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 (e.g., 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??????

Non-invasive biological imaging

Spatial distributions of radiobiological phenotypes

Dose distributions confirming to both physical and biological attributes

- Tumor burden and clonogen density
- Proliferating activity
- Radiosensitivity
- Energy status (relative to SLDR)
- pH (for hypoxia)
- others
Biology

**The Reductionist View**
Conventional therapy: Deliver a homogeneous dose to the target volume

**A Heterotypic Cell Biology**
Biological adaptive therapy: Deliver higher dose to radio-resistant subvolumes of the tumour (boost)

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

<table>
<thead>
<tr>
<th>PET radiotracer</th>
<th>Function</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG)</td>
<td>Glucose metabolism</td>
<td>All tumors</td>
</tr>
<tr>
<td>$^{11}$C-methionine ($^{11}$C-MET)</td>
<td>Amino acid metabolism</td>
<td>Brain/H&amp;N/breast/ lung/GU</td>
</tr>
<tr>
<td>$^{11}$C-tyrosine ($^{11}$C-TYR)</td>
<td>Amino acid metabolism</td>
<td>Brain tumors</td>
</tr>
<tr>
<td>$^{15}$C-oxygen ($^{15}$C-O2)</td>
<td>Blood flow</td>
<td>Brain tumors</td>
</tr>
<tr>
<td>18$[F]$-fluoromisonidazole</td>
<td>Hypoxia</td>
<td>All tumors</td>
</tr>
<tr>
<td>$^{15}$C-carbon monoxide ($^{15}$C-O)</td>
<td>Blood volume</td>
<td>Brain tumors</td>
</tr>
<tr>
<td>Oxygen-15 ($^{15}$O$_2$)</td>
<td>Oxygen metabolism</td>
<td>Brain tumors</td>
</tr>
<tr>
<td>$^{11}$C-5-hydroxy tryptophan ($^{11}$C-5-HTP)</td>
<td>Serotonin levels</td>
<td>NE/GI</td>
</tr>
<tr>
<td>$^{15}$O-water (H$_2^{15}$O)</td>
<td>Blood flow</td>
<td>Thyroid tumors</td>
</tr>
<tr>
<td>$^{11}$C-L-dihydroxyphenylalanine ($^{11}$C-L-DOPA)</td>
<td>Dopamine levels</td>
<td>NE/pancreatic</td>
</tr>
<tr>
<td>$^{18}$F-fluoro-2$'$-deoxyuridine ($^{18}$F-FUdR)</td>
<td>Nucleic acid metabolism</td>
<td>Brain tumors</td>
</tr>
</tbody>
</table>

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.
5. Identification of relapse and recurrence versus other imaging non-specific changes and increased tumor markers.
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.
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.
15. Once data is acquired it is sent to RTP software.
16. RTP software must validate the DICOM compatibility of CT or PET.
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>
<thead>
<tr>
<th>Site</th>
<th>Characteristics of CT and PET for staging in different tumour sites</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(CT) PET (%)</td>
<td>(CT) (%)</td>
<td>(CT) PET (%)</td>
<td>(CT) (%)</td>
<td>(CT) PET (%)</td>
</tr>
<tr>
<td>Head and Neck⁴³,⁴⁴,⁵¹,⁵³,⁵⁶,⁵⁹–⁶¹,⁶³,⁶⁴,⁶⁶,⁶⁷</td>
<td>Primary tumour</td>
<td>88–93</td>
<td>100</td>
<td>96</td>
<td>98.5</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
<td>70–96</td>
<td>66–88</td>
<td>74–98.5</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>Lymphoma⁴⁷,⁵⁰</td>
<td>Primary tumour</td>
<td>90</td>
<td>81</td>
<td>93</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
<td>57–100</td>
<td>63</td>
<td>63–100</td>
<td>96</td>
<td>63–100</td>
</tr>
<tr>
<td>Gynaecology⁴⁹,⁵²</td>
<td>Primary tumour</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
<td>54–100</td>
<td>21–73</td>
<td>87–100</td>
<td>76</td>
<td>84</td>
</tr>
<tr>
<td>Bladder⁴⁹,⁵⁸</td>
<td>Lymph nodes</td>
<td>67–78</td>
<td></td>
<td>86–100</td>
<td>63–100</td>
<td>83–100</td>
</tr>
<tr>
<td>Prostate⁴⁹,⁵⁸</td>
<td>Primary tumour</td>
<td>0–64</td>
<td></td>
<td>72–400</td>
<td>100</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
<td>0–67</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastro-oesophageal⁴⁸,⁶²,⁶⁵</td>
<td>Lymph nodes</td>
<td>51–74</td>
<td></td>
<td>47–50</td>
<td>84–90</td>
<td>69</td>
</tr>
<tr>
<td>Colorectum⁴²,⁴⁹</td>
<td>Primary tumour</td>
<td>90–100</td>
<td></td>
<td>43</td>
<td></td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Lymph nodes</td>
<td>29</td>
<td></td>
<td>29</td>
<td>85–96</td>
<td>85</td>
</tr>
</tbody>
</table>
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.

\[
\text{Threshold SUV} = 0.307 \times \text{Mean Target SUV} + 0.588
\]

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.
The image shows a bar chart comparing GTV and PTV changes for H & N Cancer, Thoracic Cancer, and Pelvic Cancer. The chart illustrates percentage volume changes across different regions and categories, with distinct bars indicating variations in treatment outcomes or response to therapy.
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.

![Image of 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 ⁶⁷Cu-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.
Other targets

EGFR

Cyclin D

With the current 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.
Requirement for dose uniformity within 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

- PET
- IUDR
- Tumor growth

- MRI/MRS
- choline/citrate
- Tumor burden

Biological Eye View

PTV

Biol. Tgt. Volume
The concept of a "biological target volume"

FDG  FLT  Cu-ATSM  MMP

Metabolism  Proliferation  Hypoxia  Angiogenesis

+  CT

(From Apisanthanrax, Rad. Res. 163, 2005)
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
1. Better definition of GTV specially in gliomas. Hence better sparing of normal brain possible. Also tried in meningiomas.

<table>
<thead>
<tr>
<th>Finding</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MET uptake corresponded to Gd enhancement</td>
<td>5/39 (13)</td>
</tr>
<tr>
<td>MET uptake located outside Gd enhancement</td>
<td>29/39 (74)</td>
</tr>
<tr>
<td>Gd enhancement located outside MET uptake</td>
<td>27/39 (69)</td>
</tr>
</tbody>
</table>

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

2. Differentiates between recurrence and radiation induced late toxicity.

3. Dose Escalation

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.
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.*

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