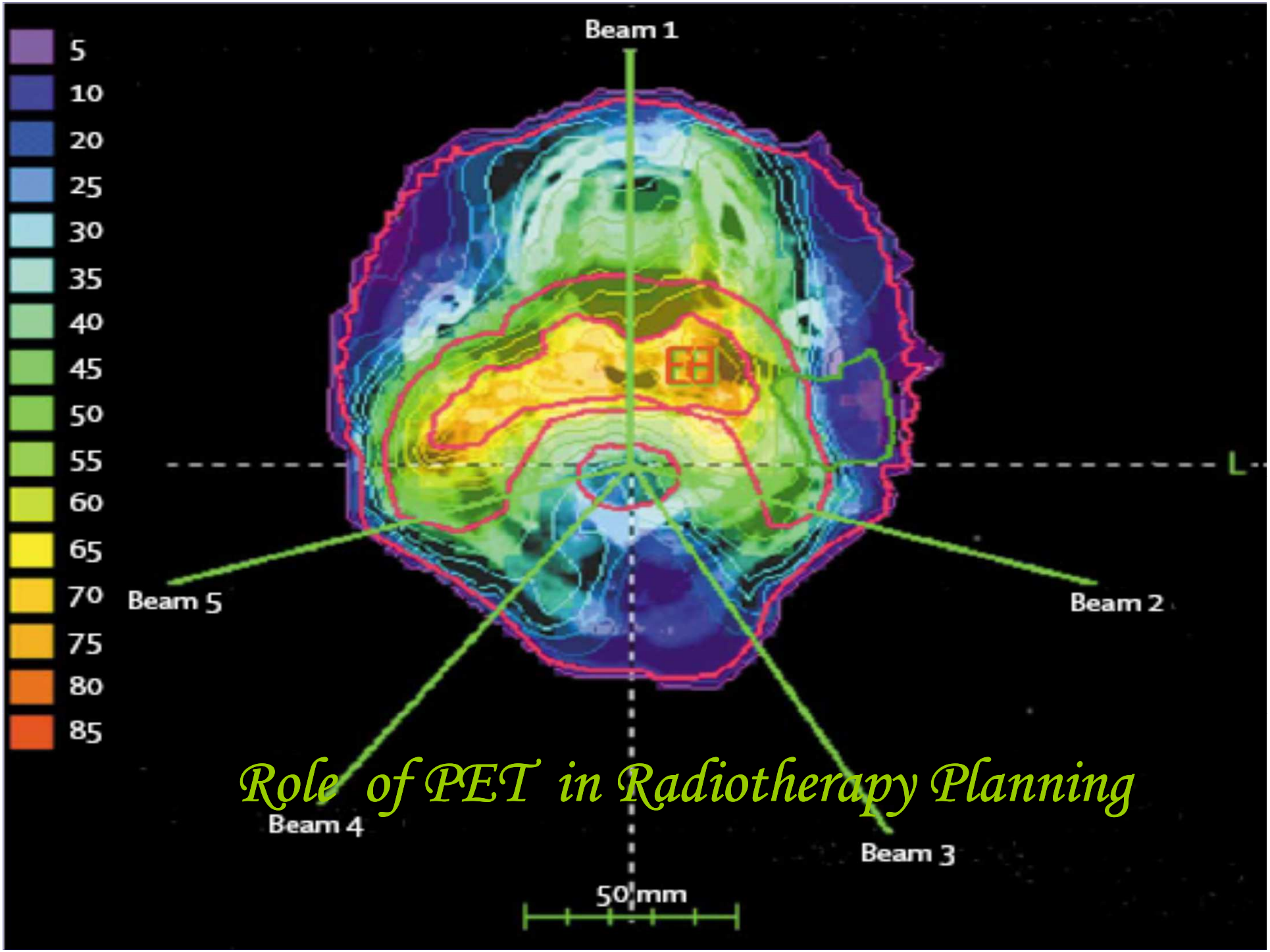
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Beam 1
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Beam 4
Beam 5
L
50 mm
Role of PET in Radiotherapy Planning

IMPROVEMENTS IN IMAGING

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

Past – Anatomic

Present – Biological/ Mechanistic

Wide spectrum of information

Hence "BIOLOGICAL"

Metabolic

Biochemical

Physiological

Functional

Also **molecular**

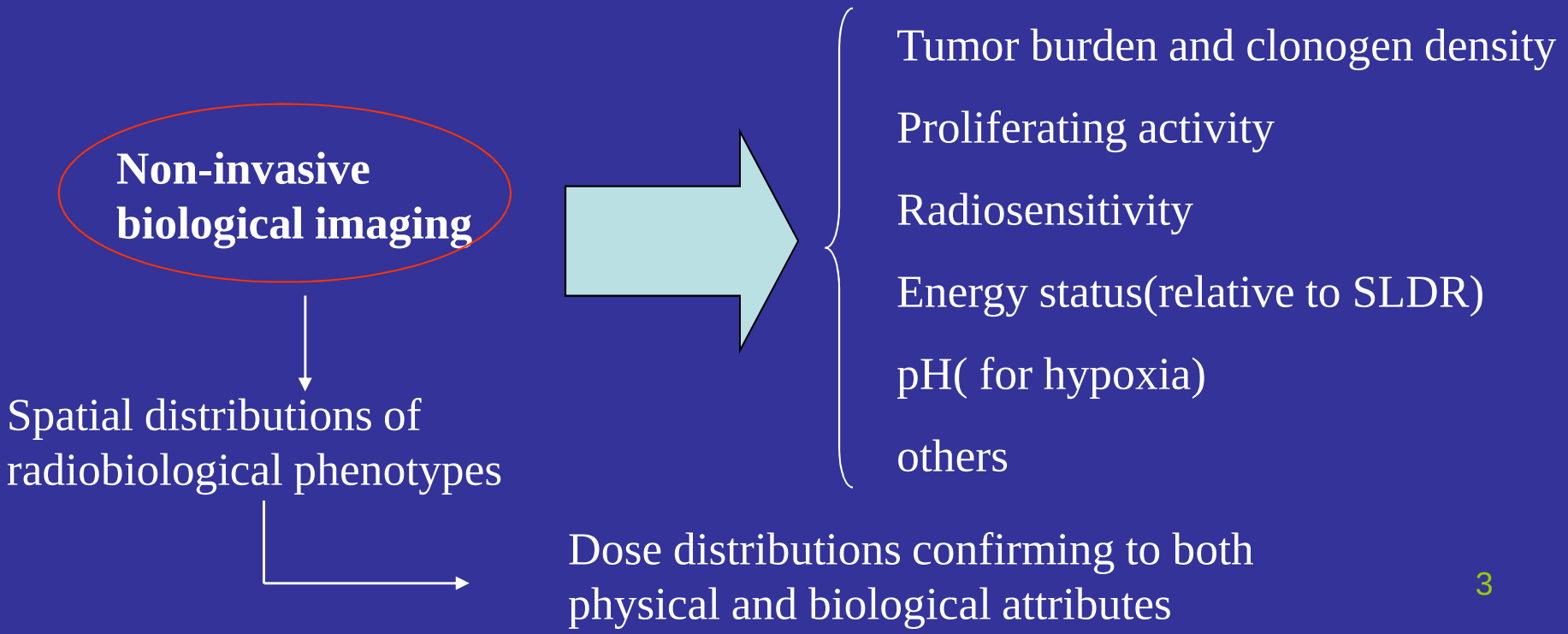
genotypic

phenotypic

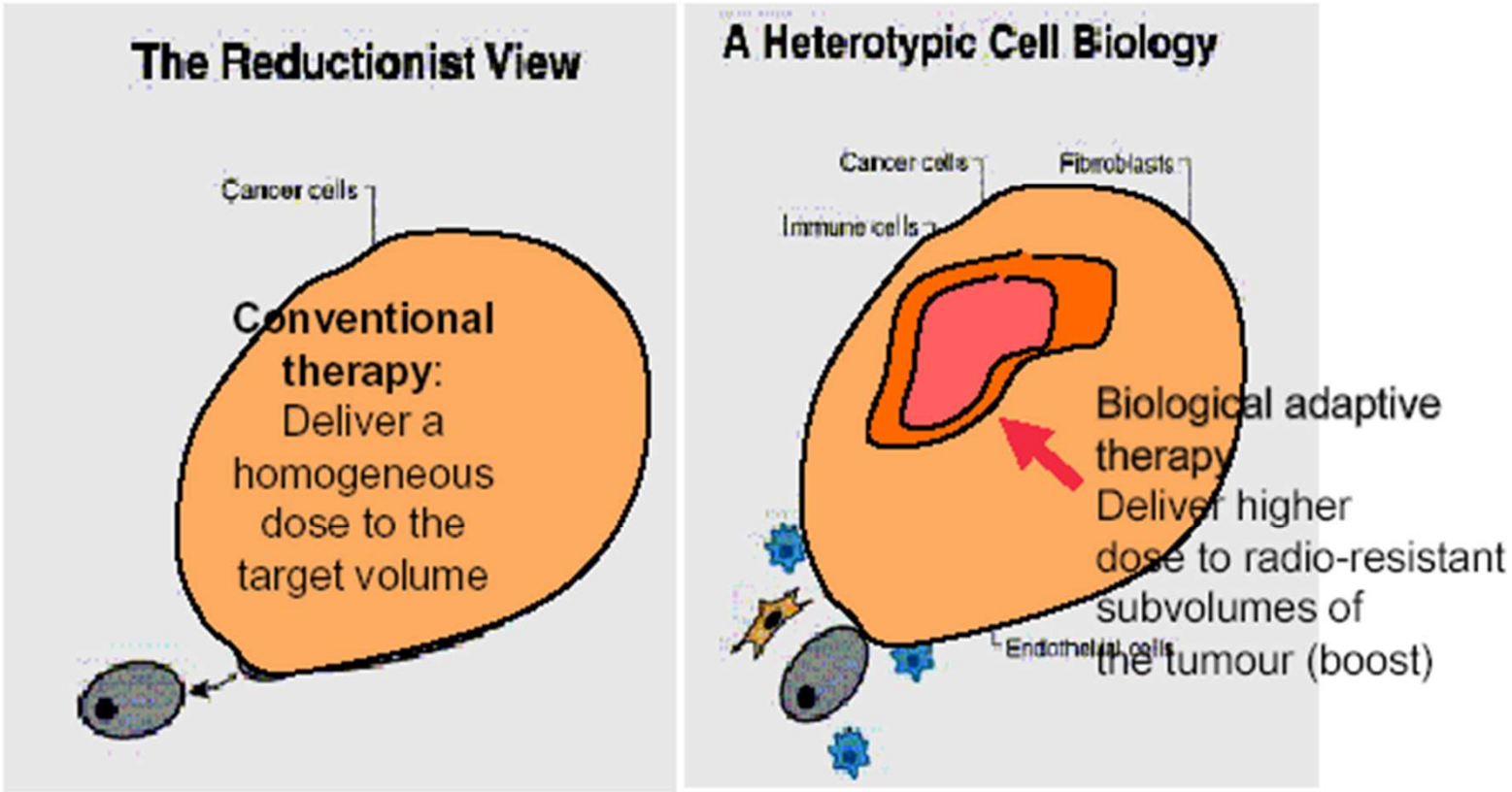
RADIOBIOLOGICAL IMAGES

For RT planning, images that give information about factors (eg. Tumor hypoxia, Tpot) that influence radiosensitivity and treatment outcome.

Ability of IMRT to **paint**(2D) or **sculpt**(3D) the dose and to produce exquisitely conformal dose distributions within the constraints of radiation and propagation begs to question??????????? How to paint/sculpt??????

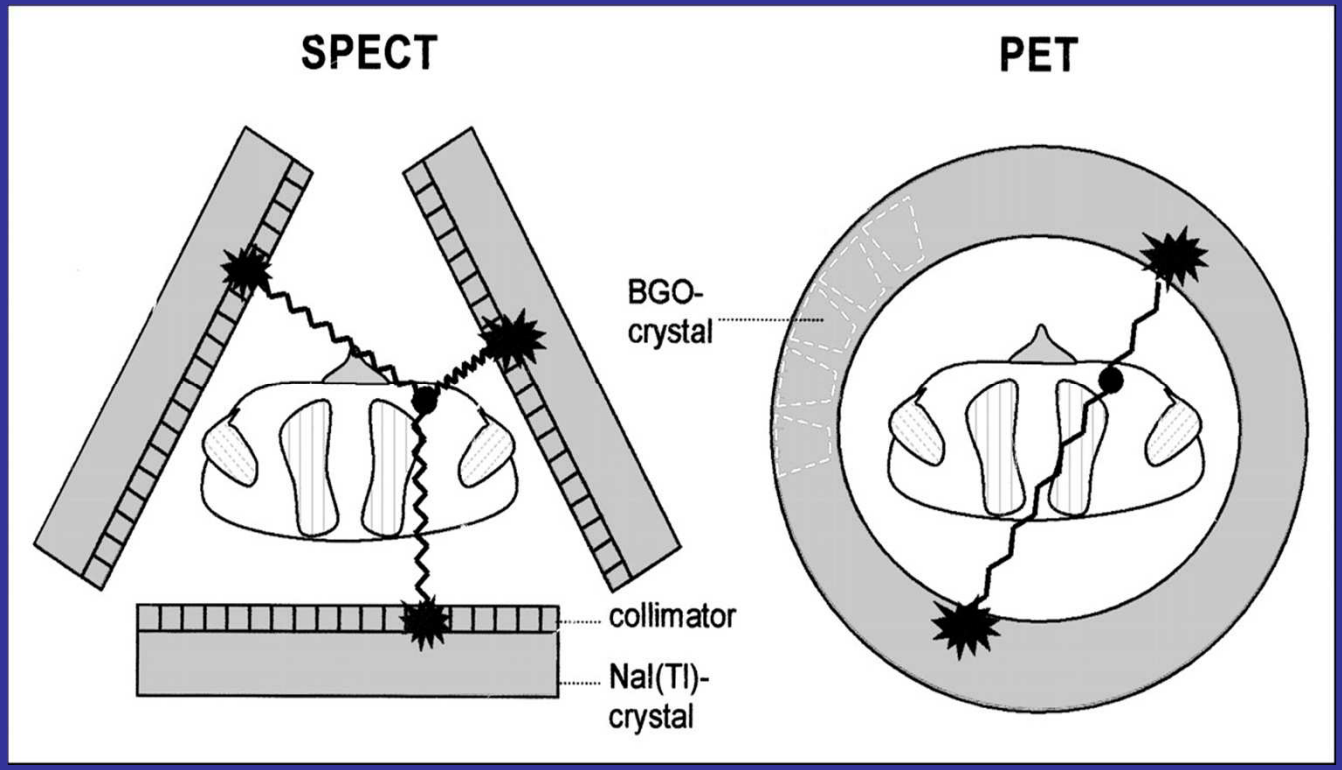


Biology



D. Hanaha, R. A. Weinberg, Cell,Vol. 100, 57-70,2000

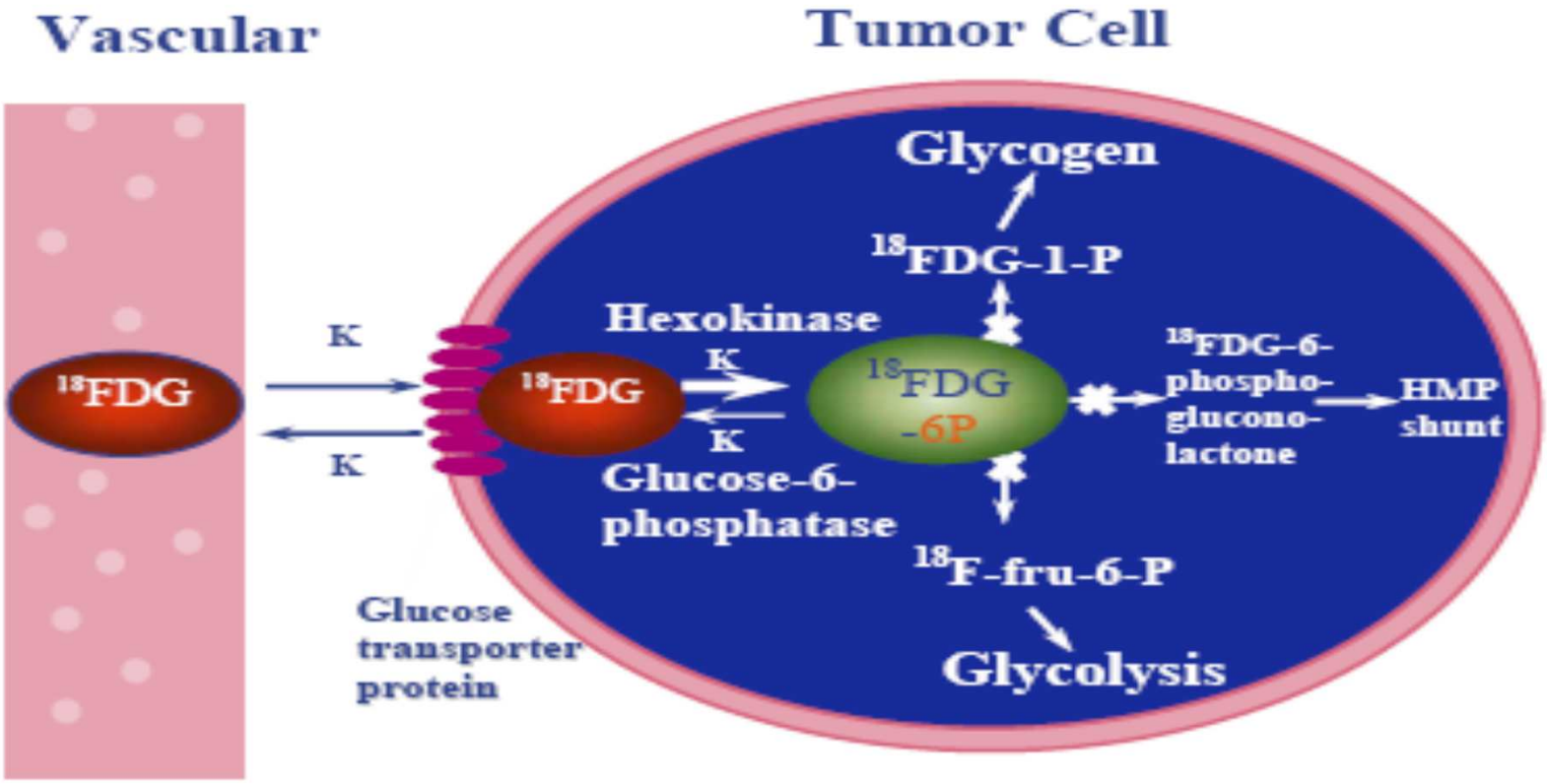
POSITRON EMISSION TOMOGRAPHY



Works by detecting photons that are emitted by positron emitting radiopharmaceuticals such as FDG.

Photons emitted must have a specific energy(511 MeV) and are always emitted in opposite direction.

POSITRON EMISSION TOMOGRAPHY



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.

ROLE OF PET

BASIS FOR ROLE

1. Capacity to distinguish metabolically active tissue from scar.
2. Detection of functional/metabolic activity of cells
3. Quantification of metabolic activity of cells
4. Characteristic capability to detect signal intensity changes rather than lesion size.
5. Very importantly it is 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 for radiotherapy planning and guidance.

ROLE OF PET

Maximal role in rapidly proliferating/poorly differentiated/high grade tumors- FDG Avid tumors.

Tumors with high metabolic rate- Lymphoma

Head and neck cancers

NSCLC and SCLC

Gynecological cancers

Prostate cancer with slow proliferation rate of tumor- PET has a limited role.

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 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.
14. Gating- registration problems between PET and CT and as well as target movement can be elegantly adhered with gating.

PET scans will volume average(favour depicting lesion in end expiratory phase) – hence better to have simulation CT of chest during moderate end expiration breath hold phase.

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.

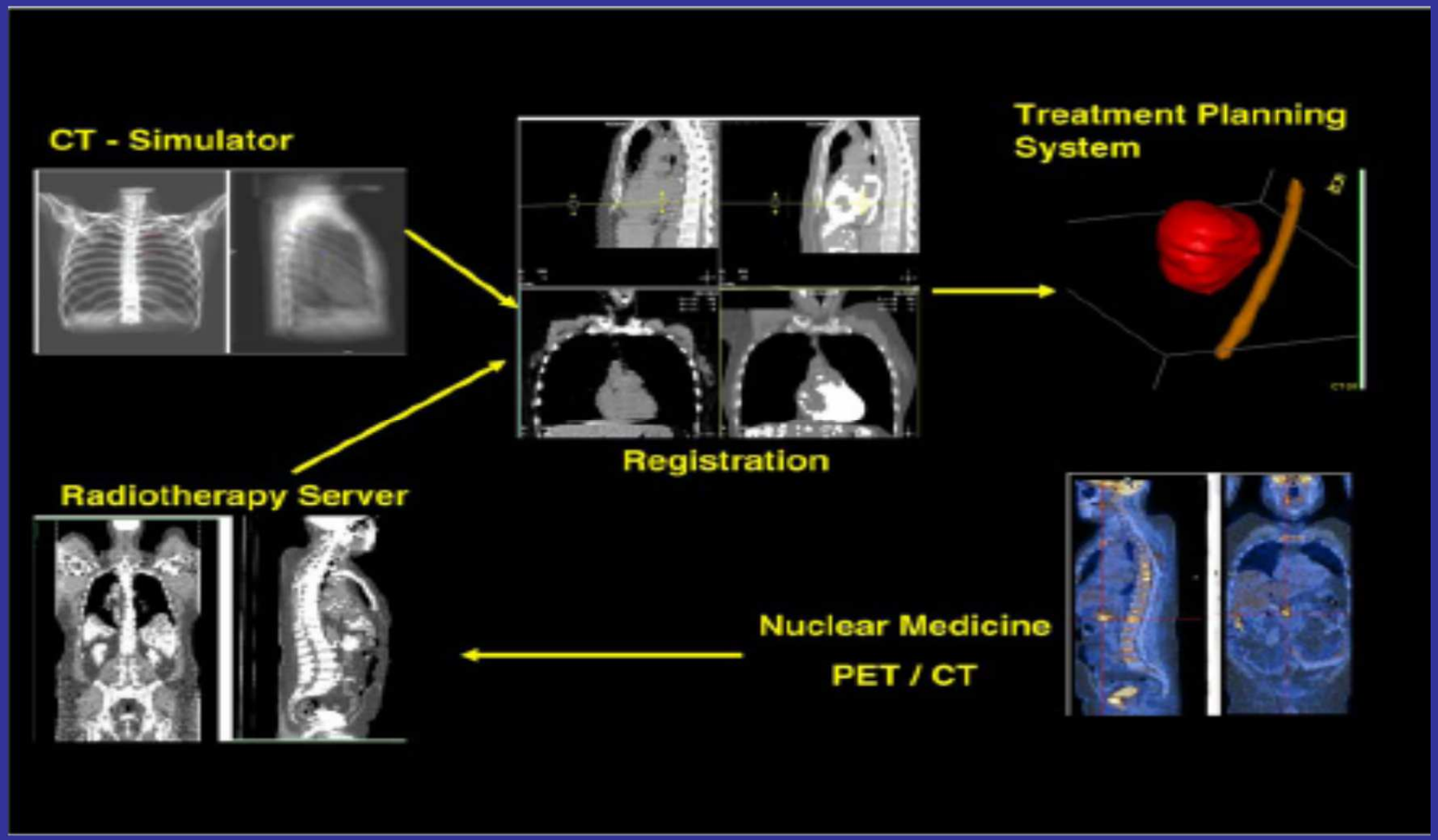


Table 1 Impact of (staging-) PET scan on radiotherapy treatment		
	Changes in staging	Effect on radiotherapy
T-stage	Larger extension of primary tumour (upstaging) Less extension of primary tumour (downstaging)	Enlargement of radiotherapy fields to avoid geographical miss Change of radiotherapy indication from curative to palliative Decrease in radiotherapy fields and hence decrease in radiation exposure of normal tissues, and thus possible allowing dose escalation Change of radiotherapy indication from palliative to curative
N-stage	Detection of new site of lymph node involvement (upstaging) Omission of enlarged lymph nodes, diagnosed as malignant on CT or MRI (down staging)	Enlargement of radiotherapy fields to avoid geographical miss Change of radiotherapy indication from curative to palliative Change of radiotherapy indication from palliative to curative Decrease in radiotherapy fields and hence decrease in radiation exposure of normal tissues, and thus possible allowing dose escalation
M-stage	Detection of distant metastases	Change of radiotherapy 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

QUALITIES OF PET FOR EACH SITE

Table 2 Characteristics of CT and PET for staging in different tumour sites

Site	Sensitivity		Specificity		PPV		NPV		Accuracy	
	(CT) PET (%)	CT (%)	(CT) PET (%)	CT (%)	(CT) PET (%)	CT (%)	(CT) PET (%)	CT (%)	(CT) PET (%)	CT (%)
Head and Neck[43,44,51,53,56,59–61,63,64,66,67]										
Primary tumour	88–93	51–96	100	86					94	94
Lymph nodes	70–96	66–88	82–100	74–98.5	96	95	98.5	92	75–96	70-87
Lung[45,47,50,54]										
Lymph nodes	77–91	33–83	67–92	66–90	67–90	46–71	77–97	68–86	73–92	65–80
Lymphoma[37]										
Primary tumour	90	81	93	69	74	48	91	87	88	64
Breast[46,49,55]										
Lymph nodes	57–100	63	63–100	96	63–100	74	60–99	92	90	90
Gynaecology[49,52]										
Primary tumour	97									
Lymph nodes	54–100	21–73	87–100	76	84		95			
Bladder[49,58]										
Lymph nodes	67–78		86–100		63–100		83–100		67	70–90
Prostate[49,58]										
Primary tumour	0–64		72–400		100		60		60	
Lymph nodes	0–67									
Gastro-oesophageal[48,62,65]										
Lymph nodes	51–74	47–50	84–90	69	60–89	29	40		82–83	64–68
Colorectal[42,49]										
Primary tumour	90–100		43		90		100			
Lymph nodes	29	29	85–96	85						

TARGET DELINEATION

What is the optimal PET volume for radiation therapy?

Who Needs To contour?

What about tumors that are positive on CT but negative on PET and vice versa?

What is the Optimal PET volume for Radiation Therapy?

1. Unlike on CT's, where tumors have well defined anatomic margins, edges of tumors appear fuzzy.
2. Philosophy should be "PET finds it CT defines it".
3. Some exceptions – PET is used to define tumor edge –

   Neck/Pelvic mass that blends in with tumor surrounding soft tissue or in a lung mass where the tumor's edge cannot be distinguished from accompanying atelectasis.

4. Manual segmentation
5. Automatic segmentation based on SUV
6. SUV- average activity per unit volume normalized to the injected dose and patient's body weight.

What is the Optimal PET volume for Radiation Therapy?

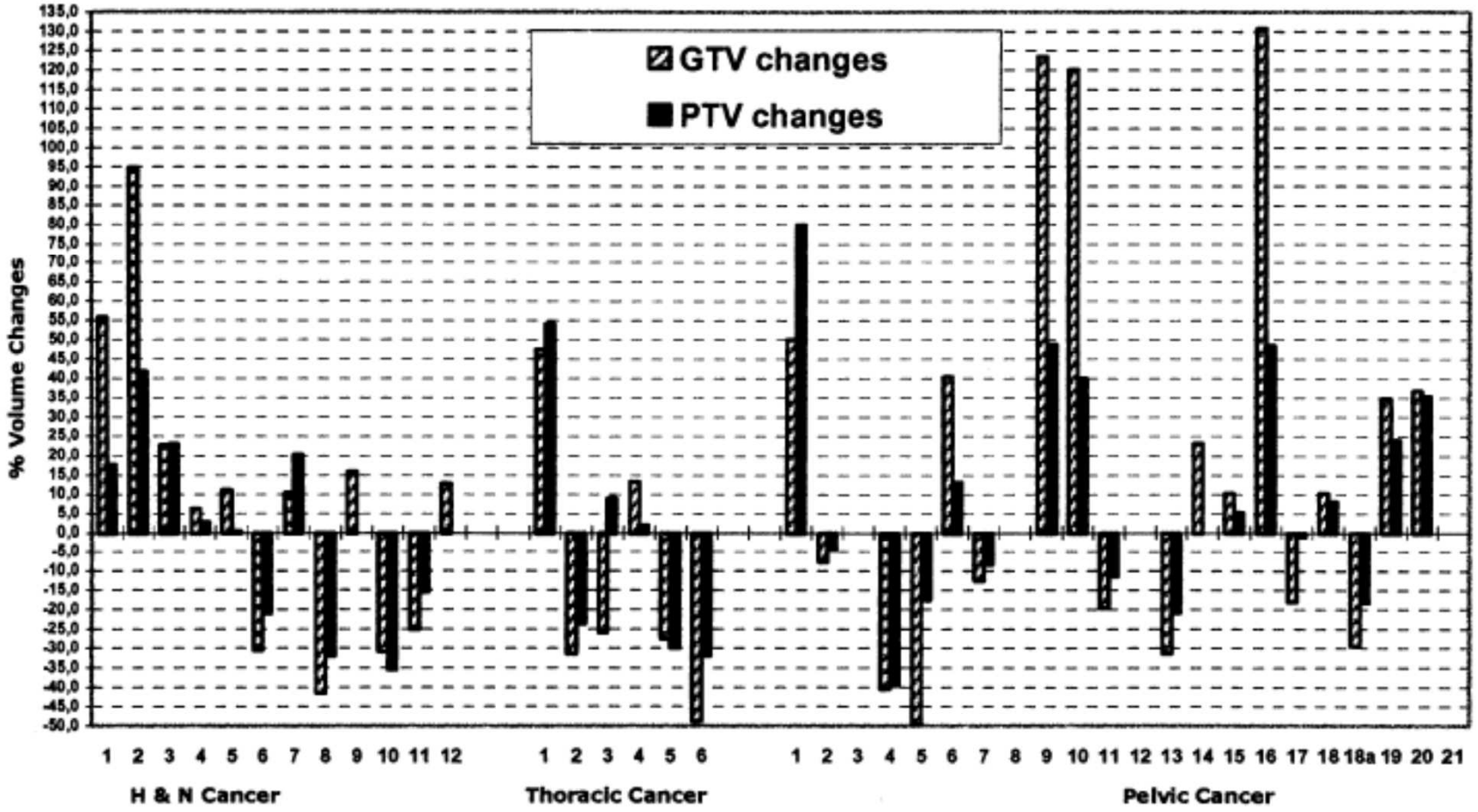
An FDG-PET GTV can be systematically defined using a threshold SUV according to regressive function.

Threshold SUV = 0.307 X Mean Target SUV +0.588

Threshold SUV is strongly dependent on mean target SUV but not independently related to background FDG concentration and target volume.

Some have arbitrarily defined 50/40% intensity level relative to tumor maximum for contouring/auto contouring..

Some have auto-contoured all areas with a standardized uptake value of 2.5 , above which most experts are comfortable interpreting as positive for NSCLC. For other sites – no consensus.


GTV changes
PTV changes
% Volume Changes
135,0
130,0
125,0
120,0
115,0
110,0
105,0
100,0
95,0
90,0
85,0
80,0
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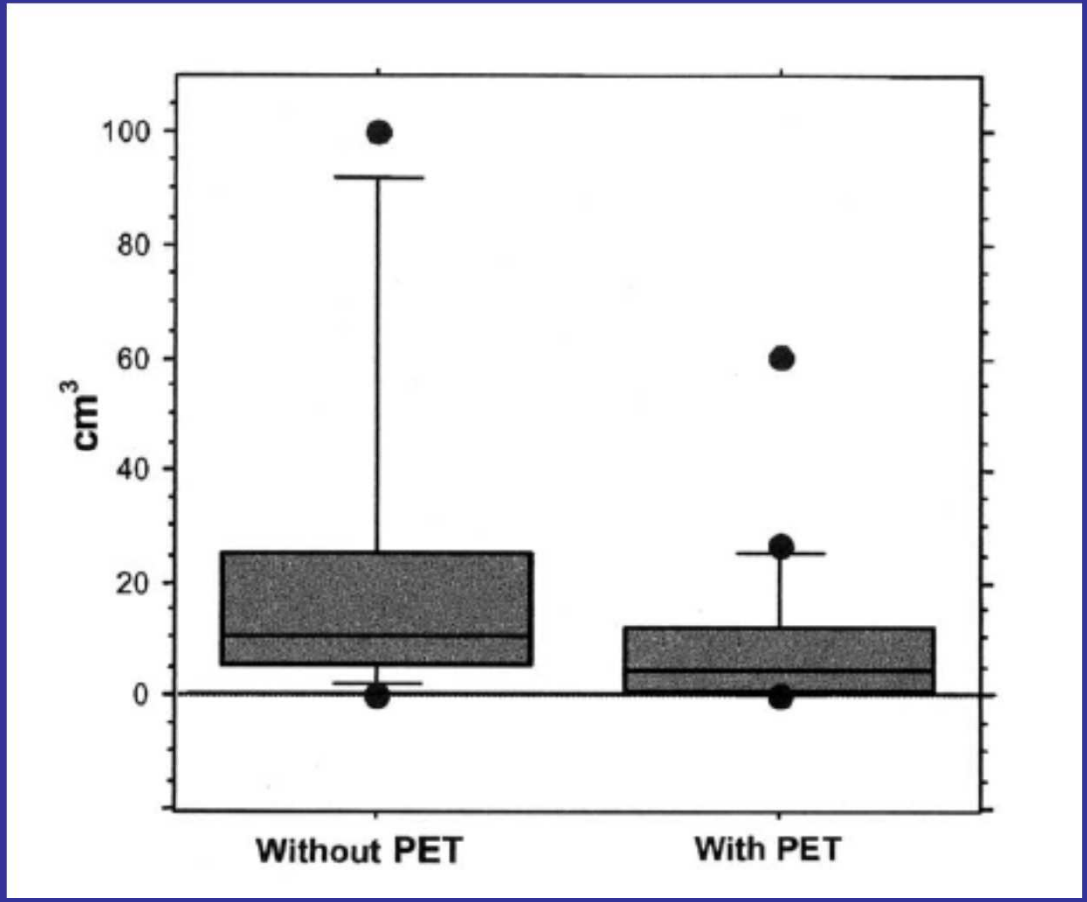
-35,0
-40,0
-45,0
-50,0
1 2 3 4 5 6 7 8 9 10 11 12
H & N Cancer
1 2 3 4 5 6
Thoracic Cancer
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 18a 19 20 21
Pelvic Cancer

INTEROBSERVER VARIABILITY



Who Needs To contour?

Radiation oncologist vs. Nuclear medicine expert

FDG uptake subject to lot of variability – normal physiological uptake.

post-surgery sites

irradiated sites

areas of inflammation

SUV variability – Patient LBW

activity of injected isotope

BSA

Collaboration with nuclear medicine expert

As experience grows –requirement will be far less frequent.

What about tumors that are 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.

Molecular Profiling of Tumors

Both NMR and nuclear medicine assays are used for non-invasive molecular imaging. Nuclear medicine assays have upper hand till date because of better signal to noise ratios.

Tumor burden and clonogen density

PET with FDG serves as proxy for tumor burden. FDG is also a function of microvasculature for delivery of micronutrients, number of tumor cells in volume and proliferation rate.

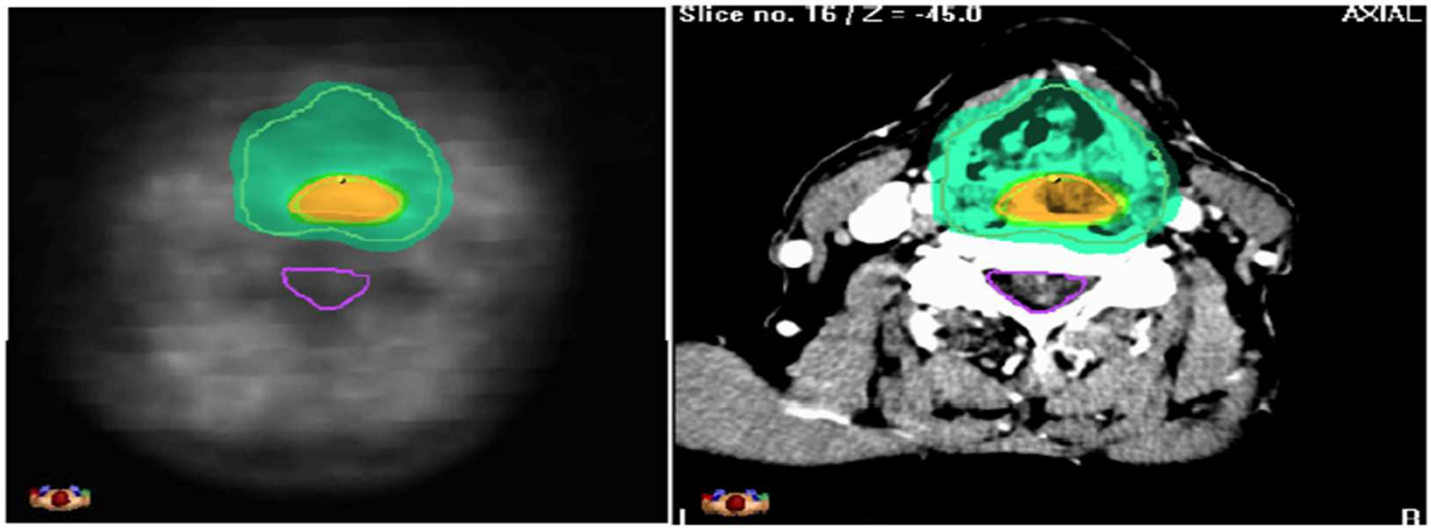
Hypoxia Markers

Vanilla markers- Radionucleide compounds that contain a 2-nitroimidazole group (F-18-misonidazole, 123I iodoazomycin arabinoside

Chocolate markers- Copper –62 labelled diacetyl-bismethyl isosemicarbazone. Rely on reduction of chelated metal for this selective deposition in hypoxic tissues.

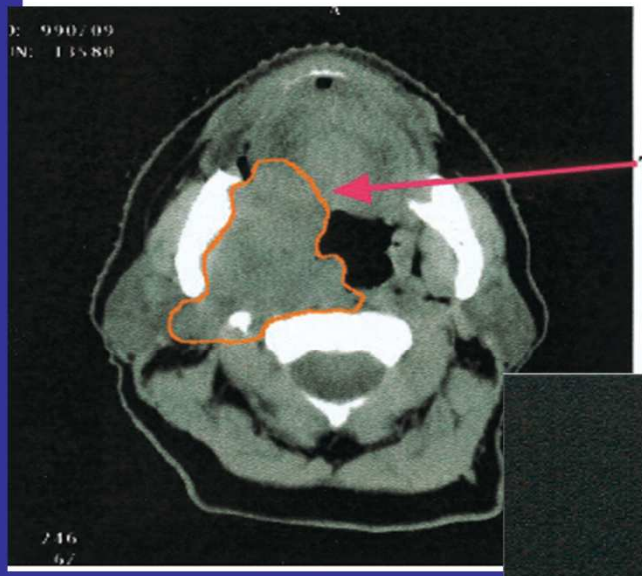
Chocolate swirls- metal chelating ligands complexed with one or more azomycin substituents.

Molecular Profiling: Imaging of hypoxia with PET (18F-FAZA + CT)



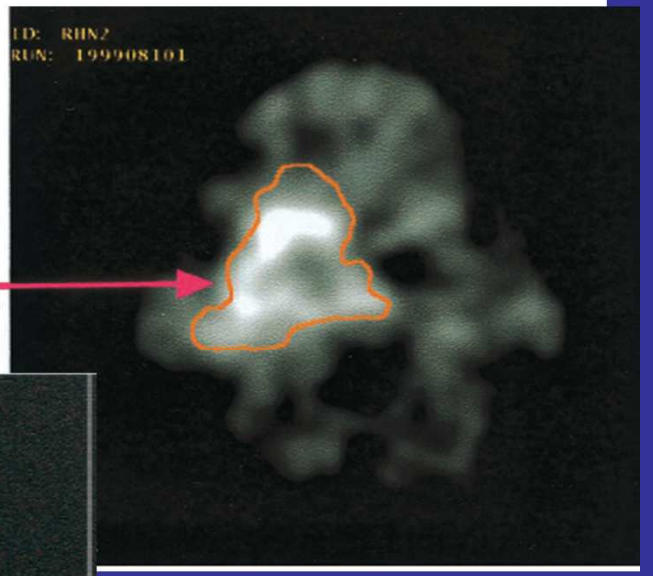
A NOVEL APPROACH TO OVERCOME HYPOXIC TUMOR RESISTANCE: Cu-ATSM-GUIDED INTENSITY-MODULATED RADIATION THERAPY

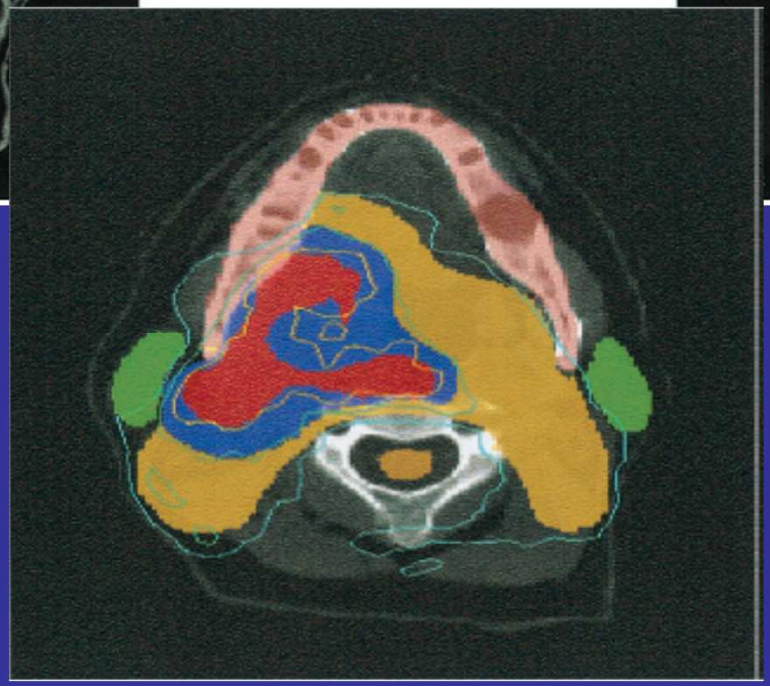
K. S. Clifford Chao, M.D.,* Walter R. Bosch, Ph.D.,* Sasa Mutic, M.S.,* Jason S. Lewis, Ph.D.,† Farrokh Dehdashti, M.D.,‡ Mark A. Mintun, M.D.,†‡ James F. Dempsey, Ph.D.,* Carlos A. Perez, M.D.,* James A. Purdy, Ph.D.,* and Michael J. Welch, Ph.D.†



Tumor volume was defined on CT scan

The tumor contour was shown on the corresponding ^{60}Cu-ATSM image after image registration and fusion



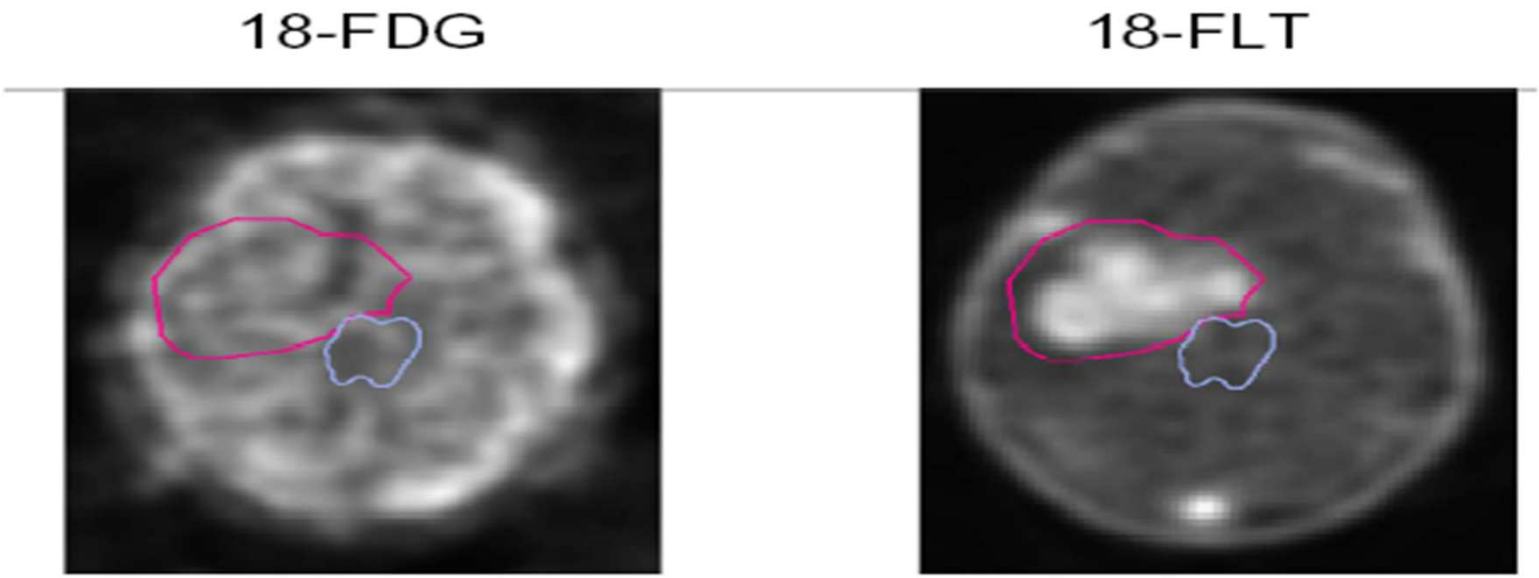


Tumor Proliferation

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.

Molecular Profiling: Imaging of proliferation with PET (18FLT)



Future Molecular Profiling of Tumors

Other targets

EGFR

Cyclin D

With the curent advances in molecular risk profiling and search for fingerprinting of malignant phenotypes that are sensitive to a specific type of modified RT(accelerated /hyperfractionated).

Many new Theragnostic imaging modalities are likely to be identified.

Theragnostic Imaging

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.

BIOLOGICAL TARGET VOLUME/ BIOLOGICAL EYE VIEW

Requirement for dose uniformity with in PTV in external beam treatment planning has been largely a matter of tradition and convention.

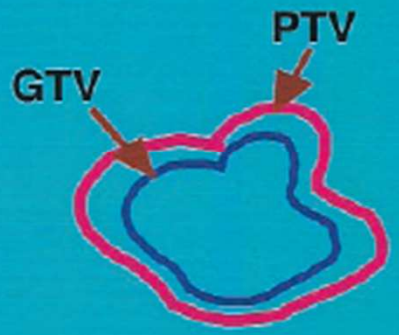
Ability of IMRT to deliver non-uniform dose patterns by design brings to fore the question of how paint or dose sculpt.

In this regard biological images may be value.

UCSF – use of biological images for treatment planning and delivery is the work of researchers at UCSF.

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

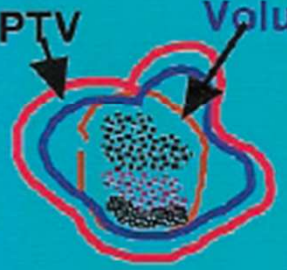
• MRI/MRS
• choline/citrate
Tumor burden

• PET
• IUDR
Tumor growth

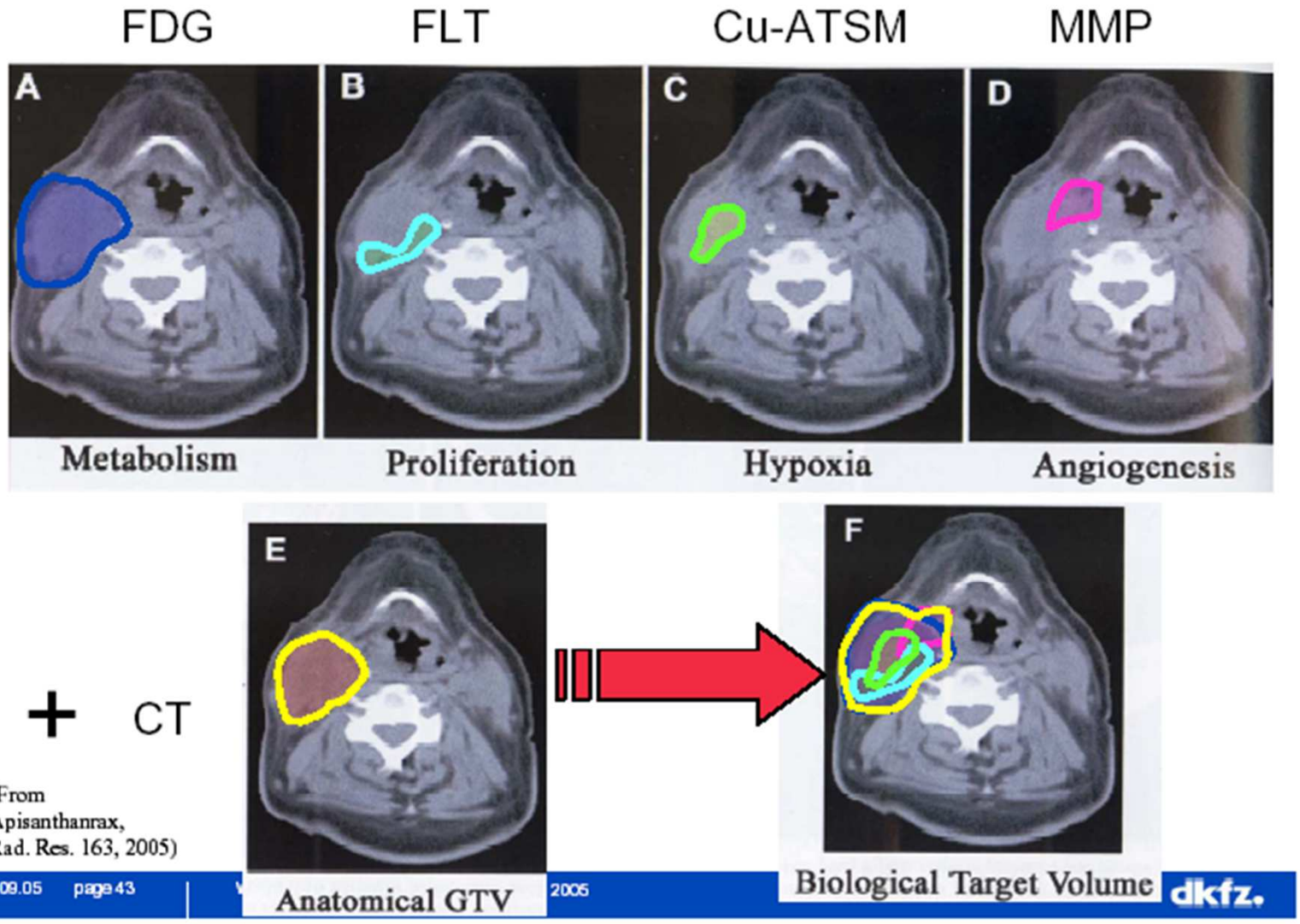
Biological
Eye View

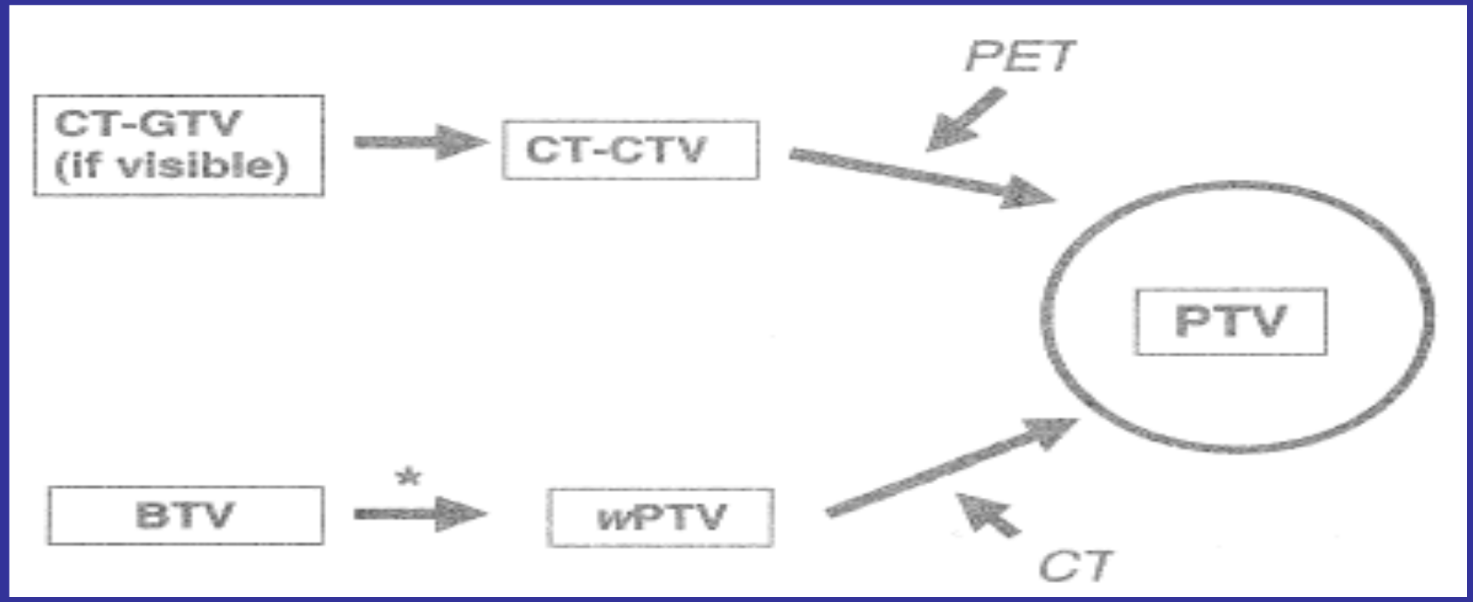
Biol. Tgt.
Volume

PTV



The concept of a „biological target volume“





PET-based planning inverses the process of PTV def. from anatomic information.

PET based RT planning can be automated starting with BTV, which represents tumor specific target volumes that result in a preliminary working PTV.

Anatomic information and constraints from CT are used in a second step for manual refinement.

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, equivalent to extent of hot spot depicted by PET complemented with information given by CT.

Design of PET portals involve a change in the mediastinal field margins only if a hotspot seen in PET is clearly outside the CT fields.

PET for Mediastinum-

Most important when elective mediastinal radiation is not considered.

In the setting of neoadjuvant therapy.

Useful when nodal sites are marginal on CT scan to ensure that all gross disease can be better identified.

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.

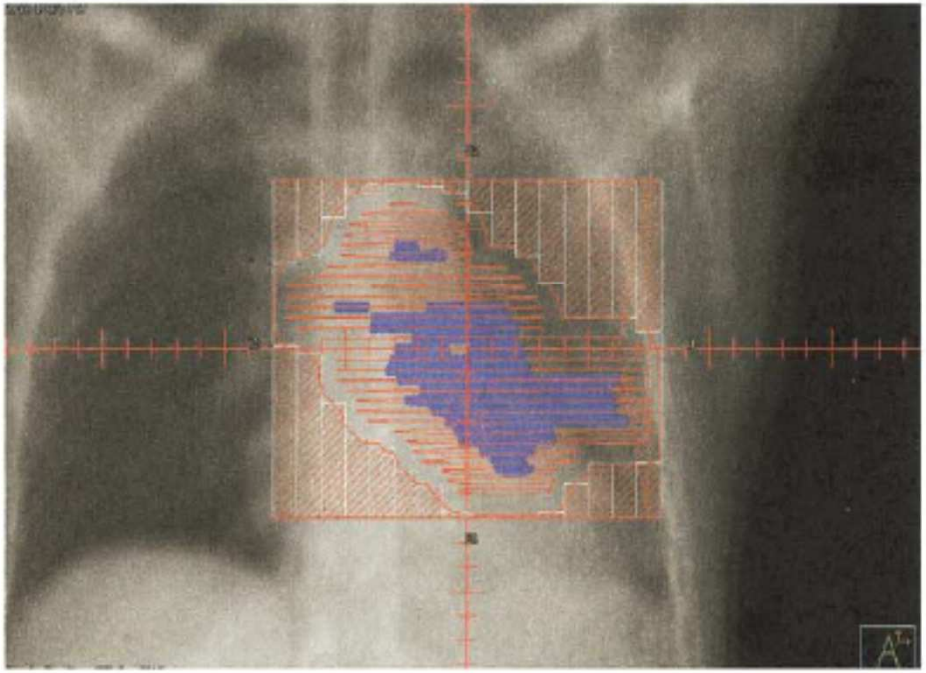
PET intensity as a marker of biological behavior

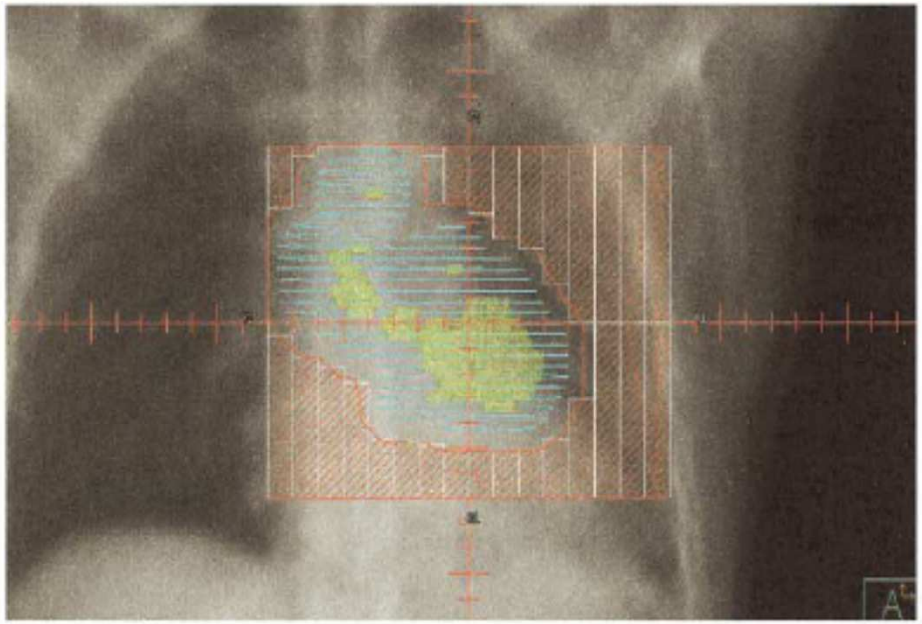
2yrsurvival SUV < 5- 91%;/ SUV<7 - 83%; / SUV < 10 –52%.

PET to stage after neoadjuvant therapy

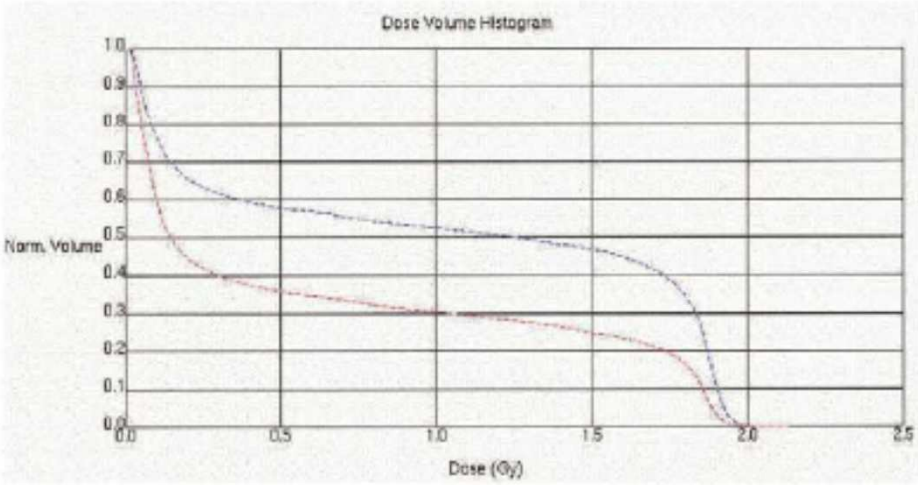
Early changes in PET to assess response to treatment

(a)





(c)

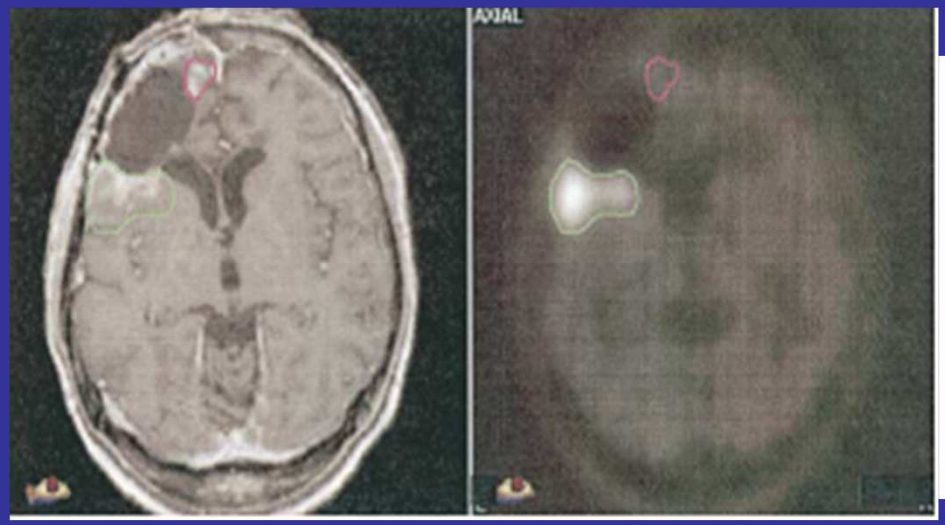

Dose Volume Histogram
Norm. Volume
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0.0
0.5
1.0
1.5
2.0
2.5
Dose (Gy)

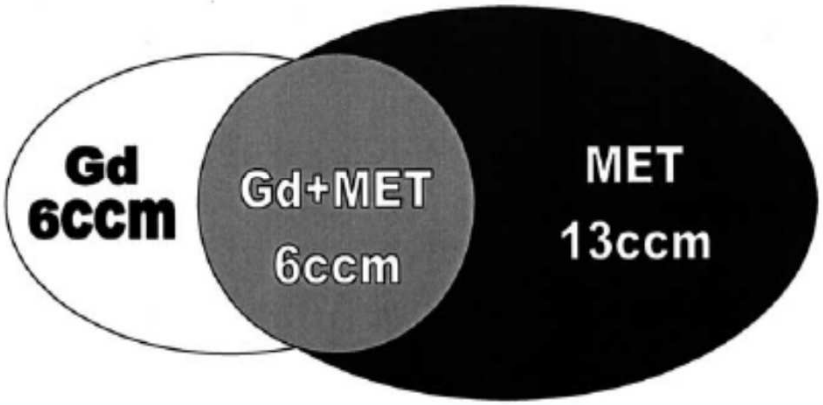
Role of PET in Planning for Gliomas

1. Better definition of GTV specially in gliomas. Hence better sparing of normal brain possible. Also tried in meningiomas.

Table 4. Results of comparison of Gd and MET in 39 patients using PET/MRI fusion images

Finding	*n* (%)
MET uptake corresponded to Gd enhancement	5/39 (13)
MET uptake located outside Gd enhancement	29/39 (74)
Gd enhancement located outside MET uptake	27/39 (69)





Role of PET in Planning for Gliomas

2. Differentiates between recurrence and radiation induced late toxicity.

3. Dose Escalation

[F-18]-FLUORODEOXYGLUCOSE POSITRON EMISSION TOMOGRAPHY FOR TARGETING RADIATION DOSE ESCALATION FOR PATIENTS WITH GLIOBLASTOMA MULTIFORME: CLINICAL OUTCOMES AND PATTERNS OF FAILURE

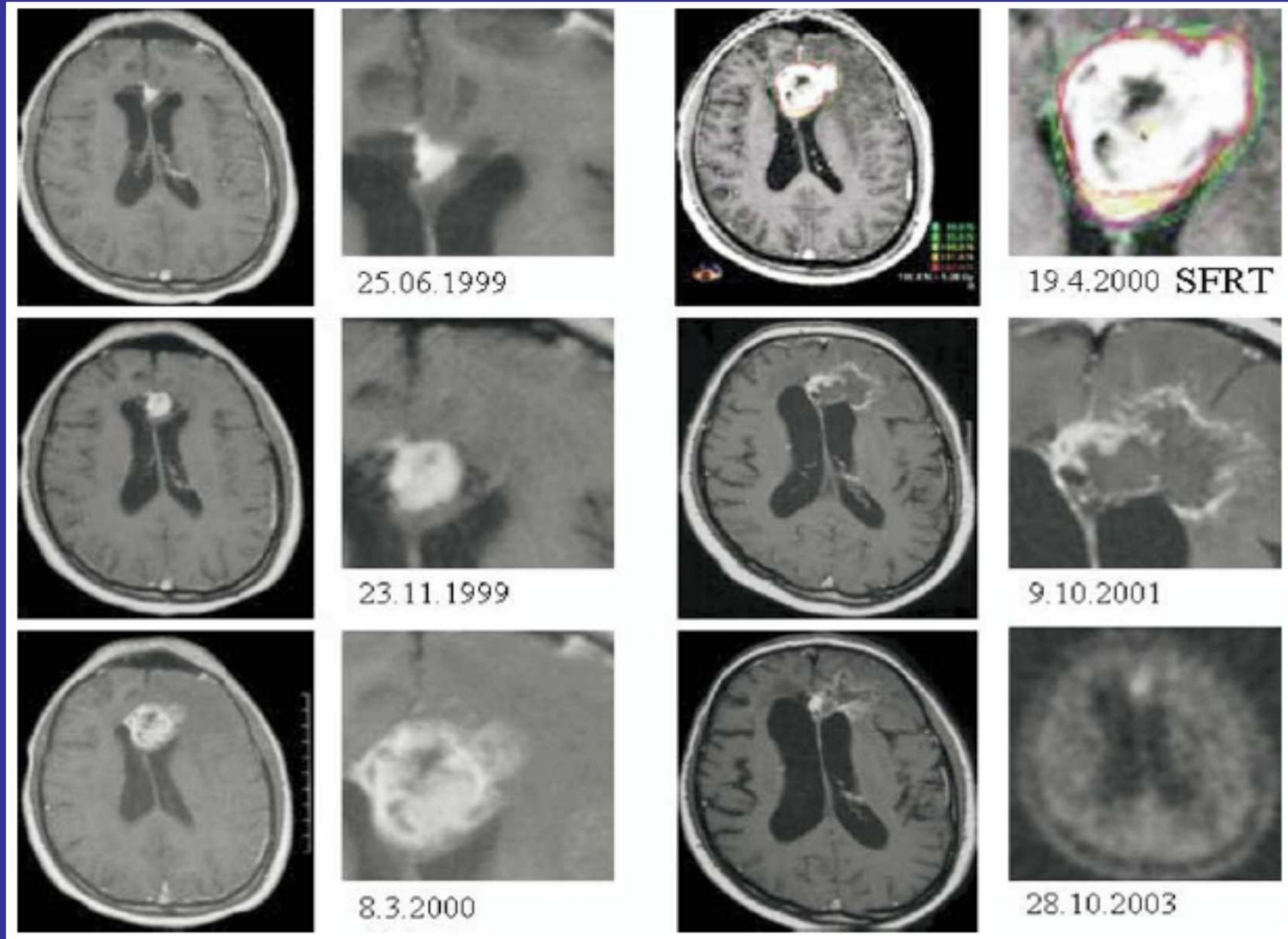
James G. Douglas, M.D., M.S.,*† Keith J. Stelzer, M.D., Ph.D.,*‡ David A. Mankoff, M.D.,§ Kevin S. Tralins, M.D.,* Kenneth A. Krohn, Ph.D.,§ Mark Muzi, M.S.,§ Daniel L. Silbergeld, M.D.,† Robert C. Rostomily, M.D.,† Jeffrey Scharnhorst, B.S.,‖ and Alexander M. Spence, M.D.‖

Departments of *Radiation Oncology, †Neurological Surgery, §Nuclear Medicine, and ‖Neurology, University of Washington Medical Center, Seattle, WA; ‡Celilo Radiation Therapy, Mid-Columbia Medical Center, The Dalles, OR

80Gy was delivered. But there was no improvement in OS. But it was very feasible.

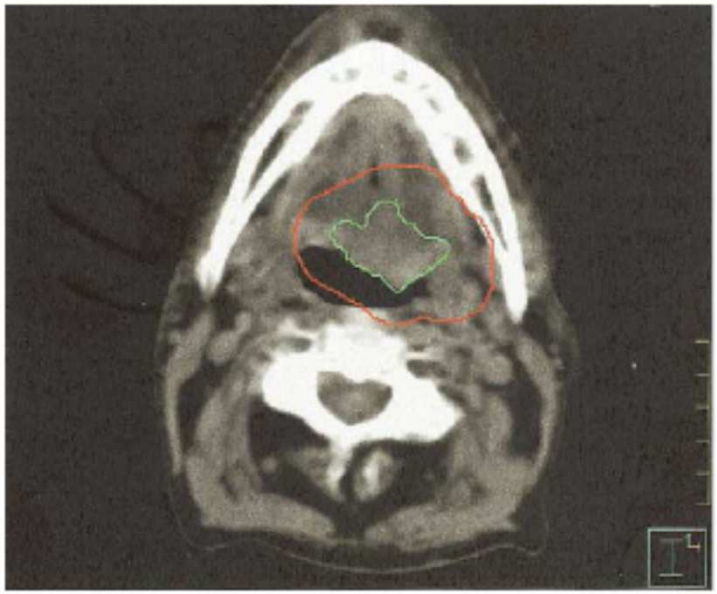
REIRRADIATION OF RECURRENT HIGH-GRADE GLIOMAS USING AMINO ACID PET (SPECT)/CT/MRI IMAGE FUSION TO DETERMINE GROSS TUMOR VOLUME FOR STEREOTACTIC FRACTIONATED RADIOTHERAPY

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.*

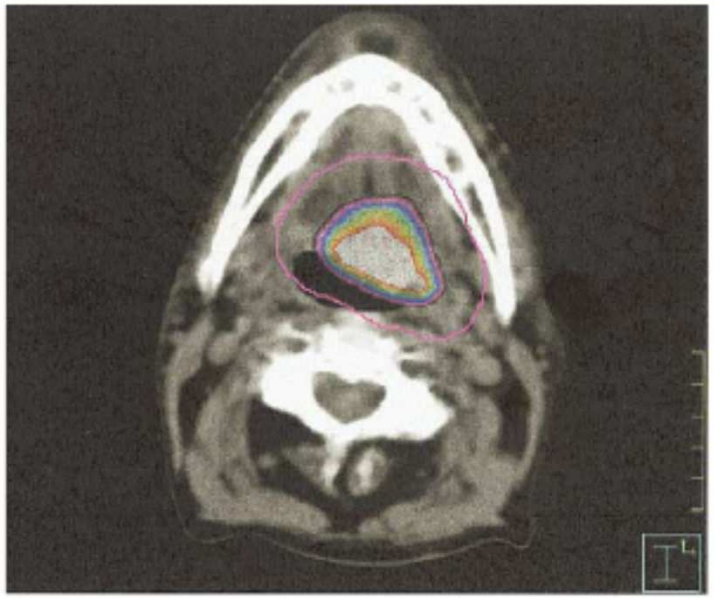


Role of PET in RT Planning

1. Role of PET in Head and neck cancers
2. Role of PET in lymphoma
3. Role of PET in cancer cervix and management of para-aortic nodes.
4. Role in management of esophageal cancers.
5. Role of PET in prostate cancers.



(a)



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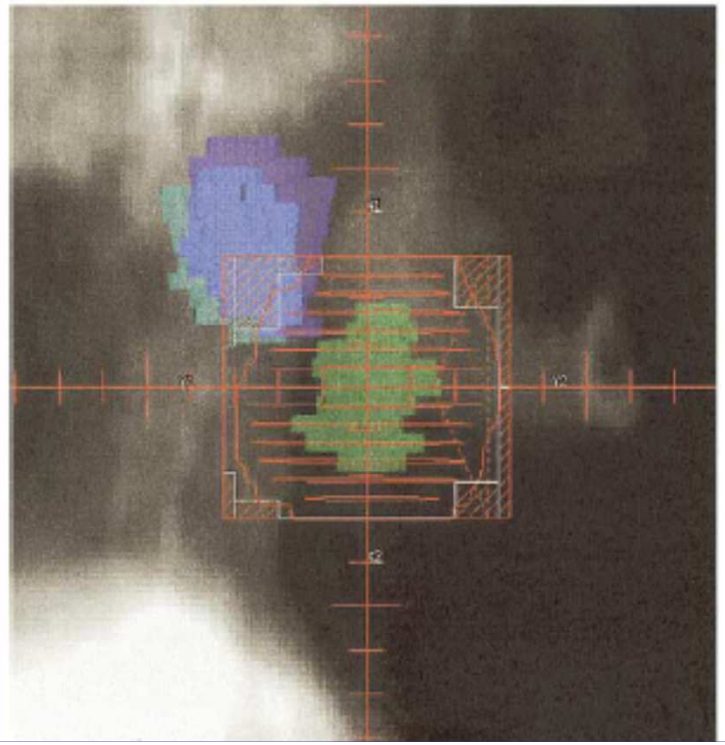

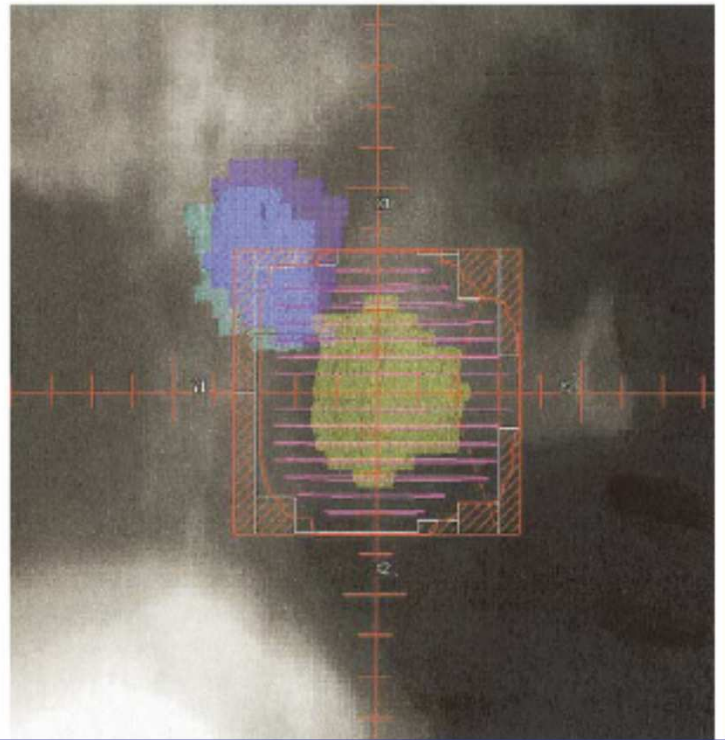

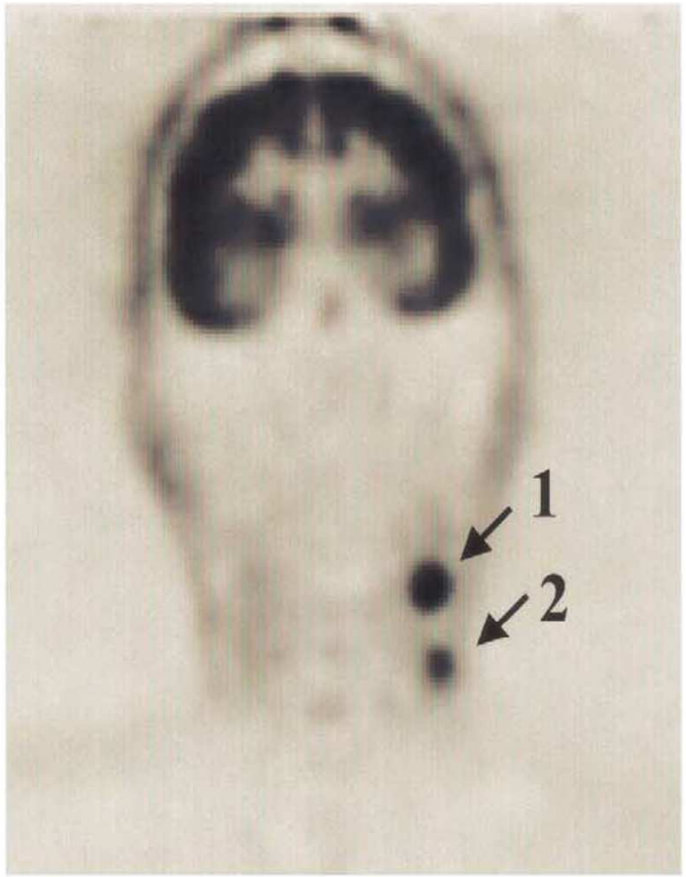
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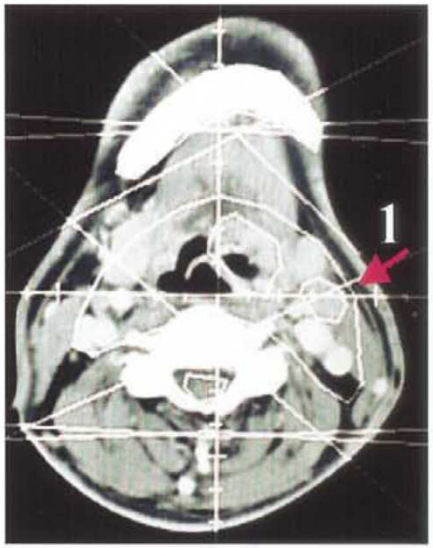
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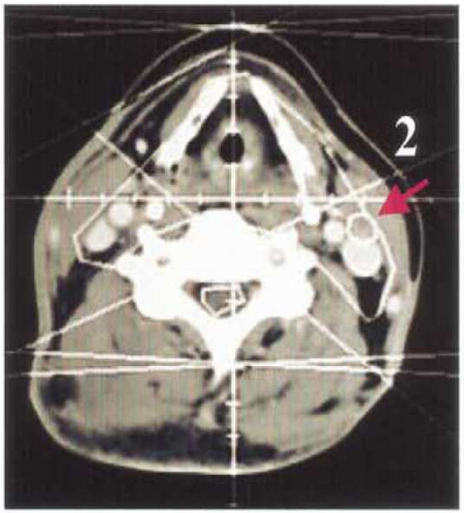
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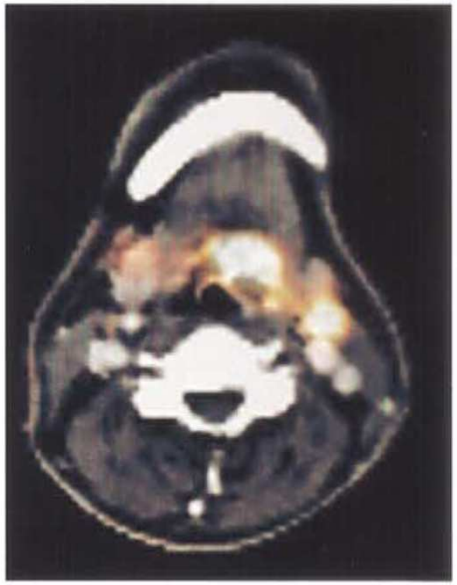
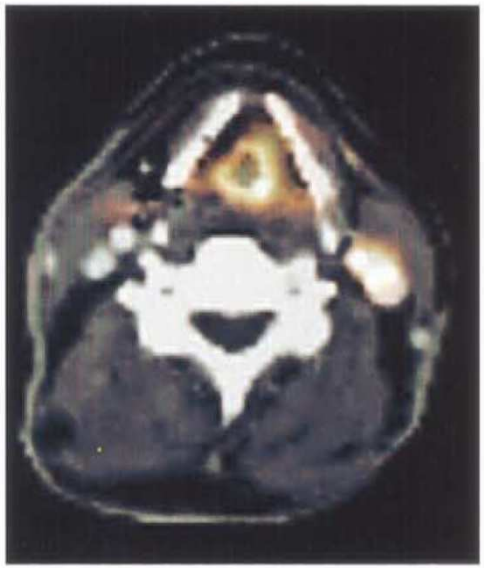




Role of PET in Planning for Cancer Cervix

Better definition of GTV / PTV.

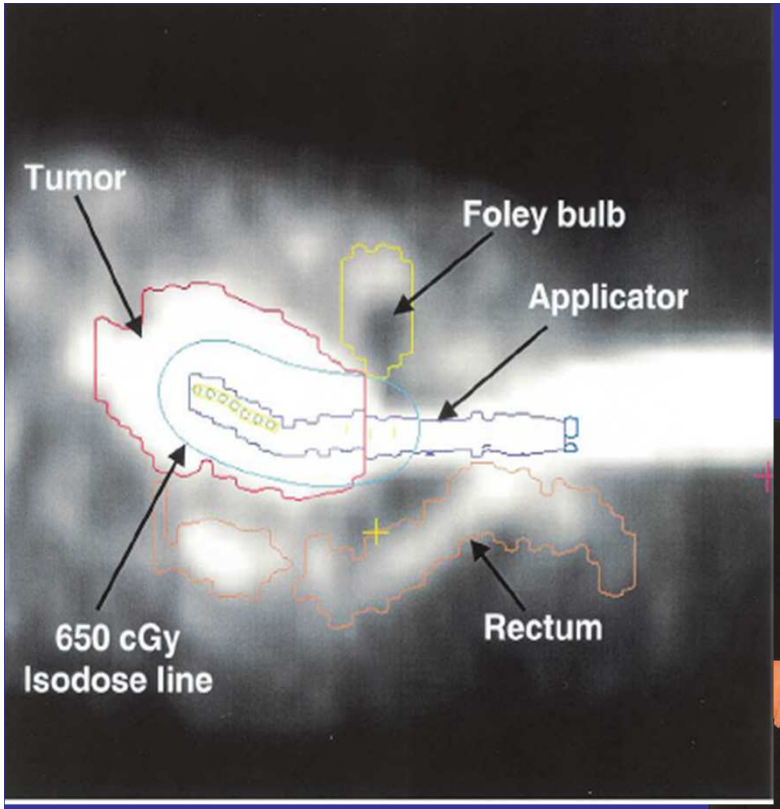
Dose escalation

Cervix brachytherapy.

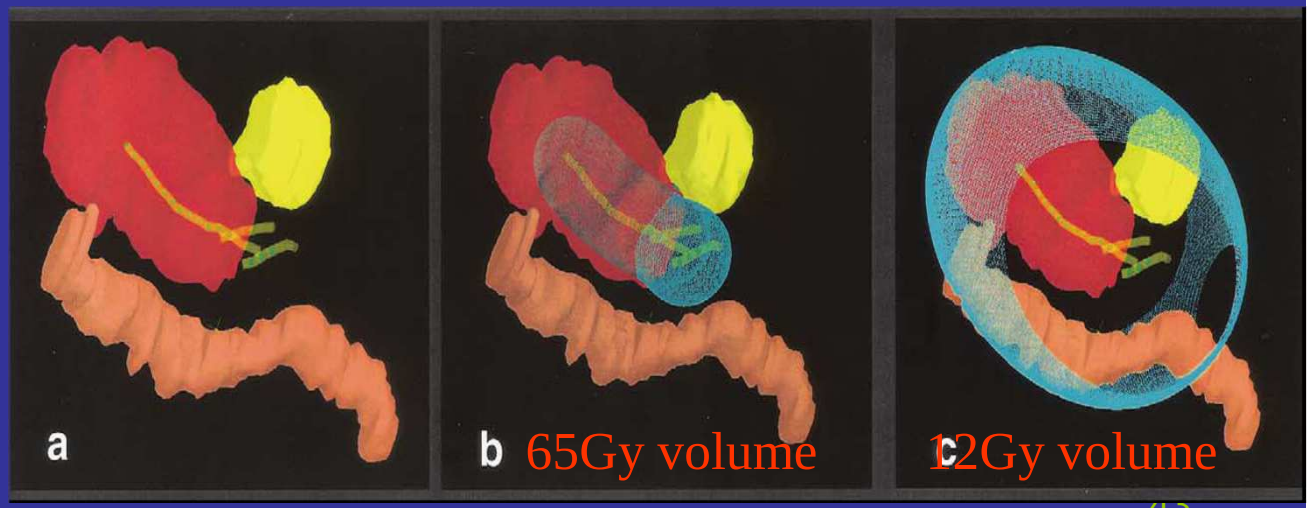
PET-GUIDED IMRT FOR CERVICAL CARCINOMA WITH POSITIVE PARA-AORTIC LYMPH NODES—A DOSE-ESCALATION TREATMENT PLANNING STUDY

SASA MUTIC, M.S.,* ROBERT S. MALYAPA, M.D., PH.D.,* PERRY W. GRIGSBY, M.D.,* FARROKH DEHDASHTI, M.D.,† TOM R. MILLER, M.D., PH.D.,† IMRAN ZOBERI, M.D.,* WALTER R. BOSCH, D.SC.,* JACQUELINE ESTHAPPAN, PH.D.,* AND DANIEL A. LOW, PH.D.*

*Department of Radiation Oncology and †Division of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO


Tumor
Foley bulb
Applicator
650 cGy
Isodose line
Rectum


b
65Gy volume
c
47.5Gy volume


a
b 65Gy volume
c 32Gy volume