BNMS 2008: Highlights and Perspectives on the Future of Nuclear Medicine

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President
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Distribution of Abstracts BNMS 2008
Nuclear Medicine in Current Practice - Where We Are

• Diagnostic strategies
  – Primary disease diagnosis and staging
  – Define progressive disease
  – Define recurrence
  – Identification of locoregional or distant metastases
  – Differentiate scar from viable tumor

• (Identifying treatment response/disease progression)

• Radioisotope therapy
The added value of multislice SPECT/CT in patients with equivocal bony metastasis from carcinoma of the prostate

Vincent Helyar MSc, Medical Student, KCL School of Medicine

13 August 2008
## Introduction

<table>
<thead>
<tr>
<th></th>
<th><strong>Pro’s</strong></th>
<th><strong>Con’s</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone scintigraphy</strong></td>
<td>• High sensitivity</td>
<td>• Low specificity</td>
</tr>
<tr>
<td></td>
<td>• Widely available, well documented</td>
<td></td>
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<tr>
<td></td>
<td>• Cost effective</td>
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<tr>
<td><strong>SPECT</strong></td>
<td>• Better anatomical localization</td>
<td>• Difficulty localizing anatomy in vertebral column</td>
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<tr>
<td></td>
<td>• Improved sensitivity and specificity</td>
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<tr>
<td><strong>SPECT/CT</strong></td>
<td>• Fused functional and anatomical imaging</td>
<td>• ↑ radiation dose</td>
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<tr>
<td></td>
<td>• High sensitivity &amp; specificity</td>
<td>• 1.5x cost of BS</td>
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</table>
Objectives

- Assess the added value of SPECT/CT in diagnosing bony metastasis in CaP
  - Inter-observer agreement
  - Diagnostic confidence
Results
Conclusions

- The addition of SPECT/CT
  - Improved specificity by better anatomical localization
  - Enhanced diagnostic confidence of observers
  - Increased inter-observer agreement

- Potential benefits of adopting SPECT/CT for the diagnosis of metastases from CaP
  - Shorter diagnostic workup for patients with equivocal lesions
  - Quicker time to Rx, aim = 100% on Rx within 1 month of referral (97.7% now)
  - One-stop shop – reduced need for further imaging studies
P47

AUDIT OF THE APPROPRIATENESS OF REFERRAL FOR PET/CT SCANNING AND THE VARIABILITY OF SEMIQUANTITATIVE UPTAKE VALUES OF OESOPHAGEAL CANCER

G Shabo, MJ O’Doherty

Clinical PET Centre, St Thomas’ Hospital, London, UK
OBJECTIVES

• to assess the appropriateness of the referral requests in all patients with oesophageal cancer compared to our set guidelines of staging and recurrence

• to look at the outcome following PET/CT scanning to assess the effect on management

• to review the uptake characteristics of the primary tumour in adenocarcinoma and squamous cell carcinoma of oesophagus to assess whether this uptake is sufficient to measure response to treatment
RESULTS SUMMARY

- 99% of referrals were appropriate
  → the audit standards were met

- 120 questionnaires were sent out and 63 (52.5%) were returned

- 28/63 (44.4%): PET/CT changed management as
  - in 11/28 prevented surgery
  - in 2/28 prompted a biopsy
  - in 9/28 proceeded to palliative care
  - in 6/28 management change was not specified

- 15/63 (23.8%): PET/CT helped in decision making

- 20/63 (31.75%): PET/CT did not change management
  → PET/CT had a significant role in changing the management in ⅔ of cases

- SUV max (median and range) were (10.5 and [2.9–80.5]) for adenocarcinoma,
  (13.93 and [12.65 – 15.2]) for adenosquamous cell carcinoma and (13.35 and [2.5 – 39.8]) for squamous cell carcinoma

  → $SUV_{\text{max}}$ values are sufficient in most tumours for response measurement
The Evolution of Diagnostic Imaging

**PAST**

- **Anatomic**
  - Plain films, CT, MRI, US

- **Functional**
  - Angiography, Doppler US, NM, MRI, PET

**PRESENT**

- **Hybrid**
  - PET/CT, SPECT/CT

- **Molecular**
  - NM, PET, SPECT, MRS, Optical, Contrast-Enhanced MRI/US/CT

**“FUTURE”**
Tools for Molecular Imaging Translational Research

Schwaiger M. Br J Rad 2002; 75:S67-S73
Serial Assessment of Hypoxia in A431 Xenografts Using FAZA and Pimonidazole Binding

Solomon, B. et al. Mol Cancer Ther 2005;4:1417-1422
Hypoxia-targeted radionuclide therapy: hypoxia-selective toxicity and DNA damage induced by $^{64}$CuATSM

A Weeks$^1$, R Paul$^2$, P Marsden$^2$, P Blower$^2$, D Lloyd$^1$

$^1$Department of Biosciences, University of Kent
$^2$Division of Imaging Sciences, King’s College London
Measuring cellular responses to Cu\textsuperscript{64}ATSM

Cells were treated with Cu\textsuperscript{64}ATSM in 24 well plates in normoxic or hypoxic conditions

Measure cellular uptake using gamma counter

Determine cellular toxicity with Clonogenic survival assay

Measure DNA damage with Single cell gel electrophoresis (Comet) assay
Summary

- Selective uptake of Cu$^{64}$ATSM into MCF-7 cells was observed in hypoxia and anoxia.
- Increased toxicity and DNA damage were demonstrated in hypoxic and anoxic MCF-7 cells.
- Increased hypoxic uptake was sufficient to overcome the reduced radiosensitivity of hypoxic cells.
- Potential for hypoxia-targeted therapy?
Why Do We Image Cancer

- Identify the presence or absence of tumor
  - Primary diagnosis and staging
  - Treatment effect
  - Follow-up and restaging
- “The one millimeter challenge”
Why Should We Image Cancer

- Disease and “Omic” characterization
  - Tumor
  - Individual
- Predicting progression/outcome
- Predicting/assaying treatment response
- Treatment stratification
- Predicting/assaying toxicity
- (Personalized medicine)
Molecular Imaging

Molecular imaging is the visualization, characterization, and measurement of biological processes at the molecular and cellular levels in humans and other living systems.

- Molecular imaging typically includes two- or three-dimensional imaging as well as quantification over time.

- The techniques used include radiotracer imaging/nuclear medicine, MRI, MRS, optical imaging, ultrasound and others.
Is This Molecular Imaging?
FDG Imaging in a Patient with Raised Thyroglobulin Assay
FDG to Predict Response to Gleevec:
This May be Molecular Imaging

21 patients with GIST and other STS imaged pre and
8 days post chemo:
EORTC criteria for response
PET response seen in 13/21

(CT response in 10/21 at 8 weeks)
One year PFS in responders - 92%
One year PFS in non-responders - 12%

Biomarkers

“Biomarkers are used for risk assessment, prevention, early detection, diagnosis, prognosis and recurrence of different diseases including cancer”

Medical Imaging

- **Radiology** gives structure, anatomy and specificity
  (Mineral content; detailed structure)
- **PET/Nuclear Medicine** gives function, biochemistry, physiology and sensitivity
  (Glucose metabolism; hypoxia; function; hybrid imaging)
- **Molecular Imaging** gives molecular, biological and “omic” assays for individualized treatment plans
- **Imaging Biomarkers** provide in vivo assays “for risk assessment, prevention, early detection, diagnosis, prognosis and recurrence of different diseases including cancer”
Current Challenges in Nuclear Medicine

- Research Funding
- Economics
- Regulatory
- Education
- Clinical Trials
Procedure Trends of PET & PET/CT in Europe

Source: PET and Molecular Imaging-Europe 2006
Figure 2.18: Total patient throughput - Europe

Patients examined in each country

Source: Medical Options-PET 2006 survey
Table 2.2: Diagnostic procedure costs

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Equipment Cost €,000</th>
<th>Staff</th>
<th>Siting Cost €,000</th>
<th>Annual Cost €,000</th>
<th>Consumable cost €,000</th>
<th>Annual Throughput</th>
<th>Cost/scan €</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET/CT</td>
<td>€2,200</td>
<td>2</td>
<td>€750</td>
<td>€1,177</td>
<td>€400</td>
<td>2,000</td>
<td>€996</td>
</tr>
<tr>
<td>Nuclear Medicine</td>
<td>€490</td>
<td>2</td>
<td>€60</td>
<td>€419</td>
<td>€50</td>
<td>2,000</td>
<td>€262</td>
</tr>
<tr>
<td>MR</td>
<td>€975</td>
<td>2</td>
<td>€250</td>
<td>€720</td>
<td>€40</td>
<td>3,000</td>
<td>€234</td>
</tr>
<tr>
<td>CT</td>
<td>€750</td>
<td>2</td>
<td>€100</td>
<td>€572</td>
<td>€30</td>
<td>5,000</td>
<td>€103</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>€135</td>
<td>1</td>
<td>€60</td>
<td>€144</td>
<td>€40</td>
<td>2,000</td>
<td>€91</td>
</tr>
</tbody>
</table>

Source: Medical Options.

Note: Cost/scan is the cost to the provider for the scan. Annual costs are based primarily on cost of the equipment, sitting and technical staffing. Capital costs are written off over seven years. Maintenance is assumed at 12% of the equipment purchase price. Siting refers to costs involved in placing equipment in a new location. Staff refers to staff required to perform the examination. Consumables include contrast or radiopharmaceuticals. Throughputs are typical. Reductions in annual costs will be obtained for extending the life of equipment, reduced expenditure on sitting and/or amortising sitting costs over a longer period, increasing scan volume. The costs exclude reading fees.
Issues Associated with Dissemination of PET /MI in Clinical Practice and Translational Research

- Development of PET tracers
  - Regulations
  - GCP/GMP
  - Intellectual property
- Clinical trials
  - Design, conduct, validation, quantification
  - Definition of response/Imaging biomarkers
  - Outcomes research
- Trust and Belief
  - Health Technology Assessment
  - Clinical practice issues
- Appropriately trained personnel
- Turf
Integrating Molecular Imaging and Molecular Medicine Research

- Imaging Biomarkers
- Clinical Outcomes
- Radiochemistry
- Pharmacogenetics
- Drug Development
- Molecular Biology
- Experimental Therapeutics
- Translational Research
- Genomics/Proteomics/Metabolomics
- Clinical Trials & HTA
- Regulatory Issues
- Pharmaceutical Industry
Future Questions for Imaging Biomarkers in Clinical Practice & Clinical research

- Staging and diagnosis and recurrence and metastatic burden
  - Differentiating scar from recurrence
- Monitoring treatment response
- Tumor heterogeneity
- Treatment planning
- Predicting treatment response
- Proteomic, genomic, metabolomic, pharmacogenomic characterization
- Facilitating drug development/clinical trials/surrogate outcome marker
- Molecular medicine
- Prediction / detection of normal tissue damage
Non-Invasive Approaches to a Molecular Diagnosis: Oligodendroglioma

MRI

Histology

1p Status

Outcome

Survival %

months

0 100 200

Survival %

months

0 100 200

Courtesy of P Forsyth MD University of Calgary
Molecular Imaging in Drug Development

- **In vivo biological characterization:**
  - of NCE biology/binding
  - of drug/disease interaction
- **PK/PD characterization**
- **Assess if effectiveness in humans is similar to initial animal studies**
- **Response to the drug:**
- **Titrate drug to disease response in tissue:**
- **Determine if therapy restored a normal process affected by disease.**
What is Measurable with Molecular Imaging

Objectives

- Patient selection
- Concentrations needed for activity at the site of action
- Specific action on the molecular target or pathway
- Induction of the desired biologic effect
- Resulting clinical response
- Patient outcome

Measurable Endpoints

- Expression of molecular target (erbB2), Physiologic state (hypoxia)
- Pharmacokinetic properties in plasma and/or tissue
- Target inhibition in tumors and/or surrogate normal tissue
- Inhibition of proliferation, invasion, angiogenesis, induction of apoptosis, differentiation or senescence
- Tumor regression, cytostasis
- Disease-free survival, performance status, quality of life, overall survival

From Fig 1: Minimally Invasive Pharmacokinetic and Pharmacodynamic Technologies in Hypothesis-Testing Clinical Trials of Innovative Therapies.
Simultaneous Assessment of Metabolism and Vascularity of Non Small Cell Lung cancer using perfusion CT-PET:
A feasibility study.

M Shastry, T Win, R Endonzo, H Batchelor, V Prakash, M Berovic, L Menezes, S Janes, A M Groves, P J Ell and K Miles*
Institute of Nuclear medicine, UCL, London
*Clinical Imaging Centre, Brighton
Aim

- Derive parameters from:
  FDG PET /CT scan
  Dynamic Contrast enhanced CT

- To explore the relationship between the two sets of parameters
Methods

- 13 patients, mean age 68 years, range 57-79 years
- Male 8, Females 5
- Newly diagnosed Non small cell lung cancers
- PET for accurate staging
### Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV</td>
<td>9.9</td>
<td>3.9 - 17.7</td>
</tr>
<tr>
<td>Tumour Size (cm)</td>
<td>3.64</td>
<td>1.9 - 6.7</td>
</tr>
<tr>
<td>Max enhancement (Hu)</td>
<td>40.14</td>
<td>20.8 - 78</td>
</tr>
<tr>
<td>Perfusion (ml/min/100g)</td>
<td>0.98</td>
<td>0.31 - 9.52</td>
</tr>
</tbody>
</table>
Conclusion

Initial findings suggest that there are trends between peak enhancement and metabolism, but more data is required to confirm this.
Left Ventricular Diastolic Dysfunction and Herceptin

Ann Tweddel, Graham Wright, Kat Cockburn, Gillian Ingham, Jackie Mason, A Chaturverdi

Departments of Nuclear Cardiology and Clinical Oncology
Hull and East Yorkshire NHS Trust
Results

56 Patients followed up
  2 went to echo for follow up
  3 died
    1 became pregnant

18 LVEF fell by >5% (32%)

12/18 developed diastolic dysfunction (67%)
Summary

The development of diastolic dysfunction may be an early marker of worsening left ventricular function in patients undergoing treatment with Herceptin. Further work is needed to confirm this, and to elucidate the mechanisms involved.
Regulatory Challenges

• Cost of bringing new and orphan drugs to market, particularly new imaging probes

• Increasing recognition of the importance of imaging biomarkers in drug development

• Evolving FDA/EMEA guidelines for radiopharmaceuticals, biologics and other agents
Schematic representation of a eukaryotic cell depicting molecular processes that are potentially suitable for molecular imaging.

Schematic compliments of Leonard I. Wiebe, PhD.
Radiopharmaceutical Development

- No new successful radiopharmaceuticals in 10 years
  - FDG is an exception - but not conventional development
- Multiple tracers around for > 10 years but not developed
  - FLT, FMISO, FES, Bombesin etc
- No national or international strategy for
  - Clinical trials
  - Intellectual Property
  - Funding translational development
- No mechanism for HTA and educating funding decisions
Radiopharmaceutical Development

- Targeting strategy
- Intervention
  - ATP and O-15 water (Hussain R et al A11)
- Preclinical development
  - microPET imaging (Zhao C et al A19)
- Translational and clinical development
  - Ga-68 Dotatate (Quigley AM A26)
- Radiolabel
  - Cu-61 and Cu-64 (Paul et al Kings College A17)
What is the life cycle of a radiopharmaceutical product?

James R Ballinger
Department of Nuclear Medicine
Guy’s and St Thomas NHS Trust
London UK
• **Background:**
  – The patent on sestamibi is about to expire
  – This is the first time that a major product has faced competition from generics
  – It seemed an opportune time to look at the life cycle of radiopharmaceuticals

• **Methods:**
  – The number of publications in PubMed were tabulated per year for products introduced in the last 20 years and their predecessors
  – Subjective assessments of product success were made
Figure 1: Thallium-201, sestamibi, tetrofosmin

- $^{201}$TI had a run of 17 years before being overtaken by sestamibi
- Sestamibi rose extremely rapidly and exceeded use of $^{201}$TI
- Tetrofosmin failed to reproduce the rise of sestamibi, but is commercially successful
Conclusions

• Evolution:
  – Sestamibi and tetrofosmin largely replaced thallium but also expanded market
  – MAG3 replaced hippuran but did not expand market

• Revolution:
  – Pentetreotide created a new market, which is likely to expand with $^{68}$Ga PET
    • Depreotide failed to translate that market
    • Other $^{99m}$Tc analogues may be more successful
  – Ioflupane created new market; $^{99m}$Tc analogue likely to be successful
  – Extent of use of therapeutic antibodies (e.g. Zevalin) has been disappointing
Education Challenges

• Ensuring practitioners keep abreast of emerging technologies and cutting-edge research
• Communicating and meeting new CME requirements
• Reaching out to and educating other specialists and patients
• Ensuring academic curricula incorporate new technologies
• Ensuring adequate supply of new practitioners and researchers
  – Appropriately trained
  – Competitive
  – Clinically involved
• Involvement of whole community in practice development
Education Challenges - an evolutionary paradigm

- New generation of imager:
  - Common first path
    - Physics and principles of imaging
    - Cross sectional imaging
  - Specialized second path
    - Functional imaging
    - Biology
    - Chemistry
    - Outcomes and clinical trials training
    - Radiobiology and radioisotope therapy
    - Clinical subspecialization
- Next generation of radiopharmaceutical scientists
DEPARTMENT NUCLEAR MEDICINE
SOUTHAMPTON GENERAL HOSPITAL

- J Harris
- G Satterthwaite
- C Walker
- N Nagaraj
OUR EXPERIENCE OF NCLS

- Recent trends in UK practice
- 4 Years at SUHT
  - 2,800 studies
  - Maintained safety
  - Patient-friendly
  - Achieving targets
WHERE WE ARE NOW

- Increased Provision of Service leading to reduced waiting time of 4 weeks
- Without compromising Safety Standards and efficiency
FUTURE AT SUHT

- Maintain current standards
- Continue developing the competency programme for new trainees at:
  - Stress leader level
  - Assistant level
Role of Molecular Imaging in Improving Translational Research

- Integrate functional imaging and molecular medicine
- Enhance treatment planning and monitoring
- Facilitate pharmaceutical trials
- Surrogate outcomes markers - Imaging Biomarkers
- Predictive assays of treatment response
- Improve patient outcomes
- Improve health care resource utilization
The impact of $^{18}$F-FDG PET-CT images on GTV delineation for patients with NSCLC

Kathryn Carson¹, Gerry Hanna², Ruth Eakin², Jonathan McAleese², David Stewart², Ashraf Zatari³, Viv Cosgrove³, Linda Young², Tom Lynch⁴, and Alan Hounsell³

1. N.I. Regional Medical Physics Agency, Nuclear Medicine, Royal Victoria Hospital
2. Dept of Oncology, NI Cancer Centre
3. N.I. Regional Medical Physics Agency, Radiotherapy, N.I. Cancer Centre
4. Radiology Dept, Belfast City Hospital
Aim of the study

• To compare gross tumour volumes (GTVs) delineated using either CT alone or $^{18}$F-FDG PET-CT during radiotherapy planning for NSCLC patients
Methods

- 28 NSCLC patients
  - 22 male, 6 female
  - 14 had induction chemotherapy

- Referred for radical RT
  - Have had staging diagnostic PET-CT

- Dedicated radiotherapy planning PET-CT
  - Treated based on CT plan
  - PET used for research only

- 4 Radiation Oncologists independently delineated the GTV on:
  - CT images alone
  - Fused PET-CT images
Summary of Results

- Significant alteration of GTV volumes by inclusion of PET information

<table>
<thead>
<tr>
<th>% change</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GTV&lt;sub&gt;CT&lt;/sub&gt; larger</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>20.5</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>4.5</td>
</tr>
</tbody>
</table>

- Significant reduction in inter-observer variability when planning PET-CT RTP scan is used compared to CT alone
Patient with atelectasis showing differences in $GTV_{CT}$ and $GTV_{FUSED}$

$GTV_{CT}$ shown in red
$GTV_{FUSED}$ shown in blue
Conclusions

- The use of a PET-CT RTP scan leads to changes in the GTV compared to that defined using CT alone.

- Reduces inter-observer variability particularly for induction chemotherapy group.

- Optimal use of PET-CT in RTP for NSCLC and its precise role require further work before introduction into routine clinical practice.
Clinical Trial Challenges

- Clinical Trials of new diagnostic probes
- Clinical Trials of new radioisotope therapeutics
- Radiolabelled probes as imaging biomarkers in Phase 1, 2 and 3 pharmaceutical trials
  - Sestamibi in cardiac outcomes research
  - PIB in Alzheimers research
  - Hypoxia imaging in tirapazamine development
Role of Molecular Imaging in Expanding the Clinical Role of Imaging in New Treatment Paradigms

- Integrate functional imaging and molecular medicine
- Enhance treatment planning and monitoring
  - Drug therapy
  - Radiation therapy
- Facilitate pharmaceutical trials
- Surrogate outcomes markers
- Predictive assays of treatment response
- Improve patient outcomes
- Improve health care resource utilization
Clinical Trial Challenges

- Need to prove clinical utility of imaging and therapy agents
  - Framework
  - Funding of clinical trials
  - More clinical trials for new agents
  - Incorporation of MI/Imaging Biomarkers in pharma trials
- Develop data to support regulatory change to facilitate imaging biomarker proof-of-principle studies
- Cross platform and cross centre validation and QA/QC
- Identify appropriate outcomes measures
Organisation of a national RCT in early stage HD involving FDG PET

SF Barrington MJ O'Doherty J MacKewn P Schleyer P Mouncey W Qian T Illidge R Pettengell P Hoskin B Hancock J Radford

The PET Imaging Centre at St Thomas’
Background

- Prospective RCT in PET desirable
- Ideally PET should be available to patients close to treatment centre
- Consistency required in QC, scan acquisition, and interpretation
- Comparable results across multiple sites
National RCT involving PET + HD
Methods

Physicist core lab visited
- To scan a standard EU phantom
- Test data transfer
- Sign up key contacts
- Agree regular QC

2 patient datasets image quality
Conclusions

- UK has successfully established a research network of PET Centres
- Collaboration has led to the delivery of consistent high imaging standards
- Agreed QC + image interpretation
- Similar methods could be used in international trials
A Simple PET/CT and SPECT/CT Co-Registration Phantom: The “Hedgehog”

B.R. Walmsley, K.L. Adamson, Guy’s & St. Thomas’ NHS Foundation Trust
Aim of Project

- A system independent phantom
- Quick and simple to use, giving immediately obvious results
- Usable in normal clinical scanning mode
- Usable with any isotope and collimator combination
- Cheap to manufacture
- No need for extra sealed sources
Root cause analysis of performance on a quality exercise for nuclear imaging in the Department of Veterans Affairs (VA), a large US healthcare system

Lorraine M. Fig, MBChB, MPH, Deb Crouch, RN and Milton D. Gross MD
Department of Veterans Affairs (VA) Nuclear Medicine & Radiation Safety Service, Washington, DC,
Department of Radiology, Division of Nuclear Medicine, University of Michigan, Ann Arbor, MI, USA
Cylindrical Imaging Phantom designed to evaluate integrated skills related to tomographic imaging

- Evaluates camera performance and technical proficiency
- Evaluates interpretative skills
2006 SPECT Phantom

Legend:
- "cold" lesions: 0.5 mm sphere
- 1.5 mm sphere
- 10 x 20 mm cylinder
- 16 x 40 mm cylinder
- "hot" lesions: 10 mm
- 15 mm
- 20 mm

![Graph showing % Failures from 1997 to 2006](graph.png)

- 1997: 3.7%
- 1998: 4.8%
- 1999: 3.3%
- 2000: 3.9%
- 2001: 3.1%
- 2002: 3.3%
- 2003: 5.1%
- 2004: 5.1%
- 2005: 5.1%
- 2006: 13%

![Images of different SPECT views](images.png)
Results: Focus on unsatisfactory performance

Problems were usually multi-factorial and compounding

• Technical factors
  • Failure to follow instructions
  • Lack of attention to detail in filling the phantom
  • Suboptimal equipment
  • Inadequate quality control procedures
  • Acquisition errors e.g. inappropriate matrix, inadequate time per stop
  • Processing errors e.g. inappropriate filters

• Interpretative errors
  • Not answering all questions
  • Misinterpretation of right vs. left
  • Misinterpretation of head vs. foot
  • Over-calling or under-calling of “lesions”
Summary of strength, weaknesses and opportunities for using minimally invasive technologies in pharmacokinetic and pharmacodynamic studies -- PET (1)

<table>
<thead>
<tr>
<th>General characteristics for imaging</th>
<th>Strengths</th>
<th>Weaknesses</th>
<th>Robustness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging glucose utilization (18F-FDG)</td>
<td>Sensitivity; specificity; kinetic resolution; low dose administered</td>
<td>Lack of chemical resolution; methodology developments required</td>
<td>3</td>
</tr>
<tr>
<td>PK of labeled drug/molecules (5-18F-fluorouracil)</td>
<td>For grading and response assessment</td>
<td>Inflammation can give false positives</td>
<td>1</td>
</tr>
<tr>
<td>Imaging cell proliferation (14C-thymidine)</td>
<td>PK obtained for tumor and normal tissues</td>
<td>Lack of chemical resolution</td>
<td>2/3</td>
</tr>
<tr>
<td>Blood flow and blood volume imaging (15O H2O/CO)</td>
<td>Direct and rapid assessment</td>
<td>Thymidine metabolism can complicate data analysis</td>
<td>2/3</td>
</tr>
<tr>
<td>Measurement of tissue pH (14C-bicarbonate)</td>
<td>Endpoint for antivascular tx; for drug uptake and clearance</td>
<td>Poor signal-to-noise ratio in some tumors</td>
<td>2/3</td>
</tr>
</tbody>
</table>

Tissue pH measured

Does not differentiate pH\textsubscript{i} from pH\textsubscript{e}

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Workman P, et al. JNCI. 2006; 98(9):580-598
Imaging Biomarkers and Appropriate Outcome Measures
Measuring response in a post RECIST world: from black and white to shades of grey


“We argue that these response criteria do not adequately evaluate the activity of the newest generation of anticancer agents.”
There are no bad anticancer agents, only bad clinical trial designs - twenty-first Hinda Rosenthal Foundation Award Lecture

- “… many new agents fail in the clinic because the appropriate clinical trials that could exploit the attributes of the new agent are not performed.”

- “Perhaps new clinical trial endpoints besides shrinkage of patients tumors are needed to assess the antitumor activity of some new agents.”

Molecular Imaging and Clinical (Trial) Outcomes

- The quantitative or qualitative change in imaging biomarkers must correlate with a specific clinical outcome.
- The quantitative or qualitative identification of a genomic or pathophysiological state with an imaging biomarker must correlate with a specific clinical outcome.
- Changes must be robust and reproducible.
- Must be reproducible across sites and platforms.
- Imaging methodologies must be validated for regulatory approval.
Measuring Treatment Effect in Clinical Trials

- Primary endpoints
- Secondary endpoints
- Anatomic remission
- Survival
- Progression free survival
- Symptom control
- Quality of life
- Biochemical control
- CA125
- Surrogate imaging endpoints/Imaging biomarkers
Profiling in Clinical Trials: Radiotracers as Imaging Biomarkers

- Expensive, massive trials due to heterogeneous patient population
- Successful drug potentially fails
- Pharmacogenomic approach
- Personalized medicine
- More rapid and successful drug development

Save and rescue by profiling
Hypoxia Imaging in GBM
Radioisotope Therapy:

The systemic administration of a targeted radionuclide utilizing short range beta particle or electron emissions to achieve a clinically important outcome for a patient with primary or metastatic cancer.
### Characteristics of Radioisotope Therapy

**Clinical Characteristics**
- Systemic administration
- Specific targeting
- Low toxicity
- Retreatment
- Adjuvant treatment
- Low complexity
- Ability to image

**Scientific Characteristics**
- VLDR/LDR
- Microdosimetry
- $T_p$ correlates with $T_b$
- Chemistry
- Availability/half life
- Cost effective supply
The LQ model greatly underestimates radiosensitivity after low doses.

Survival of T98G human glioma cells. The solid and dashed lines show the fits of the induced repair and LQ models, respectively.

Joiner MC et al.
Int J Radiat Oncol Biol Phys
meta IODO BENZYL GUANIDINE (mIBG)

noradrenaline

mIBG

University of Michigan Medical School, 1980
Guanethidine derivative
$^{131}$I or $^{123}$I label
Uptake: (a) Active (type I)
(b) Passive
Two Strategies for Radioisotope Therapy:

131IImIBG

- **“Big Bang”**
  - High unit dose
  - Toxicity rescue
  - Single treatment
  - Possibly precludes further treatments
  - High complexity
  - Always in patient

- **“Steady State”**
  - Low unit dose
  - High cumulative dose
  - Multiple treatments
  - Titrate to toxicity
  - Low complexity
  - Usually outpatient
Kaplan-Meier Survival Estimates

P=0.06

World J Surgery. 28, 1157 - 1162, 2004
What is a response with Y-90

Waterfall plot at 6 weeks

Pre-therapy

Waterfall plot at 6 months

6 months post last cycle

12 months after last cycle
HiLo

Trial of high vs low activity radioiodine, ± rhTSH, for remnant ablation in differentiated thyroid cancer: progress report.

Dr Alice Nicol,
on behalf of the HiLo trial management group
HiLo

HiLo - the first national trial of thyroid cancer in the UK

**Aims:**

- To examine whether a lower administrated activity (1.1 GBq) of radioiodine has a similar remnant ablation success rate as a higher activity (3.7 GBq)
- To examine whether patients given rhTSH have a similar ablation success rate to those who discontinue thyroid hormone replacement
468 patients with differentiated thyroid cancer

Total thyroidectomy

rhTSH (on thyroid hormone) n= 234

No rhTSH (discontinue or do not start thyroid hormone) n= 234

99mTc pre-ablation scan

Radioiodine ablation

1.1 GBq n= 117

3.7 GBq n= 117

Radioiodine ablation

1.1 GBq n= 117

3.7 GBq n= 117

6-8 months later: Success of ablation determined (diagnostic 131I scan and measurement of Tg)
Conclusions

• First national trial of thyroid cancer in the UK is underway

• Study aims to investigate:
  • Does a low activity (1.1 GBq) of radioiodine have a similar remnant ablation success rate as a high activity (3.7 GBq)
  • Do patients given rhTSH have a similar ablation success rate to those who discontinue thyroid hormone replacement

• Potential benefits to: patients, staff, NHS, environment.

• Good multi-disciplinary communication appears to be key.
Molecular Imaging from Translational Research to Clinical Trials to Clinical Practice

Clinical Research / Diagnostic Question

PET / Molecular Imaging

Parametric Image / Distribution of Function

Functional Change / Assay of Response

Clinical Practice/Improved Patient Outcome
Future Directions for Molecular Imaging

- New probes and contrast agents
  - Ownership and patent framework
  - Regulatory framework
- New imaging modalities
- Multi-modality imaging
- Bioinformatics applications
- Translation into clinical application of research technologies
- Teaching a new generation of medical specialists
- Funding
- Turf decisions
Integrating Molecular Imaging and Molecular Medicine in Clinical Practice

- Training leadership
- Imaging biomarkers and clinical trials
- Predictive assay of Rx response
- Treatment selection
- Treatment stratification
- Treatment planning
- Personalized medicine
- Improved patient outcomes
- Healthcare utilization
- Technology development & commercialization
Patient Passport: The example of Brain Tumor

Clinical Data
- demographics, brain tumor, RT, time to progression, response, etc

Tissue Bank
- 1p/19q LOH, p53, EGFR, EGFR VIII, GFAP, PTEN, AKT, CD133, etc

Imaging
- PET/MRI, CT, MRI, MRS, fMRI, etc

Molecular Profiling
“What we’re going to do is embark on a long process of cultural change--a change that may not happen, but if it doesn’t, medicine will be the poorer.”

Brian C. Lentle, M.D.