Tumor Imaging in Nuclear Medicine
Current Status and Future Prospects

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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 pentetretotide
- Adrenal tumor imaging – I-123 MIBG
- F-18 FDG
Ga-67 citrate - Lymphoma

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Ga-67 citrate - Melanoma
Ga-67 citrate

• Mechanism of uptake – bound to transferrin, uptake in tumor cells by lysosomes and ER
• Now nearly obsolete as a tumor imaging agent – outperformed by FDG PET
• 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):
  - Detect active residual disease (papillary or follicular thyroid CA).
  - Detect functioning metastases
  - Assess results of treatment
Papillary Thyroid Cancer

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Papillary Thyroid Cancer
Papillary Thyroid Carcinoma
Metastatic Thyroid Carcinoma

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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

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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 XCC 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

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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

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Nodal metastases - pelvis

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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

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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

• E.G.: Head and neck, lung, lymphoma, melanoma, esophageal, colorectal, breast, cervical CA
Positron Decay

Mettler and Guiberteau, Essentials of Nuclear Medicine Imaging, 2006, p. 361

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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

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F-18 FDG – Lung CA
DLBCL – Extensive Bone Marrow Involvement

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F-18 FDG – Metastatic Melanoma

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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 (pentetretotide)
- I-123/131 MIBG
- In-111 monoclonal antibody - Capromab 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.

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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

- PET/CT
- Brief standard therapy
- PET/CT
- Responder → Standard therapy
- Nonresponder → Alternative therapy

Before chemotherapy

After chemotherapy

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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)
Tumor Imaging - PET

• Radiotracer imaging of cancer - categories:
  • Proliferation/DNA synthesis
  • Hypoxia
  • Receptors
  • Angiogenesis
  • Metabolism – F-18 FDG/Amino acid transport
Outline of Presentation

• 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

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Outline of Presentation

• 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
  – \(^{60}/^{64}\)Cu-ATSM
  – \(^{18}\)F-MISO

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

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

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3′deoxy-3′-[\textsuperscript{18}F]fluorothymidine: [\textsuperscript{18}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 Fluorothymidine (F-18 FLT)  
  Mach, et al, PET Clinics, Jan, 2009

Fig. 4. [18F]FLT-PET in a patient with locally advanced rectal cancer. Anterior and posterior projection images demonstrate intense [18F]FLT uptake in bone that reflects the proliferation of cells in the bone marrow. There is increased accumulation of [18F]FLT in the rectal cancer (arrowhead in right panel). In addition, there is increased accumulation of [18F]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
Proliferation

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

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

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Proliferation

P:Q Ratio: Treatment Planning

- 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
18F-Labeled Benzamide Analogs

[18F]1
\[\sigma_1 = 330 \text{ nM} \]
\[\sigma_2 = 7.0 \text{ nM} \]
\[\log P = 3.06 \]

[18F]2
\[\sigma_1 = 2,150 \text{ nM} \]
\[\sigma_2 = 0.26 \text{ nM} \]
\[\log P = 3.46 \]

[18F]3
\[\sigma_1 = 1,076 \text{ nM} \]
\[\sigma_2 = 0.65 \text{ nM} \]
\[\log P = 3.89 \]

[18F]4
\[\sigma_1 = 1,304 \text{ nM} \]
\[\sigma_2 = 1.06 \text{ nM} \]
\[\log P = 4.13 \]

Proliferation – Sigma-2 Receptors

18F-Labeled Thymidine Analogs

18F-FLT

18F-FMAU

18F-Labeled Sigma-2 Radiotracer

[18F]ISO-1

P:Q Ratio: Important for Treatment Planning

Proliferating Tumor Cell (P)

Quiescent Tumor Cell (Q)

Ki-67

G0
Ki-67 (-)

G1

S

DNA

G2

M

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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)

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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

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Proliferation: F-18 ISO

EMT-6 Mouse Mammary Tumors

MicroPET  Merged  MicroCT


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

MicroPET Imaging Study in Panc-02 Tumors

Tumor

18F-FLT

18F-FMAU

18F-Iso2

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Proliferation Agents

MicroPET/CT: Murine Mammary Cancer (66)

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

$^{[18}F]$FLT

$^{[18}F]$FMAU

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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.
Outline of Presentation

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

• Imaging tumor hypoxia
  – \textsuperscript{18}F-MISO
  – \textsuperscript{60}/\textsuperscript{64}Cu-ATSM

• Imaging upregulation of receptors in tumors
  – \textsuperscript{68}Ga-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

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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.

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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)

(FMISO PET H & N Cancer)

(Spence, Clin Can Res, 2008)

(Rajendran, Clin Can Res, 2007)

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Hypoxia
Cu-ATSM

Theory:

Hypoxic cell (-O₂)

Normal cell (+O₂)
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>
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<th>Isotope</th>
<th>Half-life</th>
<th>Decay modes</th>
<th>Maximum $\beta^+$ energy (MeV)</th>
<th>Reaction</th>
<th>Natural abundance of target isotope</th>
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<td>$^{60}$Cu</td>
<td>23.7 m</td>
<td>$\beta^+/93.0$</td>
<td>3.92</td>
<td>$^{60}$Ni(p,n)</td>
<td>26.1%</td>
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<td>EC/7.0</td>
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<td>$^{61}$Cu</td>
<td>3.32 h</td>
<td>$\beta^+/60.0$</td>
<td>1.22</td>
<td>$^{61}$Ni(p,n)</td>
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<td>12.7 h</td>
<td>$\beta^+/17.8$</td>
<td>0.66</td>
<td>$^{64}$Ni(p,n)</td>
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<td>$\beta^-/38.4^*$</td>
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*Qaim et al. Radiochimica Acta 2007; 95:67-73

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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.
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 $\geq$ 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)
Cu-60 ATSM vs. F-18 FDG

Uptake of $^{60}\text{Cu(ATSM)}$ in NSCLC, Comparison with $^{18}\text{F-FDG}$
Cu-60 ATSM

**Responder**

*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 precardinal 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 $^{64}$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.
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

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Cu-60 ATSM vs. F-18 FDG

Ca Cervix - Clinical Outcome

- 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

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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

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Cu-64 ATSM vs. Cu-60 ATSM

\[ ^{64}\text{Cu-ATSM}: \text{An Imaging Comparison with } ^{60}\text{Cu-ATSM in Cancer of the Uterine Cervix} \]

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

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

**A**
- Responder
- **CT**
- $^{60}\text{Cu-ATSM-PET}$
  - T/M = 3.5
- **FDG-PET**
- $^{64}\text{Cu-ATSM-PET}$
  - T/M = 4.4

**B**
- Non-Responder
- **Fused PET/CT**
- $^{60}\text{Cu-ATSM-PET}$
  - T/M = 8.1
- **FDG-PET**
- $^{64}\text{Cu-ATSM-PET}$
  - T/M = 10.3

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

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Mallinckrodt Institute of Radiology

Washington University in St. Louis
School of Medicine

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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.
Outline of Presentation

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  – 18F-MISO

• Imaging upregulation of receptors in tumors
  – 68Ga-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

\[ ^{68}\text{Ga} \text{: a nearly ideal PET imaging radionuclide} \]

- Generator produced (\(^{68}\text{Ge} / ^{68}\text{Ga}\))
- High positron yield (90%)
- Long parent half-life (275 d)
- \( T_{1/2} = 68 \text{ min} \)
- Established chemistry
- Relatively high positron energy (1900 keV; compared to 630 keV for \(^{18}\text{F}\))
  - 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

Ga-68

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

Austria

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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

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Translational Molecular Imaging in Oncology

Currently

- FDG
- In-111 octreotide
- I-131 MIBG
- I-123 MIBG
- In-111 prostascint

Near Future

- FLT
- FDOPA
- Hypoxia
- Ga-68 DOTA-??
- FES
- FHDT
- Fluorocholine
- C-11 acetate

Later

- Reporter genes
- Aptamers
  - Prostatc
  - Neuroendocrine
- Antisense

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Tumor Imaging – Future Prospects

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