-Oncology) Task Force recommended “Amino acid PET”
  - ^{11}C-methionine (^{11}C-MET)
  - ^{11}C-choline (^{11}C-CHO)
  - ^{18}F-fluroethyl-tyrosine (^{18}F-FET)
  - ^{18}F-DOPA

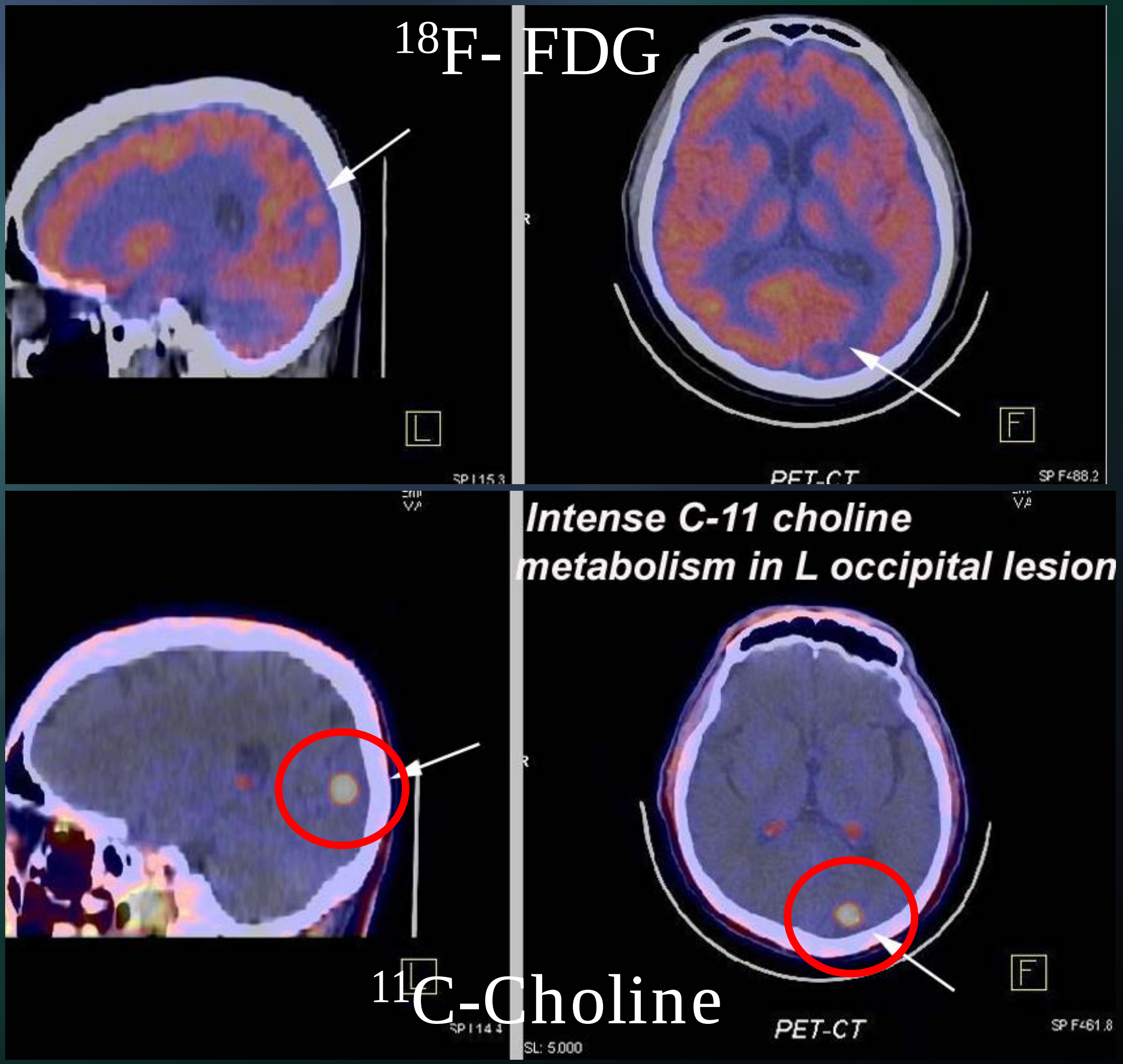
- Predict prognosis
- Improve target delineation
- Assess Rx response
- Predicts pattern of Rx failure

Unterrainer et al. Radiation Oncology (2020) 15:88

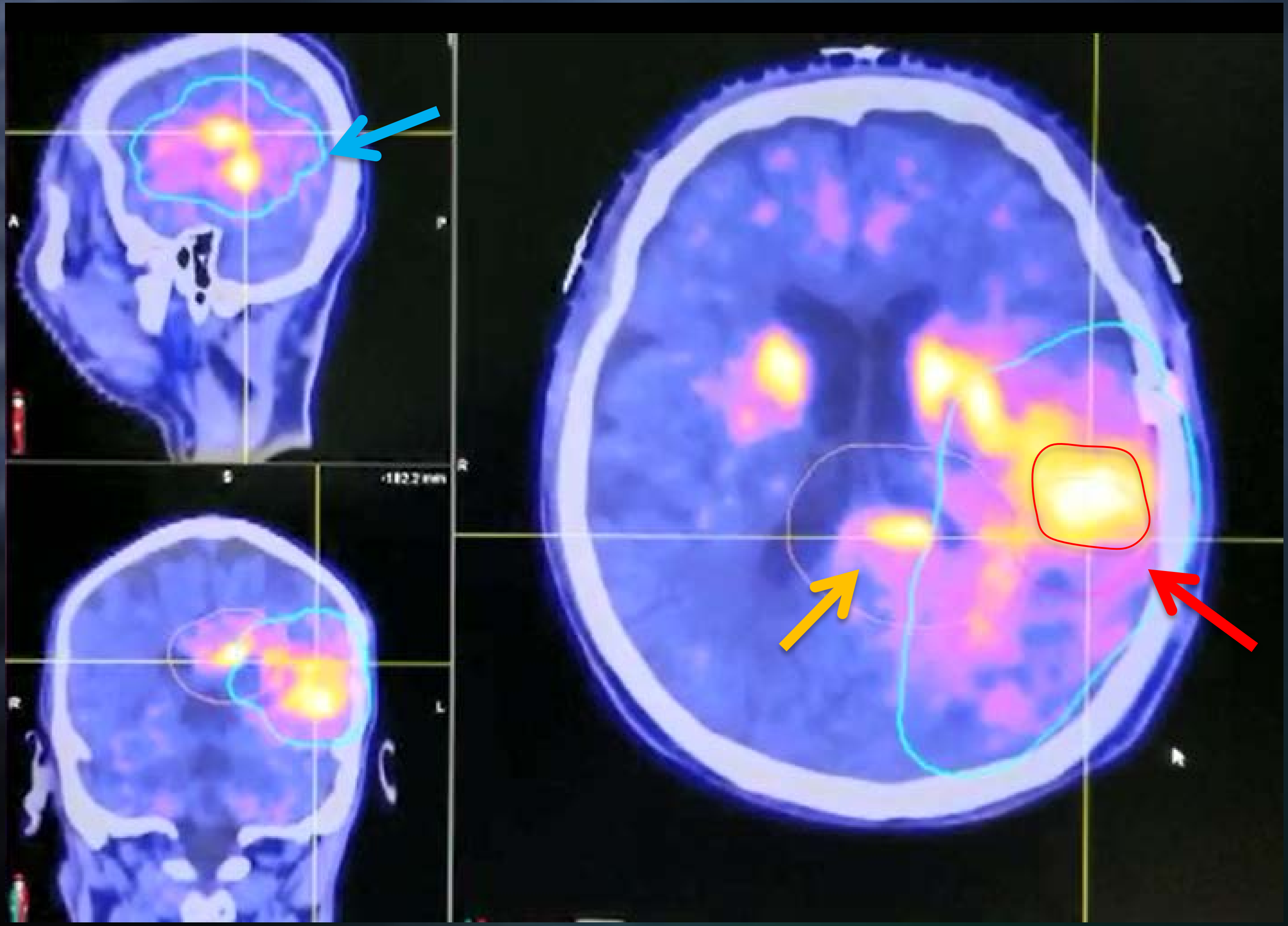
Tumor recurrence Vs scar

M/50

- Carcinoma of L lung
- L occipital brain metastasis
- X-knife radio-surgery
  2 years ago
- FU MRI
  Marginally larger L occipital nodule
- Asymptomatic



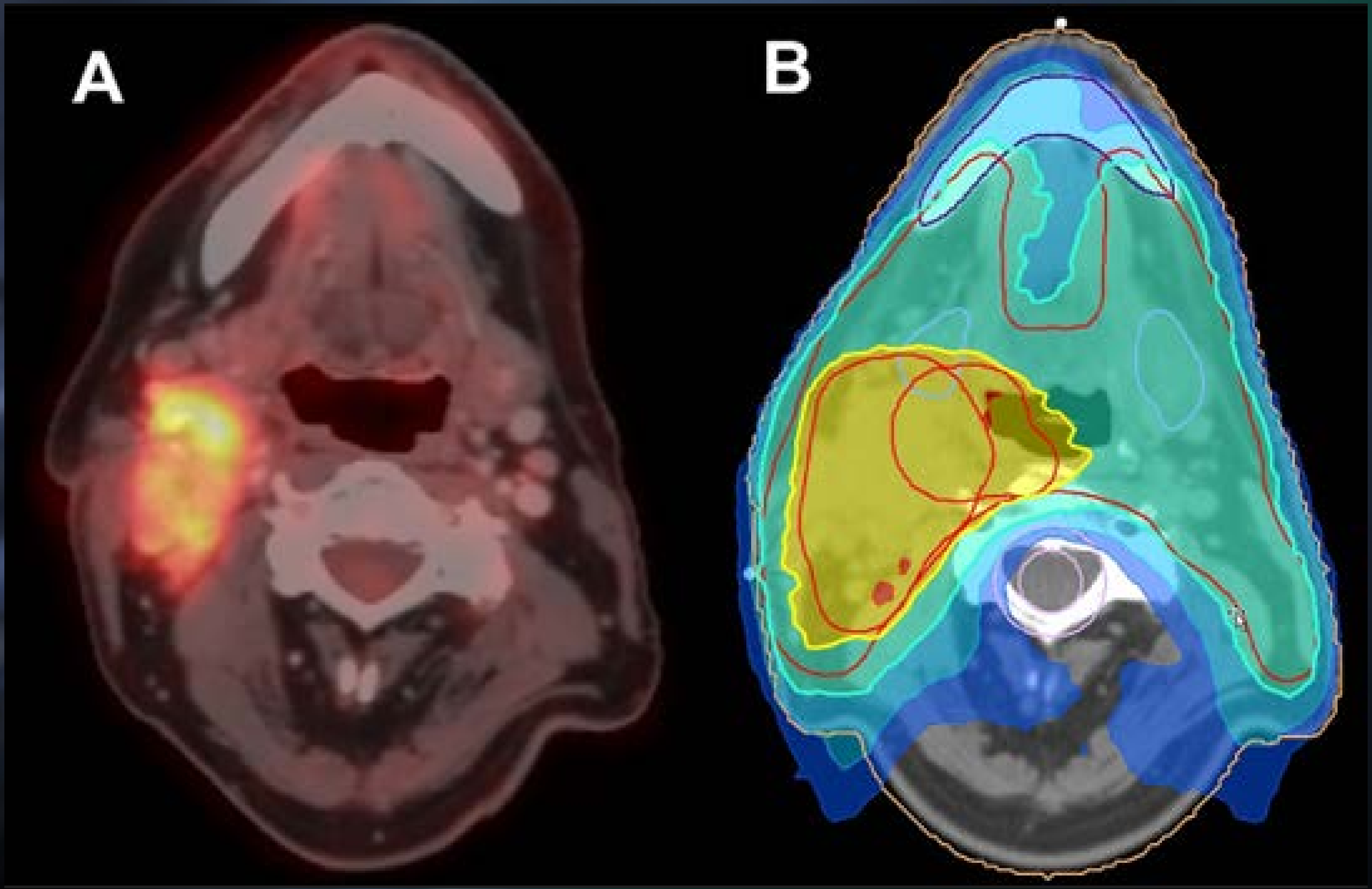
Brain Glioma post craniotomy



^{18}F-DOPA Brain PET

New
Residual
Post-op

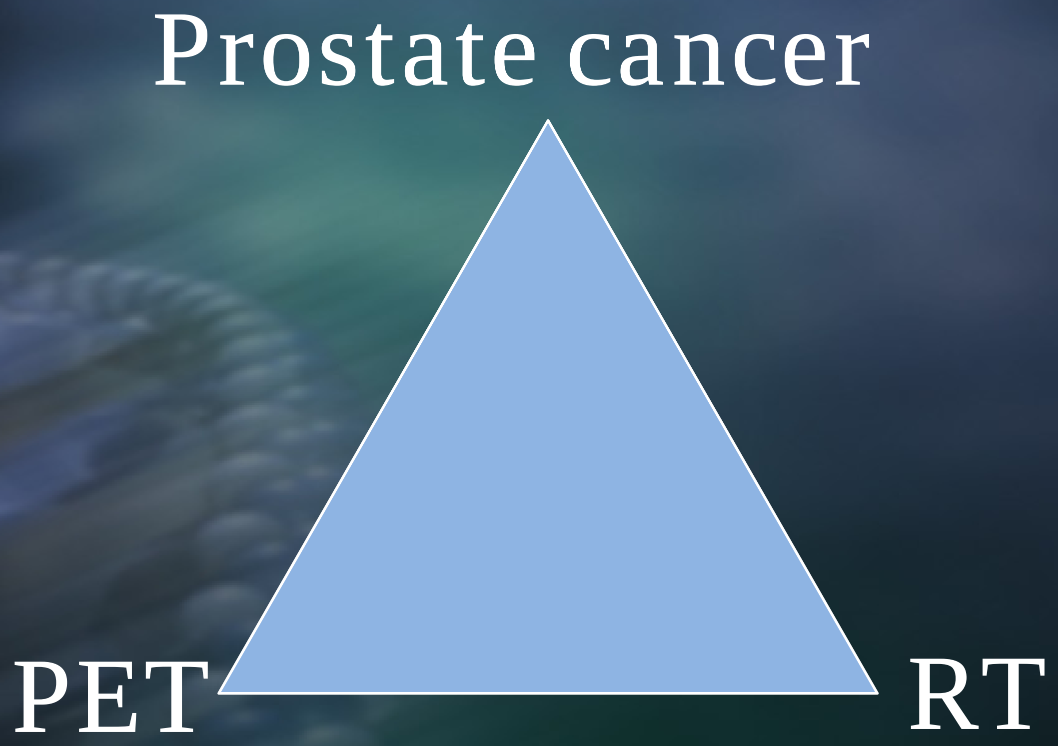
HPV^{+} SCC of R Tonsil



PET in Head & Neck Cancer (HNC)

Farina E, et al. ANTICANCER RESEARCH 37: 6523-6532 (2017)

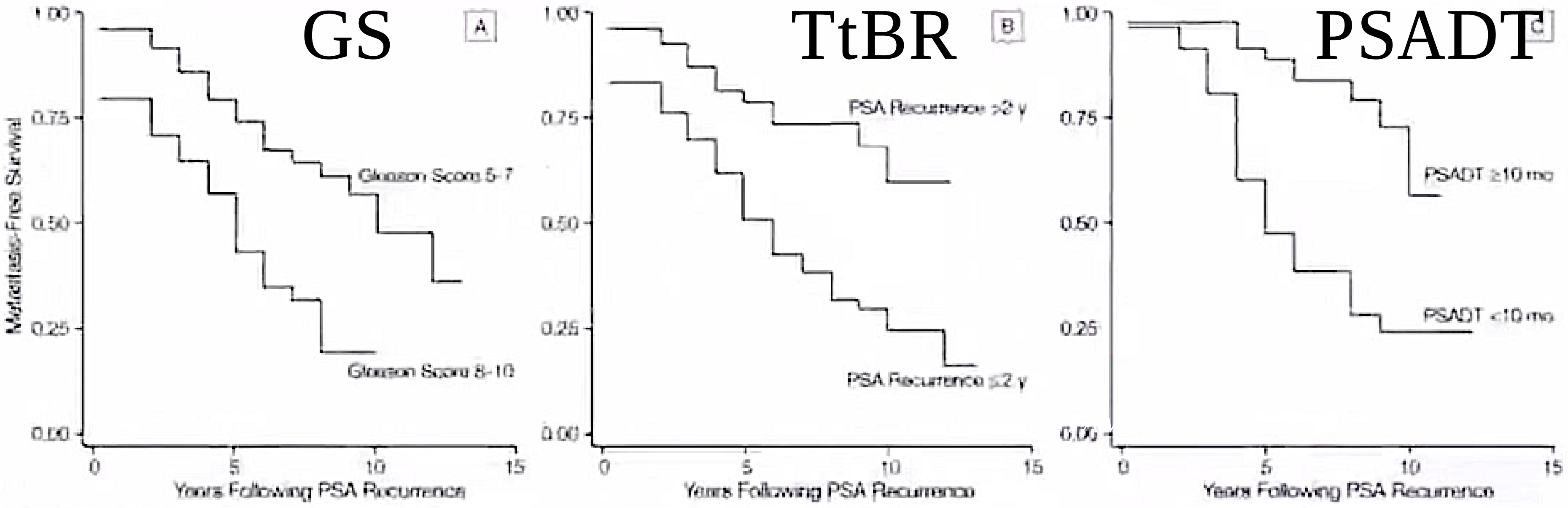
- ^{18}F-FDG PET/CT in N and M of TNM staging of HNC
- Positive lymph node metastasis decreases survival by 40-50%
- SUVmax and Total Lesion Glycolysis (TLG) of primary tumor and metastatic nodes are predictors of therapeutic failure or success.
- Metabolic center can be allocated at SUVmax location
- Hypoxic areas targeted with dose escalation up to 77 Gy
- Metabolic reduction is a sign of good locoregional control seen at 12 weeks after RT completion
- Salvage neck dissection offers no incremental benefit in the presence of metabolic improvement after RT


Prostate cancer
PET
RT

Actuarial Likelihood of Metastasis-Free Survival with biochemical recurrence (Johns Hopkins study)

304/1997 men based on Gleason score, Time to BR, PSADT:

Figure 3. Actuarial Likelihood of Metastasis-Free Survival in 304 Men With Prostate-Specific (PSA) Antigen Elevation After Radical Prostatectomy



A, Based on Gleason scores in the radical prostatectomy specimen ($P<.001$). B, Based on years until initial biochemical recurrence ($P<.001$). C, Based on prostate-specific antigen doubling time (PSADT) ($P<.001$).

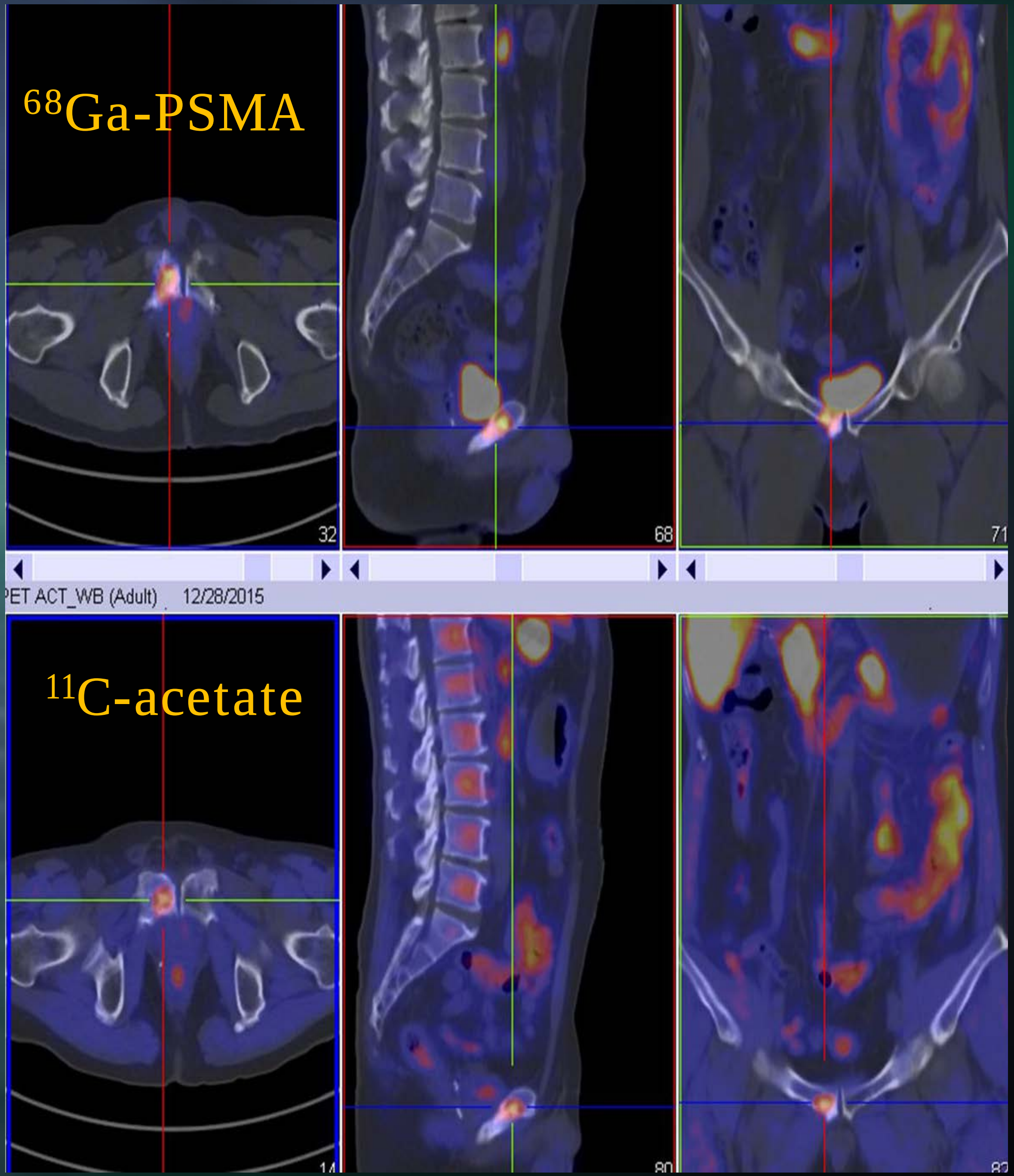
Pound et al. JAMA 1999- Vol 281, No. 17, 1591.

PSA

- <0.1 ng/ml => 0.5 ng/ml in 17m in 2015
- TtBC ~17m
- Doubling time <12m

Non-specific symptoms

Oligometastatic disease: bone



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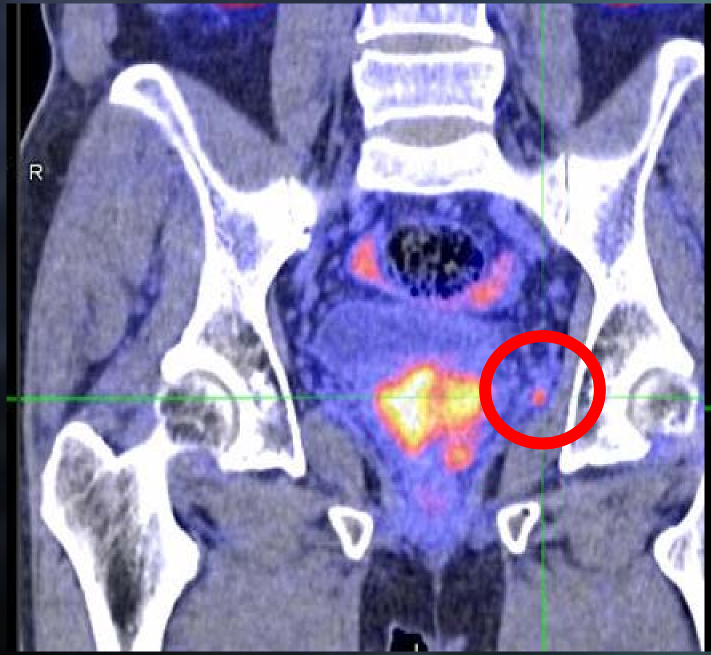
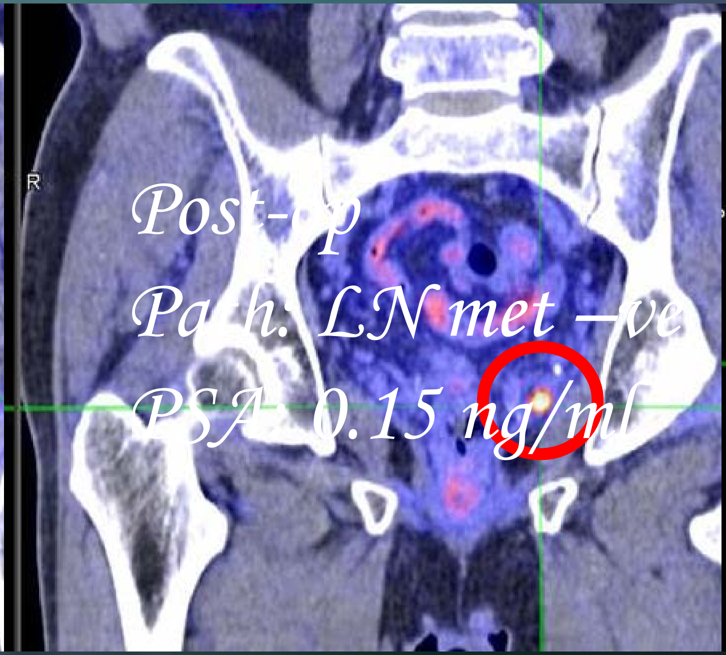
Oligometastasis Rx by RT

PSA= 7 ng/ml (pre-op)



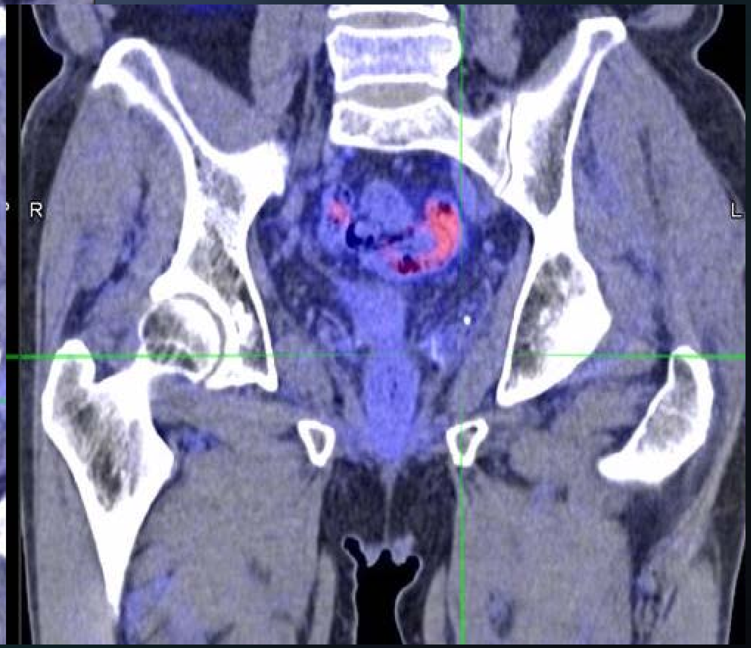
PSMA PET/CT (pre-op)

PSA= 0.15-0.2 (post-op)



PSMA PET/CT
(2-4 months post-op)

PSA= 0.05 (post-RT + ADT)



PSMA PET/CT
(2 months post-RT + ADT)

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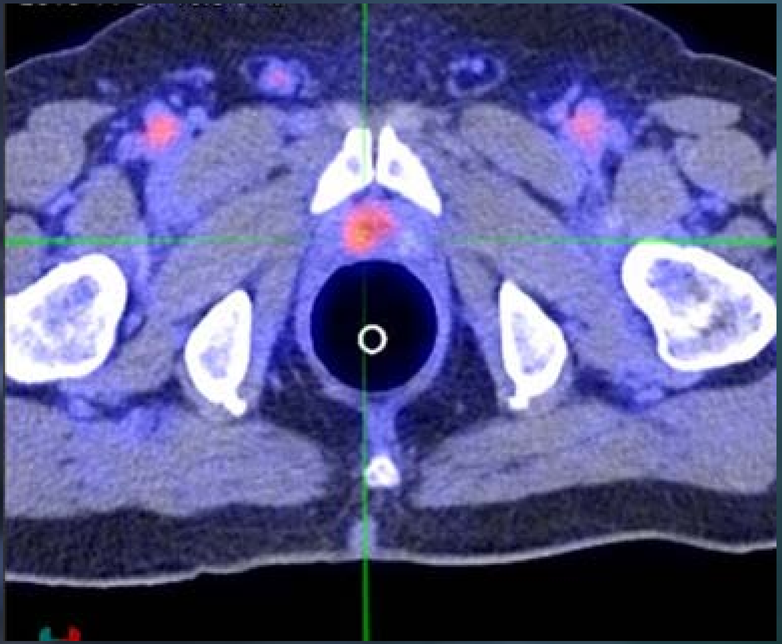
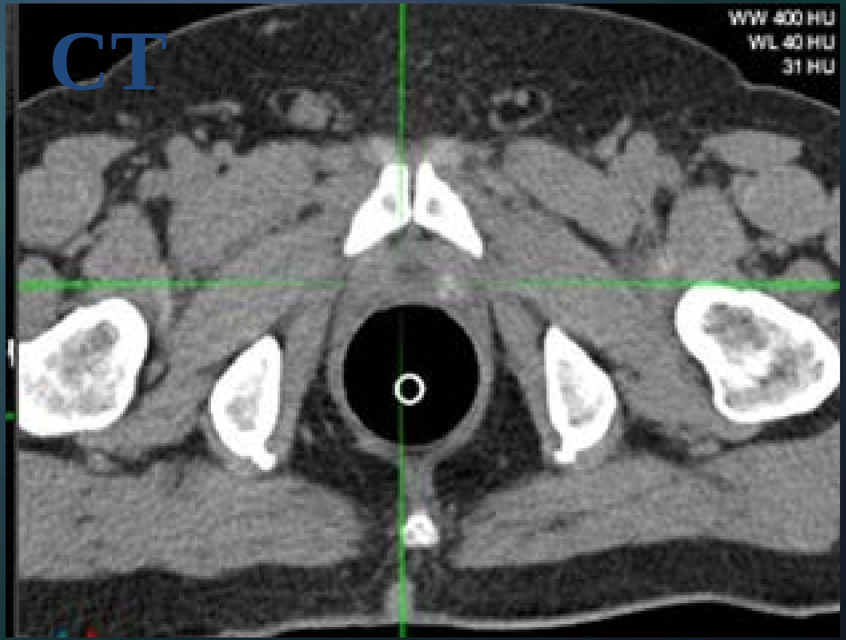
^{18}F-PSMA-1007 PET/CT

Recurrent Prostate Cancer Post-prostatectomy



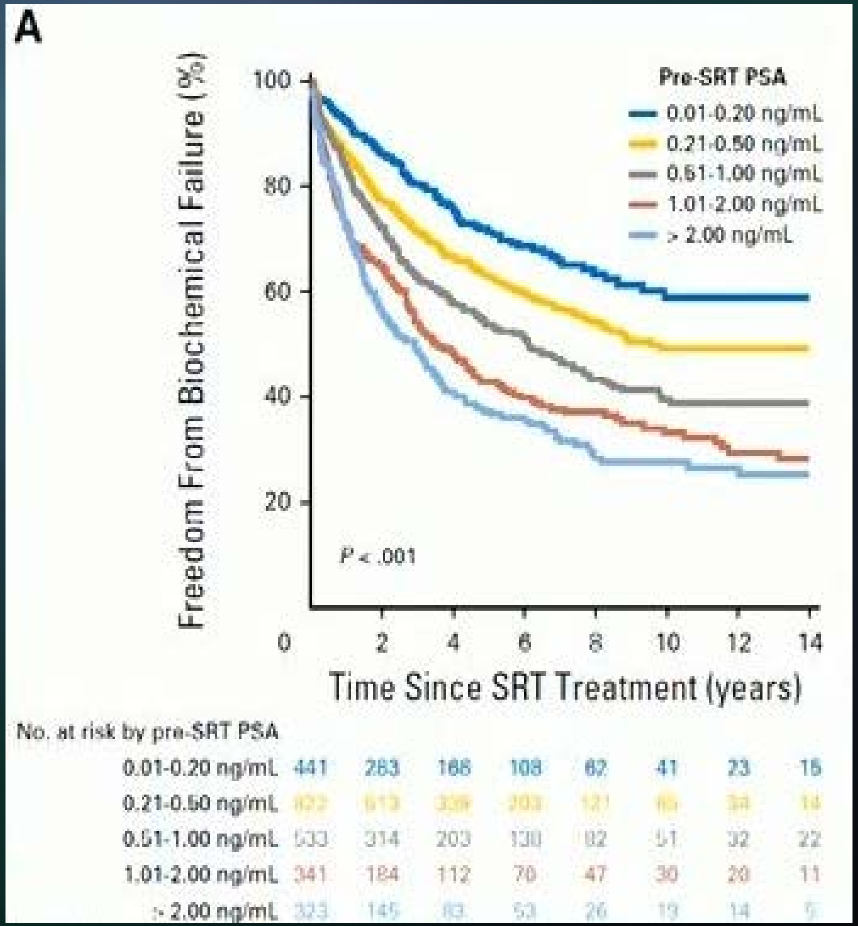


Treated by pelvic RT

Salvage RT as an option for post-prostatectomy PCa with biochemical recurrence

502 patients with biochemical relapse had salvage RT and median FU 45 months:

	n%
PSA Progression*	250 (50)
4-year progression-free probability (PFP) was 45% (95% CI 40%, 50%)	45% (95%CI 40-50%)
Distant metastases	49 (10)
Death from Prostate Cancer	20 (4)
*Defined as PSA level ≥0.1 ng/mL above post-RT nadir, continued rise in PSA level or initiation of HT	



Tendulkar et al. JCO 2016

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Role of PSMA-PET in biochemical recurrence

- In addition to confirm local recurrence or regional mets, another important role of PSMA-PET is to exclude distant mets, so that

  - MDT is at a stage where cure can be achieved (30%)
  - ADT can be postponed
  - CRPC –status can be delayed or avoided
  - Salvage Pelvic RT can be better affirmed and instituted early
  - Monitoring therapy
  - Closer FU

Other tumors planned for PET-based RT

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-020-05112-2

GUIDELINES

EANM/SNMMI practice guideline for [^{18}F]FDG PET/CT external beam radiotherapy treatment planning in uterine cervical cancer v1.0

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Received: 30 August 2020 / Accepted: 8 November 2020

Abstract

Purpose The aim of this EANM / SNMMI Practice Guideline with ESTRO endorsement is to provide general information and specific considerations about [^{18}F]FDG PET/CT in advanced uterine cervical cancer for external beam radiotherapy planning with emphasis on staging and target definition, mostly in FIGO stages IB3-IVA and IVB, treated with curative intention.

Challenges

- How to define the biological volume & boundary?
- How to implement the metabolic parameters from the diagnostic platform to the therapeutic platform?

RT Dose painting algorithms

- Boundary & distribution
- Segmentation method

  -positron range

  -biological signals

- Accurate in-house calibration
- Good maintenance
- Correct tuning per PET tracers

Medical Physics

→ Electronic signals detected in scanner

Physical parameter & reconstruction method

Differentiate TRUE count from noise, scatters, err coincidences

PET Auto-segmentation

Fixed threshold

e.g. 40% SUVmax

Adaptive threshold

$SUV_{i+1} = A_i \cdot SUV_i + B_i$

Advanced segmentation

e.g. gradient (MIM)

Statistical

Deformable

Texture, vector analysis

Artificial intelligence??

Advanced Segmentation Methods

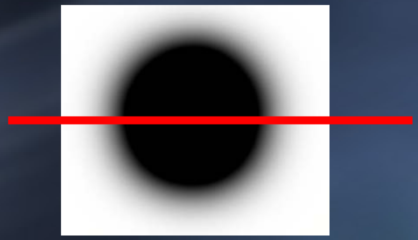
- Textural-numeric
- Region growing
- Statistical analysis
- Artificial intelligence

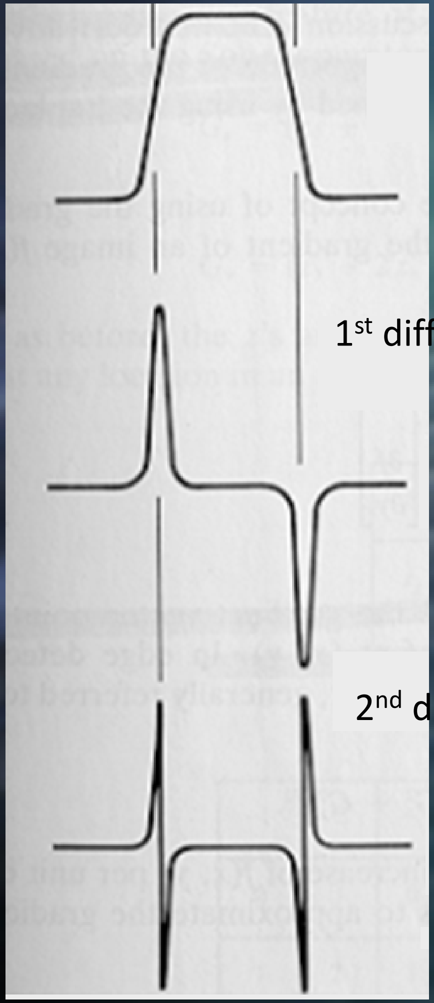
Sophistication
& complexity
Inversely related to
Ease of computation
& operation

Classification and evaluation strategies of auto-segmentation approaches for PET: Report of AAPM task group No. 211. Med Phys 44(6), June 2017

(1) Boundary & Volume definition

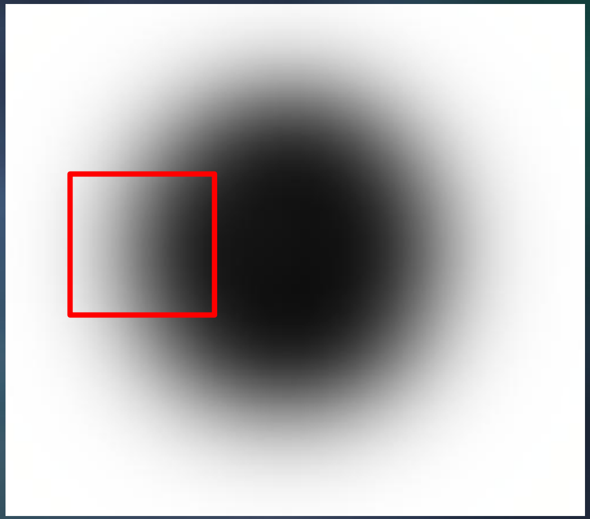
- Gradient-based metabolic texture analysis
- Delineating the location with greatest change in metabolic activity gradient vector between background and target
- Viz. voxel with a zero 2^{nd} differential
- Advantage:
  - Independent of SUVmax or SUVmean
  - Not iterative numeric, not require convergence
  - Reasonable computing time
- Disadvantage:
  - Background count dependent

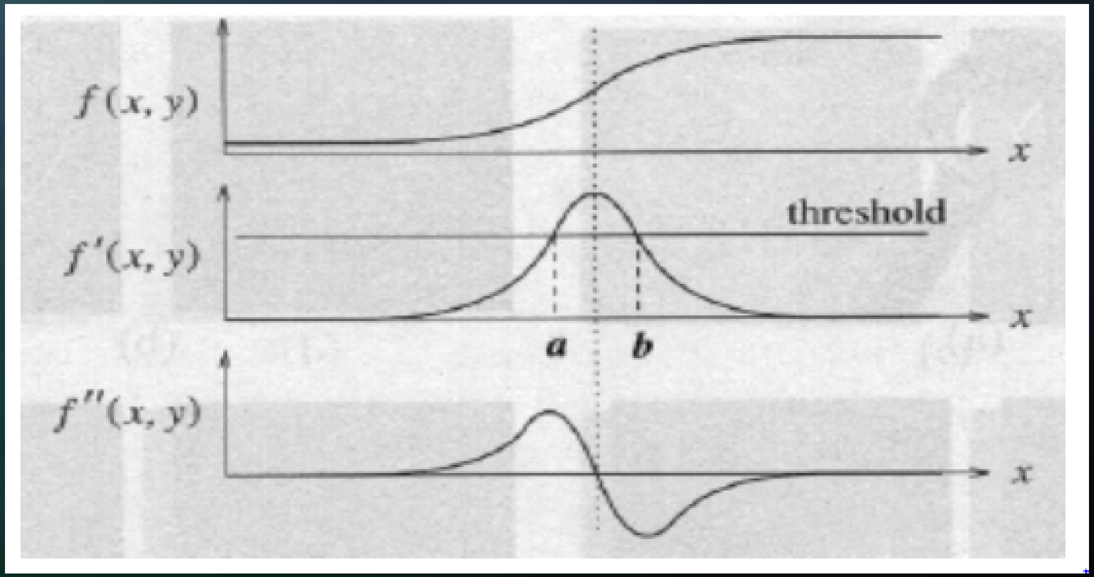




1st differential

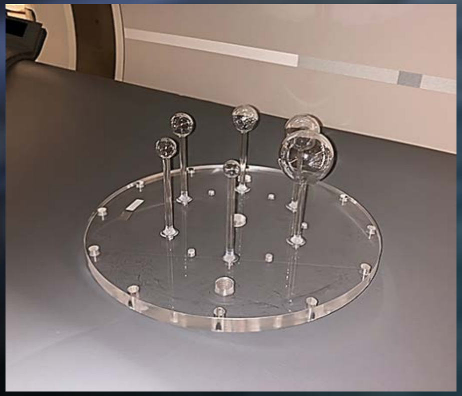
2nd differential

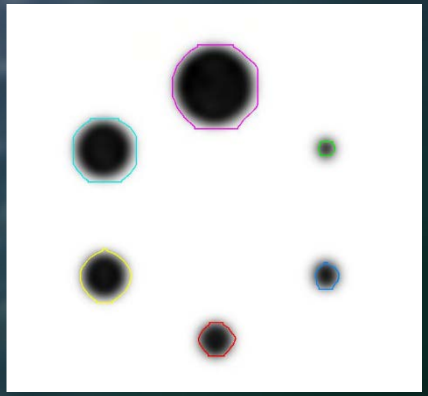


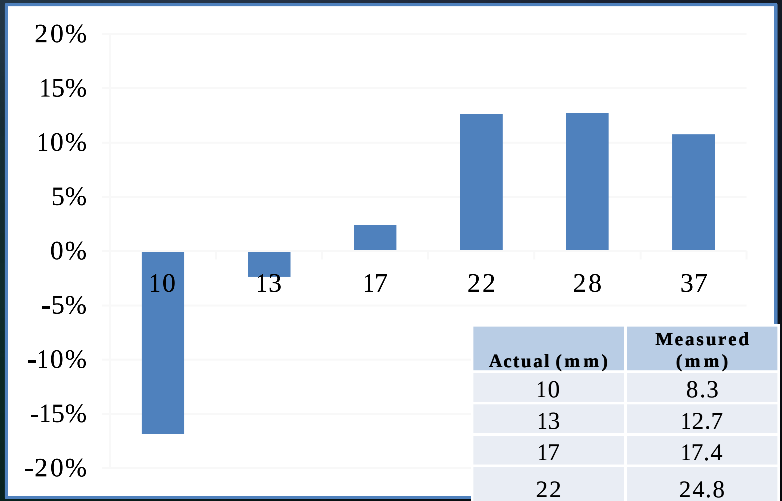


Volume calibration & validation

- Calibration tests using phantoms with/without background activities
- Biological volume automatically generated by advanced threshold method (texture-based metabolic vector 2nd differential)
- The error of LD measurement is -15% to +13%







Actual (mm)	Measured (mm)
10	8.3
13	12.7
17	17.4
22	24.8
28	31.6
37	41.0

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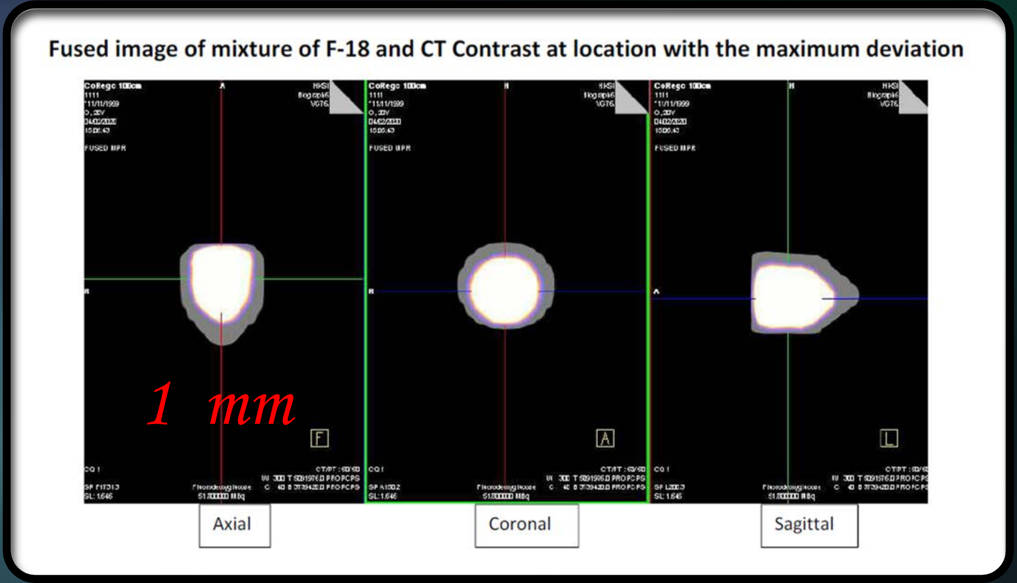
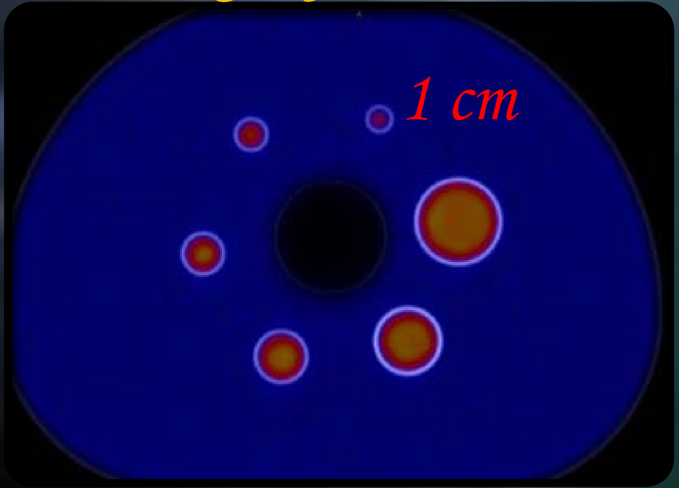
Stringent Calibration & Quality Control



Highly accurate co-registration of CT and PET



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PET Vector gradient "Petiomic" analysis

- GTV generated is 3-D
- Not requiring manual drawing on each transaxial slice along the Z-direction
- Not dependent on:
  - Operator
  - Display scheme
  - Brightness or contrast

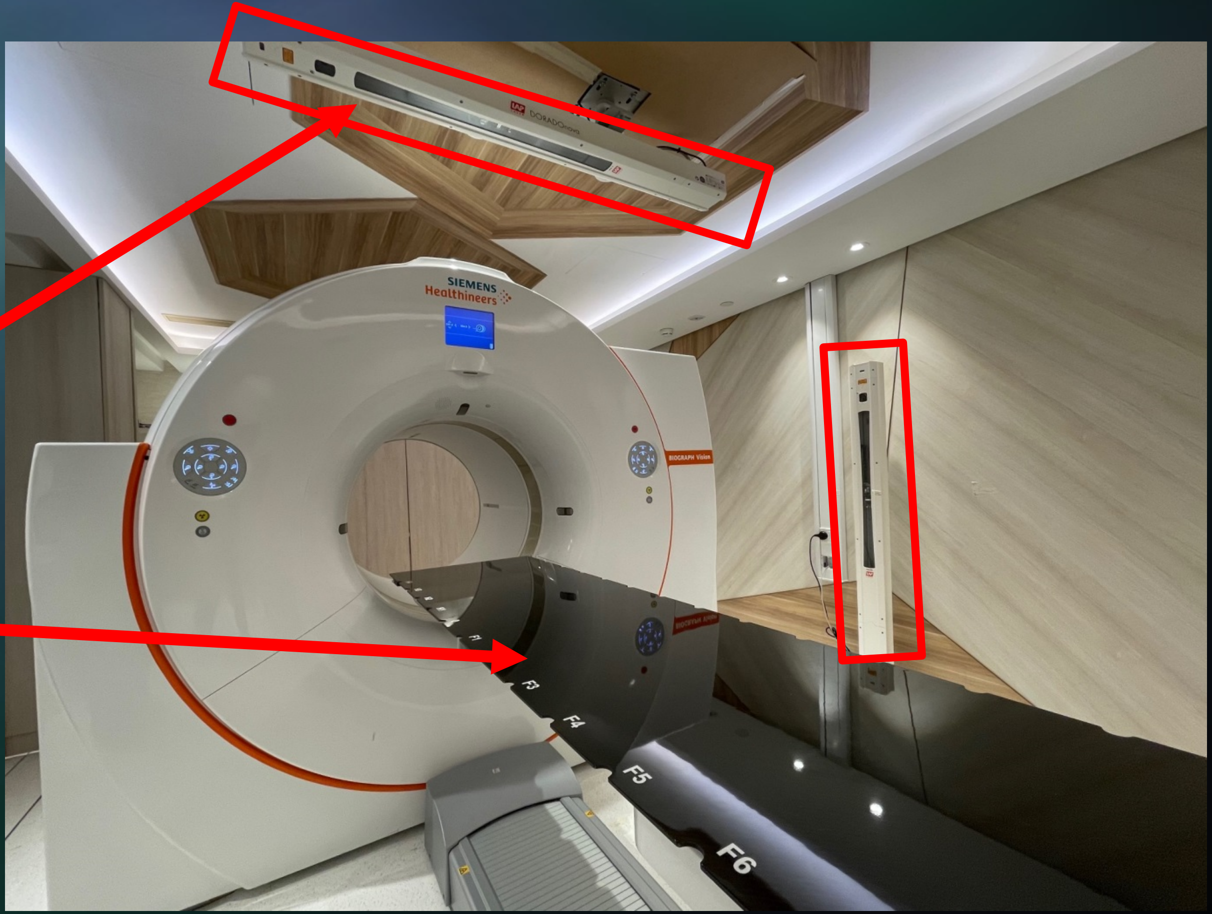
(2) Translation of the dose painting PET parameters for clinical use in RT planning

Diagnostic imaging platform → *Matching* ← Therapeutic platform

Laser positioning

Flat table insert

Gantry 78 cm



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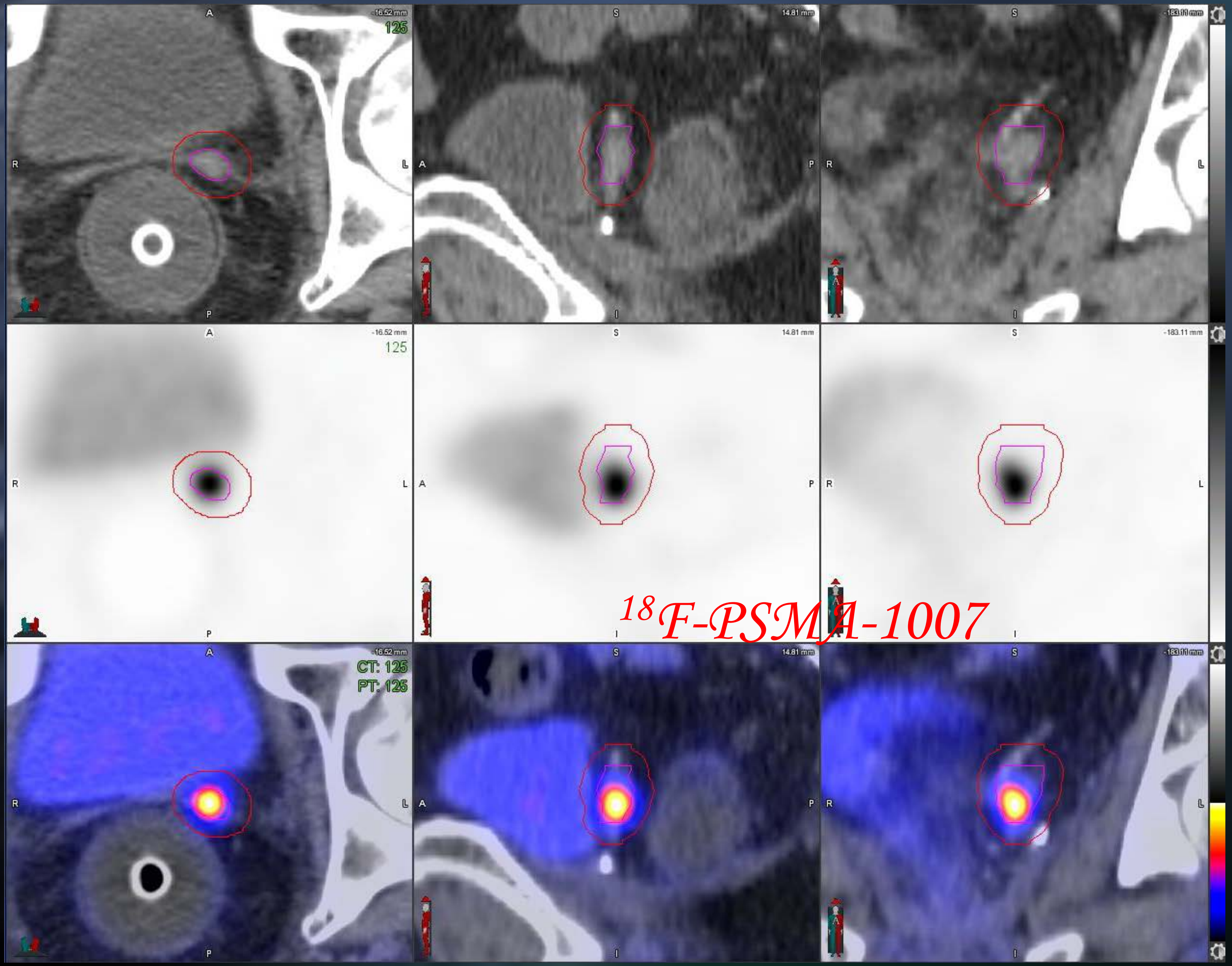
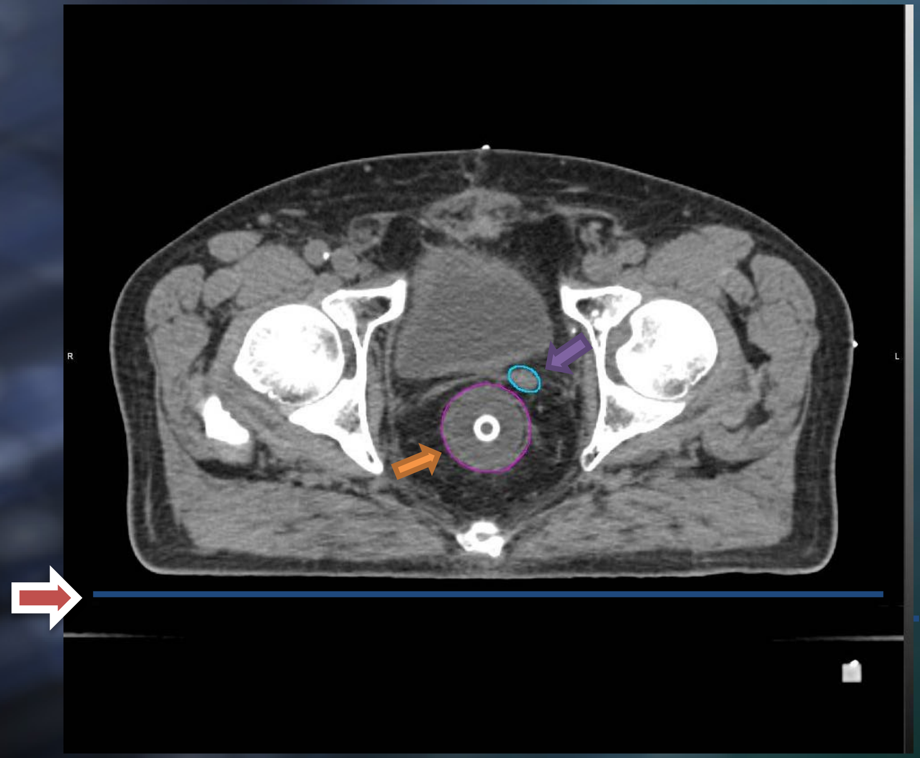
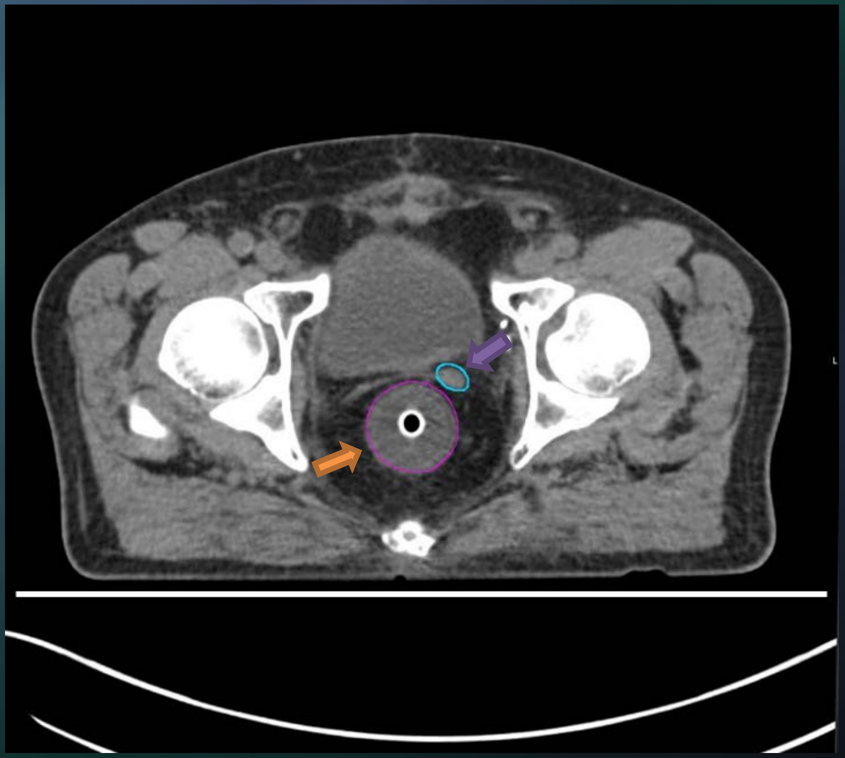
Contour Transfer Between CT Sim & PET



Easy Image Registration

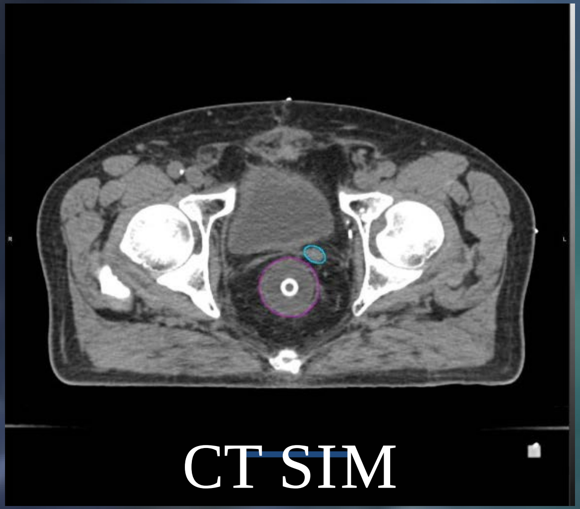


CT SIM

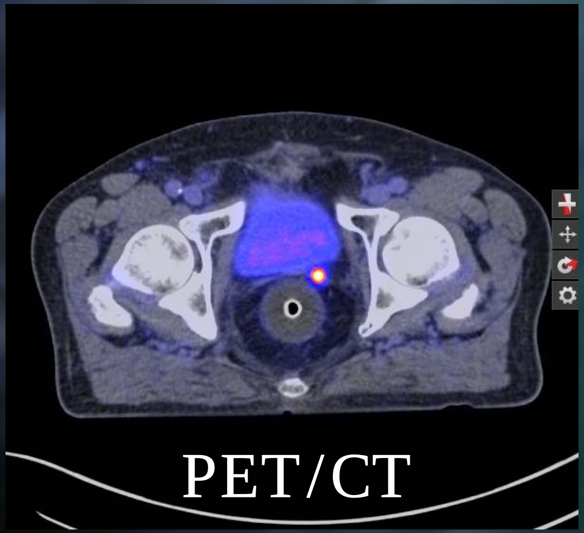


CT of PET/CT

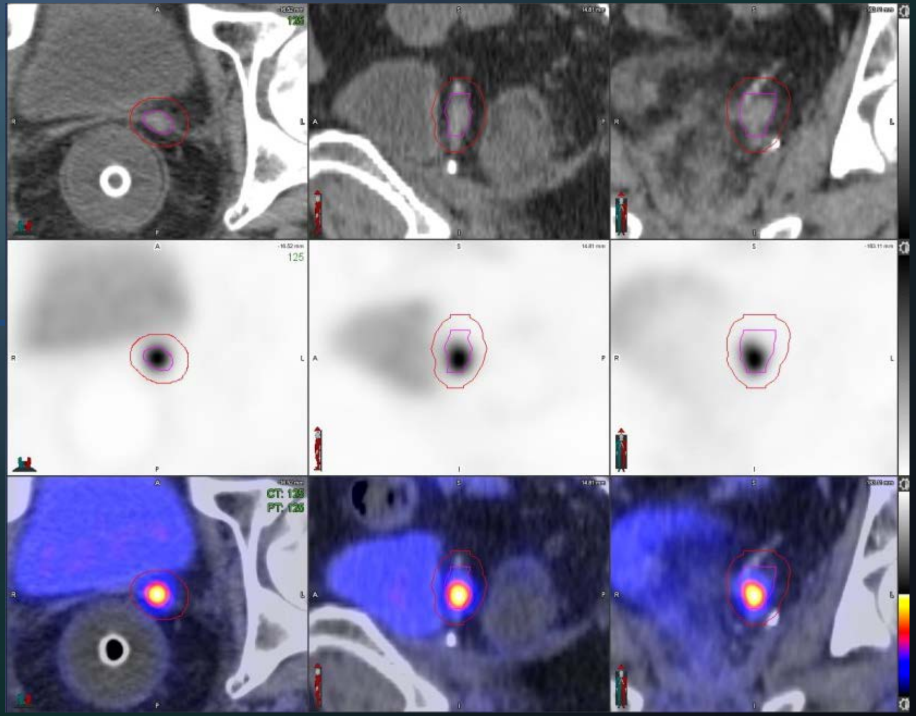
Another option for RT planning?



CT SIM



PET/CT



Planning

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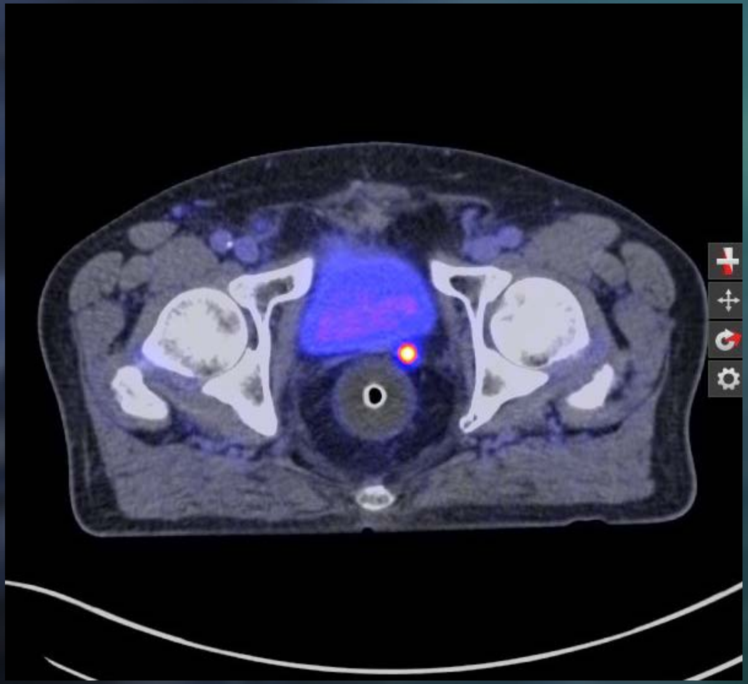
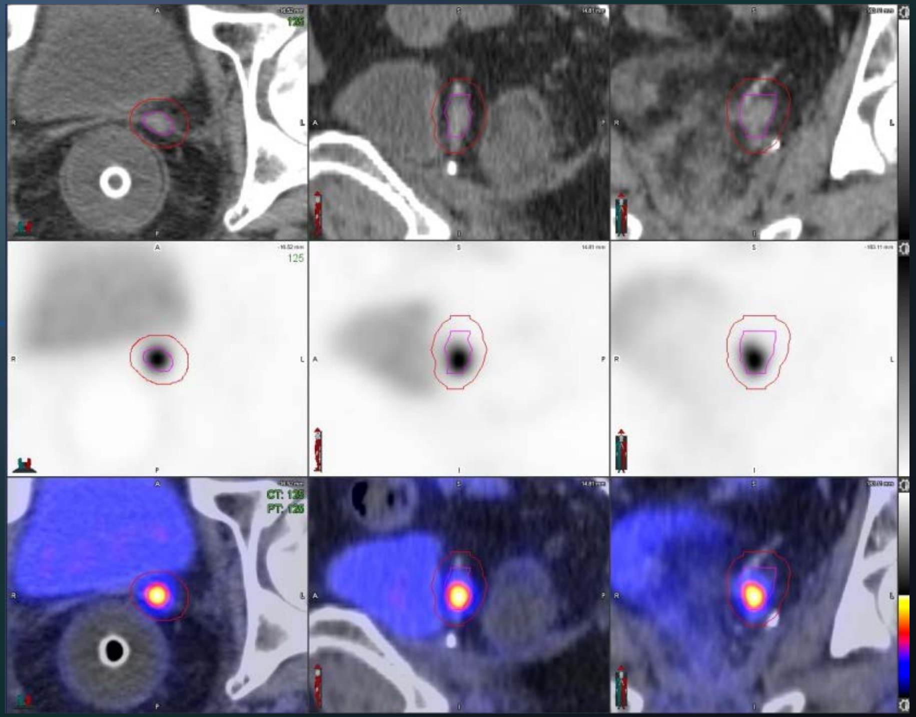
Another option for RT planning?





CT of PET/CT also used as Sim directly for CT planning

Planning

Current Statistics – RT Prostate

- 31 PET/CT based RT planning cases in 2020
- Advantages by far:
  - Good CT matching → Good PET matching
  - Least to no need for deformation correction
  - More accurate positioning & time saving
- Advantages expected with proposed algorithm:
  - Pre-calibrated for accuracy - volume & boundary
  - Less operator dependent – decreased variability
  - No need to draw on each image slice – time & efficiency

The Conclusion

- Reasons for PET/CT being RTP-friendly
  - Cancer's biochemical derangement is the basis for localization & delineation of true tumor burden before RT planning
  - Biochemical derangement may need different PET tracer probes (tracer-specific)
  - PET's tracer-specific cytokinetics help decide radiation dose, biological boundary, volume inclusion or reduction, metabolic center for dose escalation- for RT dose painting
  - Monitoring of metabolic change (location, hypoxia)

The Conclusion

PET/CT is RTP-friendly

The Conclusion

- Challenges for PET/CT in RTP
  - ♪ Translation from PET platform to RT platform through 2 key modifications

1. PET segmentation algorithm (in-house calibration, checking & implementation)
2. CT as the common denominator
   - † CT from WB PET/CT direct with RTP-intent
   - † CT from regional PET/CT add-on

   (Laser localization & flat bed insert)

The Conclusion

Solutions
To meet the
Challenges

The Vision

- "Acceptance of this 'new' framework… for guiding [RT Planning] requires … the specificity, sensitivity, precision, and accuracy of tumor staging.
- This will be the challenge for the newly emerging field of molecular diagnostics - PET."

Hellman and Weichselbaum, JCO
1995