Tumor Imaging in Nuclear Medicine: Current Status and Future Prospects

Bennett S. Greenspan, MD
SNM MWM Albuquerque, NM
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Tumor Imaging – Part I
Current Status

• Current status – agents that are FDA-approved for routine clinical use.
Tumor Imaging

- Indications for tumor imaging:
- Identification, diagnosis
- Staging/re-staging
- Identification of recurrence, residual disease
- Monitoring response to therapy
- Evaluating prognosis
Tumor Imaging - Agents

- Ga-67 citrate
- Organ imaging, e.g. thyroid, bone
- Thallium-201
- Tc-99m Sestamibi – Breast imaging
- Labeled monoclonal antibodies
- Peptide receptor imaging In-111 pentetreotide
- Adrenal tumor imaging – I-123 MIBG
- F-18 FDG
Ga-67 citrate - Lymphoma
Ga-67 citrate - Melanoma
Ga-67 citrate

• Mechanism of uptake – bound to transferrin, uptake in tumor cells by lysosomes and endoplasmic reticulum

• Now nearly obsolete as a tumor imaging agent – outperformed by FDG PET
Ga-67 citrate

• Probable only remaining indication for Ga-67 citrate in tumor imaging:
  – Differentiating hepatocellular carcinoma from regenerating nodules in patients with cirrhosis
Thyroid Carcinoma

• Indications for imaging with I-131:
  1. Detect active residual disease (papillary or follicular thyroid CA)
  2. Detect functioning metastases
  3. Assess results of treatment
Papillary Thyroid Cancer
Papillary Thyroid Cancer
Papillary Thyroid Carcinoma
Metastatic Thyroid Carcinoma
I-131 – Thyroid Carcinoma

• I-131: Oldest radionuclide (RN) in clinical use
• Images are not very pretty, due to the high gamma energy, but the information obtained is extremely useful.
• Having a gamma emission and a beta emission makes this RN uniquely suited to therapy, esp. for thyroid disease. There is no replacement on the horizon.
Bone Scan - Prostate Carcinoma – widespread bone metastases
Bone scan

• Agent: Tc-99m MDP (or HDP)
• Uptake related to blood flow and osteoblastic activity
• Very sensitive for metastases that generate an osteoblastic response (most tumors)
• Useful for staging/re-staging, assessing response to therapy, detecting recurrence or residual disease
Tc-99m Sestamibi – Breast CA - BSGI

BSGI Case Study: Left infiltrating ductal carcinoma & axillary metastasis.
Breast Specific Gamma Imaging (BSGI)

Clinical Summary: Patient with bilateral breast implants and a palpable mass. Mammographically negative, BSGI subsequently pursued. Additional XCCL view obtained to include more of the mass in the CC plane. Pathology: Infiltrating ductal carcinoma, 2.7 x 2.3 x 2.0 cm mass. Patient spared prophylactic contralateral implant removal because of normal exam on left.
BSGI - 4 mm tumor
BSGI

- Fairly new technique - utilizes small gamma camera optimized to image the breast
- Will not replace mammography, but may be a useful adjunct in certain circumstances, particularly if MRI is indicated but cannot be done.
- Greater sensitivity and specificity than conventional scintimammography.
- SNM Procedure Guideline under development
Prostascint

• Monoclonal Antibodies – Prostascint – Capromab Pendetide, labeled with In-111

• Used in patients with prostate cancer, to detect recurrent or residual disease.
SPECT/CT - Normal
Tumor in Prostate Bed
Nodal metastases - pelvis
Para-aortic nodes – Coronal images SPECT/CT
Prostascint

• Only monoclonal antibody in routine clinical use.
• Not a very good agent – less sensitive than is desirable, and images are often difficult to read.
• Also, test is performed over 4-7 days.
Peptide Receptor Imaging

- Somatostatin receptor imaging - In-111 pentetreotide (Octreotide, Octreoscan).
- Neuroendocrine tumors – derived from APUD (Amine Precursor Uptake and Decarboxylation) system cells
- Examples: carcinoid, pituitary adenoma, pancreatic islet cell tumor, small cell lung cancer, pheochromocytoma, neuroblastoma
In-111 Pentetreotide (Octreoscan) - Merkel cell tumor
Metastatic carcinoid, with meningioma
Adrenal Tumor Imaging

• Adrenal tumor imaging—
• I-123 MIBG: Pheochromocytoma, Neuroblastoma, Paraganglioma
• MIBG (metaiodobenzylguanidine) is an analog of norepinephrine
• Taken up by chromaffin cells, and therefore useful in imaging sympathetic adrenergic tissue.
Recurrent Malignant Pheochromocytoma
Stage IV Recurrent Neuroblastoma – bone marrow and liver metastases
Tumor – FDG PET

• F-18 FDG

• Used for many tumors for staging/re-staging, monitoring response to therapy, detecting recurrent or residual disease

• For example: Head and neck, lung, lymphoma, melanoma, esophageal, colorectal, breast, cervical CA
Positron Decay

Mettler and Guiberteau, Essentials of Nuclear Medicine Imaging, 2006, p. 361
Metabolism of F-18 FDG

Mettler and Guiberteau, Essentials of Nuclear Medicine Imaging, 2006, page 372
F-18 FDG H&N – Base of Tongue CA
F-18 FDG – Lung CA
DLBCL – Extensive Bone Marrow Involvement
F-18 FDG – Metastatic Melanoma
F-18 FDG Esophageal CA with Liver Metastases
F-18 FDG - Disseminated cervical cancer metastases
F-18 – FDG

• While F-18 - FDG is a “non-specific” agent, it is useful for many different malignancies. It measures glycolysis, which is increased in many tumors.

• Photon flux is 100 times greater than for conventional single photon agents, allowing for better spatial resolution.
Current Molecular Imaging in routine clinical use in Oncology (Part I)

- I-131 – thyroid
- In-111 octreotide (pentetreotide)
- I-123/131 MIBG
- In-111 monoclonal antibody - Capromobab Pendetide (Prostascint)
- Ga-67 citrate (essentially obsolete as a tumor imaging agent)
- F-18 FDG
Tumor Imaging – Part II

• Future prospects –
• Note – Except for F-18 FDG, the following agents are not FDA-approved. Many of these are in clinical trials.
How is Molecular Imaging Relevant to Clinical Medicine?

• Detection
• Treatment – especially as a precursor for targeted therapy
• Early Intervention
• Drug Discovery and Development
Molecular Imaging

- Molecular imaging (MI) –
- MI will have an expanding clinical relevance as it will become increasingly important in patient care and management in the near future; and -
- PET is the most sensitive and the most specific technique to image molecular pathways in patients
Why the Interest in Molecular Imaging?

• The ultimate goal is targeted therapy to provide personalized medicine.

• Targeted imaging: finding the right molecular probe for the right target to monitor the right disease in the right patient.

• Streamlining drug discovery: finding the right drug against the right target to treat the right disease in the right patient.
Example: Oncology

- By accurately characterizing tumor properties or biological processes, molecular imaging plays a pivotal role in guiding patient management:
  - Diagnosing
  - Staging—extent and location
  - Assessing therapeutic targets
  - Monitoring therapy
  - Evaluating prognosis
Molecular Imaging

**PET/CT in Cancer Patient Management**

- **Responder** → **Standard therapy**
- **Nonresponder** → **Alternative therapy**

- **Before chemotherapy**
  - CT
  - PET/CT

- **After chemotherapy**
  - CT
  - PET/CT
Molecular Imaging

• Therapeutic response criteria –
• Will be based on metabolic characteristics rather than size alone
• Translational research – bringing experimental imaging and therapeutic techniques to the clinic after extensive testing in experimental models (bench to bedside)
Molecular Imaging

Imaging cell functions

- Transcription
- Translation
- Signal Transduction
- Transport
- Enzyme function
- Receptor binding (surface or intracellular)
Radiotracer Imaging of cancer

• Categories:
  – Proliferation/DNA synthesis
  – Hypoxia
  – Receptors
  – Angiogenesis
  – Metabolism – F-18 FDG/Amino acid transport
Cancer Imaging Agents

- Radiopharmaceuticals for imaging cellular proliferation
  - 3’-deoxy-3’-[^{18}\text{F}]\text{fluorothymidine} ([^{18}\text{F}]\text{FLT})
  - Imaging with \(^{18}\text{F}\)-labeled sigma-2 receptor ligands

- Imaging tumor hypoxia
  - \(^{60}/^{64}\text{Cu}-\text{ATSM}\)
  - \(^{18}\text{F}-\text{MISO}\)

- Imaging upregulation of receptors in tumors
  - \(^{68}\text{Ga}\)-labeled somatostatin analogs
Cancer Imaging Agents

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Why Image Cellular Proliferation

• Rationale – Proliferative status of tumors may indicate which patients are at high risk of recurrence, as that has a profound effect on outcome from therapy.

• A change in the proliferative status of a tumor during or after therapy may also be an indicator of response and allow further tailoring of therapy.
$^{18}$F-Labeled Thymidine Analogs

- $[^{18}F]$FLT
- $[^{18}F]$FMAU
- $[^{18}F]$FBAU
- $[^{18}F]$FIAU

Diagram showing the cell cycle phases: G0, G1, S, N, A, D, and G2, with M (mitosis) as the transition point.
3′deoxy-3′-[\(^{18}\text{F}\)]fluorothymidine: \([^{18}\text{F}]\) FLT

- F-18 is the radiolabeled form of the pyrimidine nucleoside, thymidine
- FLT is retained within the cell after phosphorylation providing a measure of cellular thymidine kinase (TK1) activity, an enzyme which is closely related to cellular proliferation.
- TK1 is up-regulated in the S phase of the cell cycle
F-18 FLT

- F-18 FLT – F-18 replaces OH at 3’ position – it cannot be incorporated into DNA, and is trapped in tumor cells following phosphorylation of the 5’-hydroxy group by thymidine kinase (TK-1).
- Analogous to trapping of F-18 FDG in cells following phosphorylation by hexokinase.
- F-18 FLT is a marker of cell proliferation, but does not directly measure DNA synthesis.
F-18 FLT - Proliferation

- F-18 Fluorothymididine (F-18 FLT)  
  Mach, et al, PET Clinics, Jan, 2009

*Fig. 4.* $[^{18}F]$FLT-PET in a patient with locally advanced rectal cancer. Anterior and posterior projection images demonstrate intense $[^{18}F]$FLT uptake in bone that reflects the proliferation of cells in the bone marrow. There is increased accumulation of $[^{18}F]$FLT in the rectal cancer (arrowhead in right panel). In addition, there is increased accumulation of $[^{18}F]$FLT in the urinary bladder (arrow in the left panel), which is a normal finding.
F-18 FLT – Responder vs. Non Responder

Bading and Shields JNM 2008; 49 (6, Suppl), 65S
F-18 FLT – Responder vs. Non Responder

Bading and Shields JNM 2008; 49 (6, Suppl), 65S
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Bading and Shields JNM 2008; 49 (6, Suppl), 65S
Proliferation

FLT-PET vs. FDG-PET as Measures of Proliferation in Lung Tumors

NSCLC

CT

Colon Cancer Metastasis

Ki-67 specific MAb MIB-1

Correlation between FLT uptake and proliferative activity as indicated by Ki-67 immunostaining. Use to assess therapy response rather than primary staging lung cancer.

Buck et al., J Nucl Med 2003; 44:1426
Proliferation

P:Q Ratio: Treatment Planning

The Cell Cycle

- Has a profound effect on the outcome of chemotherapy and radiotherapy
- Tumors with a high P:Q ratio respond better to cell cycle specific agents (e.g., 5-FU and Ara-C) and/or hyperfractionated radiation therapy
- Change in proliferation can be used as an indicator of a positive response to radiation and chemotherapy
$^{18}$F-Labeled Benzamide Analogs

$[^{18}F]_1$
- $\sigma_1 = 330$ nM
- $\sigma_2 = 7.0$ nM
- $\log P = 3.06$

$[^{18}F]_2$
- $\sigma_1 = 2,150$ nM
- $\sigma_2 = 0.26$ nM
- $\log P = 3.46$

$[^{18}F]_3$
- $\sigma_1 = 1,076$ nM
- $\sigma_2 = 0.65$ nM
- $\log P = 3.89$

$[^{18}F]_4$
- $\sigma_1 = 1,304$ nM
- $\sigma_2 = 1.06$ nM
- $\log P = 4.13$

Proliferation – Sigma-2 Receptors

\[ \text{\textsuperscript{18}F-Labeled Thymidine Analogs} \quad \text{\textsuperscript{18}F-Labeled Sigma-2 Radiotracer} \]

\[ \text{[\textsuperscript{\text{18}}\text{F}]FLT} \quad \text{[\textsuperscript{\text{18}}\text{F}]FMAU} \quad \text{[\textsuperscript{\text{18}}\text{F}]ISO-1} \]

\[ \text{Proliferating Tumor Cell (P)} \quad \text{Quiescent Tumor Cell (Q)} \]

\[ \text{Ki-67} \quad \text{Ki-67 (-)} \]

P:Q Ratio: Important for Treatment Planning
Sigma-2 Receptors

Sigma-2 (σ₂) Receptors in Cancer

- Density of σ₂ receptors are overexpressed in a wide variety of solid tumor cells versus normal tissue (Vilner et al. *Cancer Research* **55**: 408-414; 1995)

**Question:** Is there a correlation between σ₂ receptor density and cell proliferation?

**Model:** mouse mammary adenocarcinoma cells (66 cells)
Sigma-2 Receptors

Sigma-2 (σ₂) Receptors in Cancer

- Density of σ₂ receptors is ~1 million copies/cell in 66P vs. 100,000 copies/cell in 66Q cells (Cancer Research 57: 156-161; 1997)

- σ₂ receptors are upregulated from Q → P transition and downregulated from Q → P transition; turnover rate about 6 days (Brit. J. Cancer 81: 925-933; 1999).

- 10:1 P:Q ratio of σ₂ receptors is also observed in solid tumor xenografts of 66 cells growing in nude mice (Brit. J. Cancer 82: 1223-1232; 2000).
Proliferation

Quiescent Normal Cell

G0

Proliferating Tumor Cell

G1

S

M

Quiescent Tumor Cell

G0

Muscle Cell

EMT6 Breast Tumor
Proliferation: F-18 ISO

EMT-6 Mouse Mammary Tumors

MicroPET  Merged  MicroCT

F-18 FLT, F-18 FMAU, F-18 ISO-1
Proliferation Agents

MicroPET/CT: Murine Mammary Cancer (66)

$[^{18}\text{F}]\text{ISO-1}$

$[^{18}\text{F}]\text{FLT}$

$[^{18}\text{F}]\text{FMAU}$
F-18 - FLT vs. F-18 - ISO

• FLT shows some promise, and is in current clinical trials sponsored by SNM
• However, FLT only shows proliferating cells in S-phase, about 2% of proliferating cells.
• F-ISO shows all of the proliferating cells, and may turn out to be a better agent for detecting proliferating cells.
Cancer Imaging Agents

• Radiopharmaceuticals for imaging cellular proliferation
  – 3’-deoxy-3’-[¹⁸F]fluorothymidine ([¹⁸F]FLT)
  – Imaging with ¹⁸F-labeled sigma-2 receptor ligands

• Imaging tumor hypoxia
  – ⁶⁰/⁶⁴Cu-ATSM
  – ¹⁸F-MISO

• Imaging upregulation of receptors in tumors
  – ⁶⁸Ga-labeled somatostatin analogs
Hypoxia

• Tumor cells that outgrow their blood supply become hypoxic, and slow their growth rate.

• Chemotherapy and radiotherapy become less effective – chemotherapy depends on proliferation rate to be effective, and cytotoxicity of radiotherapy depends on level of intracellular oxygen.
Why Image Hypoxia?

- Hypoxia influences response to treatment:
  
  (1) Radiotherapy - hypoxic cells are protected from lethal effects of conventional ionizing radiation therapy
  
  (2) Chemotherapy - effect of hypoxia on special genes and drug delivery

- Imaging of hypoxia is required in order to predict response to traditional therapies

- Imaging of hypoxia in the brain, heart and cancer have been explored
Hypoxia

Hypoxia & Radiation

Oxygen Enhancement Ratio may be as high as 3.0

Hypoxia is < 5 mm Hg pO₂

Cell Survival Curves

FMISO  FAZA
ATSM  EF5

Aerobic

Hypoxic
Hypoxia

• PET imaging agents that can be used to assess regional tumor hypoxia:

  • F-18 Misonidazole (FMISO)

  • Cu-64 ATSM
Hypoxia – F-18 FMISO

Structure of hypoxia positron emission tomography imaging agents.
**Hypoxia – F-18 FMISO**

- Most widely used PET agent for regional hypoxia.
- It is retained in hypoxic cells; it enters by passive diffusion and undergoes reduction, eventually forming covalent bonds with macromolecules, and is trapped in the cell.
- Images are of low contrast, but it can identify clinically significant regional hypoxia.
Hypoxia – F-18 FMISO

- It requires a venous blood sample taken during imaging, to determine a normalized map of a tissue to blood ratio, T/B.
- The hypoxic portion of a tumor can be characterized by a maximum T/B, or T/B greater than a defined threshold.
Hypoxia – F-18 FMISO

• Identification of hypoxic tumor may help facilitate image-directed radiotherapy.
• It appears to have the potential to predict the response to treatment (better than F-18 FDG) and provide prognostic information.
• However, there are some drawbacks to this agent.
Hypoxia – F-18 FMISO

FMISO PET
Brain Tumor
(Spence, Clin Can Res, 2008)

FMISO PET
H & N Cancer
(Rajendran, Clin Can Res, 2007)
Hypoxia
Cu-ATSM

Theory:

Hypoxic cell (-O₂) → Cu-ATSM (TRAPPED) → Normal cell (+O₂)

Normal cell (+O₂) → Cu-ATSM (NOT TRAPPED)
Cu-ATSM

• In the hypoxic cell, Cu (II) ATSM is reduced to Cu (I) ATSM.
• Cu (I) is then released from ATSM and is trapped in the hypoxic cell.
• Cu (II) is not trapped in normoxic cells.
## Copper Radionuclides

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Half-life</th>
<th>Decay modes</th>
<th>Maximum energy (MeV)</th>
<th>Reaction</th>
<th>Natural abundance of target isotope</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{60}\text{Cu}$</td>
<td>23.7 m</td>
<td>$\beta^+/93.0$&lt;br&gt;EC/7.0</td>
<td>3.92</td>
<td>$^{60}\text{Ni}(p,n)$</td>
<td>26.1%</td>
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<tr>
<td>$^{61}\text{Cu}$</td>
<td>3.32 h</td>
<td>$\beta^+/60.0$&lt;br&gt;EC/7.0</td>
<td>1.22</td>
<td>$^{61}\text{Ni}(p,n)$</td>
<td>1.25%</td>
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<tr>
<td>$^{64}\text{Cu}$</td>
<td>12.7 h</td>
<td>$\beta^+/17.8$&lt;br&gt;EC/43.8&lt;br&gt;$\beta^-/38.4^*$</td>
<td>0.66</td>
<td>$^{64}\text{Ni}(p,n)$</td>
<td>1.16%</td>
</tr>
</tbody>
</table>

*Qaim et al. Radiochimica Acta 2007; 95:67-73*
Cu-60 /Cu-64

• Most of the early clinical trials were done with Cu-60.
• However, Cu-60 has too short a half-life for multicenter clinical trials.
• The FDA wanted to confirm that Cu-64 gave similar results, and could be used in place of Cu-60; with a 12.7 hr half life, it can be used for multi-center clinical trials.
Uptake of $^{64}$Cu(ATSM), $^{64}$Cu(PTSM) and $^{18}$F-MISO in EMT6 cells after 1 h at varying levels of oxygen.

Evaluation of $^{64}$Cu-ATSM In Vitro and In Vivo in a Hypoxic Tumor Model

Jason S. Lewis, Deborah W. McCarthy, Timothy J. McCarthy, Yasuhisa Fujibayashi and Michael J. Welch

Cu-ATSM

Cu-ATSM - Clinical Studies

- To evaluate the feasibility of imaging with $^{60}$Cu-ATSM-PET in human tumors
  - Patients with NSCLC, cervix, head and neck, rectal, breast, brain studies
  - Nearly 140 imaging sessions performed
  - In patients with cancer of the cervix, 27 studies performed
Cu-60-ATSM  NSCLC

Cu-ATSM - Clinical Studies (NSCLC)

• To evaluate the feasibility of imaging with $^{60}$Cu-ATSM-PET in human tumors
  
  – Patients with non-small-cell lung cancer (NSCLC)
  – 18 patients with biopsy-proven NSCLC (age range 55-85 yrs)
  – Lesion >= 1.5 cm (2 stage IA, 2 stage IIIB, and 1 stage IV)

In vivo assessment of tumor hypoxia in lung cancer with $^{60}$Cu-ATSM

Farrokh Dehdashti$^{1, 5}$, Mark A. Mintun$^{1, 5}$, Jason S. Lewis$^{2, 5}$, Jeffrey Bradley$^{3, 5}$, Ramaswamy Govindan$^{4, 5}$, Richard Laforest$^{1, 2}$, Michael J. Welch$^{2, 5}$, Barry A. Siegel$^{1, 5}$

European Journal of Nuclear Medicine and Molecular Imaging Vol. 30, No. 6, June 2003
Cu-ATSM - Clinical Studies (NSCLC)

- Presence of tumor was confirmed in all patients on pretherapy CT and/or FDG-PET

- Treatment
  - Radiotherapy alone (11 NSCLC and 1 cervical cancer)
  - Radiation and chemotherapy (5 NSCLC and 13 cervical cancer)
  - Chemotherapy alone (3 NSCLC)

- Follow-up after therapy
  - Clinical evaluation at 4-6 weeks after completion of therapy and every 3 months thereafter for 2 years
  - CT at 3 months (NSCLC)

European Journal of Nuclear Medicine and Molecular Imaging Vol. 30, No. 6, June 2003
Cu-60 ATSM vs. F-18 FDG
Cu-60 ATSM

Fig. 2. Responder. Transaxial FDG-PET image (upper left) of the chest shows moderately intense FDG uptake (SUV 4.9) in the known lung cancer. Transaxial $^{60}$Cu-ATSM-PET image (lower left) at the same level demonstrates minimal uptake within the tumor (T/M =1.3). CT image prior to therapy (upper right) demonstrates increased soft tissue density in the precarinal space, consistent with patient's known cancer. CT image after radiotherapy (lower right) demonstrates post-radiation changes, but shows a good response of the tumor to the treatment. The patient was alive at last follow-up (46 months after the diagnosis of lung cancer) without evidence of tumor recurrence.
Cu-60 ATSM

Non-Responder

Fig. 3. Nonresponder. Transaxial FDG-PET image (upper left) of the chest shows intense FDG uptake (SUV 17.3) in the known lung cancer in the lingula. Transaxial $^{60}$Cu-ATSM-PET image (lower left) at the same level demonstrates intense uptake within the lingular cancer (T/M = 3.0). CT image prior to therapy (upper right) demonstrates a lingular mass, consistent with patient's known lung cancer. CT image (lower right) 3 months later, during chemotherapy demonstrates an increase in the size of the tumor. The patient died with progressive disease 15 months after diagnosis.

European Journal of Nuclear Medicine and Molecular Imaging Vol. 30, No. 6, June 2003
Cu-60 ATSM Predictor of Survival

Overall Survival Based on $^{60}$Cu-ATSM Uptake (T/M) in NSCLC (n=14)

*European Journal of Nuclear Medicine and Molecular Imaging Vol. 30, No. 6, June 2003*
Cu-60 ATSM vs. F-18 FDG

Ca Cervix - Clinical Outcome

- Hypoxic tumor
- Normoxic tumor

- 3-year progression-free survival 71% in patients with normoxic tumors and 28% in patients with hypoxic tumors
- No correlation between disease stage and tumor uptake
- No difference in frequency of lymph node involvement between two groups of patients

Dehdashti et al., J Nucl Med 2008; 49:201-205
Cu-64 ATSM vs. Cu-60 ATSM

64Cu-ATSM: An Imaging Comparison with 60Cu-ATSM in Cancer of the Uterine Cervix (IND 62,675)

- Toxicology generated from NCI DCIDE program (J. Lewis, PI)
- Assessed quality of 60Cu- and 64Cu-ATSM PET images
- Crossover study of 10 patients with Ib2-IVa cervical CA
  - Subjective – comparable; 64Cu-ATSM images less noisy
    - Similar quality in 8 patients
    - 64Cu-ATSM better than 60Cu-ATSM in 2 patients
  - T/M evaluation
    - Generally better target to background ratio
      (tumors seen more clearly on 64Cu-ATSM-PET in most cases)

Lewis et al., submitted
Cu-64 ATSM vs. Cu-60 ATSM

$^{64}$Cu-ATSM: An Imaging Comparison with $^{60}$Cu-ATSM in Cancer of the Uterine Cervix

CS: cascade subtraction for Cu-60 high energy gamma photons

Mallinckrodt Institute of Radiology
Washington University in St. Louis
School of Medicine
$^{64}$Cu-ATSM: An Imaging Comparison with $^{60}$Cu-ATSM in Cancer of the Uterine Cervix

- Multi-center clinical trial under development with NCI and ACRIN
Hypoxia

• In cervical CA, tumor hypoxia is predictive of decreased disease-free survival and poorer overall survival.

• Cu-64 ATSM provides prognostic information in cervical cancer that F-18 FDG is unable to provide.

• Cu-64 ATSM is strongly correlated with response to therapy and overall survival.

• Currently an ACRIN clinical trial is ongoing with Cu-64 ATSM in patients with cervical cancer.
Cancer Imaging Agents

• Radiopharmaceuticals for imaging cellular proliferation
  – 3’-deoxy-3’-[\(^{18}\)F]fluorothymidine ([\(^{18}\)F]FLT)
  – Imaging with \(^{18}\)F-labeled sigma-2 receptor ligands

• Imaging tumor hypoxia
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  – \(^{18}\)F-MISO

• Imaging upregulation of receptors in tumors
  – \(^{68}\)Ga-labeled somatostatin analogs
Receptor Imaging

Design of Specific Radiopeptide/Vector

**Targets:**
- Antigens
- Hydroxyapatite
- G-protein couple receptors

**Ligands:**
- Mabs (fragments, affibodies)
- Phosphonates
- Regulatory Peptides
Receptor Imaging

- Tumor receptors have an important role in carcinogenesis and tumor growth.
- Evaluation of tumor receptor expression is critical in cancer therapy directed at tumor receptors.
- The ability to measure expression of tumor receptors is essential for selecting patients for receptor-targeted therapy.
Receptor Imaging

• Tumor receptor imaging can:
  • 1. characterize tumor biology,
  • 2. identify therapeutic targets, and
  • 3. delineate the pharmacodynamics of targeted cancer therapy.

• Advantages: Noninvasive, measurement of receptor expression of entire disease burden, and potential for serial studies.
Gallium-68

$^{68}$Ga: a nearly ideal PET imaging radionuclide

- Generator produced ($^{68}$Ge/$^{68}$Ga)
- High positron yield (90%)
- Long parent half-life (275 d)
- $T_{1/2} = 68$ min
- Established chemistry
- Relatively high positron energy (1900 keV; compared to 630 keV for $^{18}$F)
  - Longer positron range can degrade the PET images, especially for small animal imaging
Gallium-68

Gallium-68 will become the Tc-99m for PET/CT

Tumor Receptor Targets for $^{68}$Ga Radiopharmaceuticals

- somatostatin receptors
- bombesin receptors
- epidermal growth factor receptor (EGFR)
- $\alpha$-MSH (melanocyte stimulating hormone) receptors
- $\alpha_v\beta_3$ integrin
- $^{68}$Ga can be labeled to any tumor-targeting peptide
Receptor Imaging


$^{68}$Ga-DOTA-TOC  $^{111}$In-Octreotide  $^{18}$F-Fluoride

$^{68}$Ga ($T^{1/2} = 68$ min) is generator produced
Summary – Proliferation, Hypoxia

• Proliferation:
  – FLT has applications in determining proliferative status of tumors having implications in predicting aggressiveness and monitoring therapy
  – Radiolabeled DNA precursors underestimate the P:Q ratio
  – $\sigma_2$ receptor imaging agents show promise in animal studies but need to be validated in human imaging studies

• Hypoxia
  – $^{60}$Cu-ATSM has shown promise in several clinical studies for imaging hypoxia in NSCLC, head and neck, rectal and cervical cancers
  – $^{64}$Cu-ATSM provides higher quality images and is currently under IND with a multi-center trial to begin soon
  – Caution should be advised that this agent does not image hypoxia in all tumor types, i.e. prostate cancer
Summary – Receptors

• Receptor Targeted Agents:
  – Somatostatin is one tumor receptor that has been heavily studied both pre-clinically as well as clinically
  – The implementation of PET agents ($^{68}$Ga) compared to SPECT ($^{111}$In) has greatly improved the tumor targeting and non-target tissue clearance
Translational Molecular Imaging in Oncology

- Current
  - I-131 – Thyroid
  - In-111 octreotide
  - I-123/131 MIBG
  - In-111 capromab
  - F-18 FDG

- Near Future
  - Proliferation
    - F-18 FLT/ISO
  - Hypoxia
    - Cu-64 ATSM/FMISO
  - Receptors
  - Angiogenesis
## Translational Molecular Imaging in Oncology

<table>
<thead>
<tr>
<th>Currently</th>
<th>Near Future</th>
<th>Later</th>
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</thead>
<tbody>
<tr>
<td>FDG</td>
<td>FLT</td>
<td>Reporter genes</td>
</tr>
<tr>
<td>In-111 octreotide</td>
<td>FDOPA</td>
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<td>I-123 MIBG</td>
<td>Ga-68 DOTA-??</td>
<td>– Neuroendocrine</td>
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<td>FES</td>
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<td>Fluorocholine</td>
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<td>C-11 acetate</td>
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Tumor Imaging – Future Prospects

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