Monitoring Chemotherapy and Molecular Targeted Therapy in Solid Tumours using PET

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FDG PET Breast Cancer
Wahl, R.L. , 1989

N = 1

My first experience of PET in cancer evaluation
PET for Therapy Monitoring

Metabolic Response is a Continuum

$N = 1$

% of baseline

Days post-treatment

Measuring wooden spheres under a foam sheet with palpation and rulers established the methodology for response assessment.

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**THE EFFECT OF MEASURING ERROR ON THE RESULTS OF THERAPEUTIC TRIALS IN ADVANCED CANCER**

CHARLES G. MOERTEL, MD, and JAMES A. HANLEY, PhD

In this study, 16 experienced oncologists each measured 12 simulated tumor masses employing their usual clinical methods. Unknown to the oncologists, two pairs of these tumors were identical in size. This permitted a total of 64 measurement comparisons of the same investigator measuring the same size mass and 1920 comparisons of different investigators measuring the same size mass. If a 50% reduction in the product of perpendicular diameters is accepted as a criterion, the objective response rate due to measuring error alone was 7.8% by the same investigator and 6.8% by different investigators. If a 25% reduction criterion is used, the respective "placebo" response rates were 19% and 25%. In the clinical setting it is recommended that the 50% reduction criterion be employed and that the investigator should anticipate an objective response rate of 5 to 10% due to human error in tumor measurement.


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**Reporting Results of Cancer Treatment**

A. B. MILLER, MB, FRCP(C), B. HOOGSTRATEN, MD, M. STAQUET, MD, AND A. WINKLER, MD

On the initiative of the World Health Organization, two meetings on the Standardization of Reporting Results of Cancer Treatment have been held with representatives and members of several organizations. Recommendations have been developed for standardized approaches to the recording of baseline data relating to the patient, the tumor, laboratory and radiologic data, the reporting of treatment, grading of acute and subacute toxicity, reporting of response, recurrence and disease-free interval, and reporting results of therapy. These recommendations, already endorsed by a number of organizations, are proposed for international acceptance and use to make it possible for investigators to compare validly their results with those of others.

RARELY
ENLIGHTENING
COMMONLY
INEFFECTIVE
SURVEILLANCE
TECHNIQUE
The Importance of Methodology

“However beautiful the strategy, you should occasionally look at the results.”
Winston Churchill, British prime minister
PET/CT - Form and Function in Harmony
An Evolution in Technology
but a Revolution in Oncology

- Solid tumours can lead to secondary morphological changes in adjacent tissues that confounds initial tumour measurement
Advantages of PET/CT - Lesion Conspicuity

SCR-DxCT

D56-DxCT

NEWLY ENLARGED LYMPH NODE

SCR-FDG

D56-FDG
PET for Therapy Monitoring of Solid Tumours

**FDG Methodology**

- Analysis techniques
  - Qualitative
  - Semi-quantitative
    - Tumor to background ratios (TBR)
    - Standardized uptake value (SUV)
  - Quantitative
    - Compartmental modeling
    - Patlak graphical analysis
PET For Therapeutic Monitoring
Peter Mac Qualitative Response Criteria

- Qualitative reporting done based on SUV-calibrated images displayed on same threshold and in standardised rainbow colour-scale
- Peter Mac Response Definitions for FDG
  - **Complete Metabolic Response (CMR)**
    Lesion uptake equal to or less than mediastinal blood pool
  - **Partial Metabolic Response (PMR)**
    Lesion uptake reduced compared to baseline but remains higher than blood pool
  - **Stable Metabolic Disease (SMD)**
    No significant change in extent or intensity of uptake
  - **Progressive Metabolic Disease (PMD)**
    Increase in either intensity or extent of uptake abnormality

How To Read PET/CT

Importance of Colour-Scale

Hot Metal

Rainbow
The Importance of Pattern Recognition

- The human brain is adapted for pattern recognition
The Importance of Pattern Recognition

• Has this patient progressed?

Baseline                    Post-RT
The Importance of Pattern Recognition

• Although patterns are important, mimics abound and interpretation requires interposition of intelligence!
PET for Therapy Monitoring

Lung Cancer

- NSCLC of the right hilum
- Treated with radical radiotherapy and Iressa
- PMR

Baseline                          Post-RT
PET for Therapy Monitoring

Lung Cancer

Estimated percentage surviving over Years following restaging PET scan

CMR
PMR
SMD/PMD

P = 0.0001

MacManus et al, J Clin Oncol 2003
PET for Therapy Monitoring

Lung Cancer

Multifactor Analysis of Survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>P-value</th>
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<tbody>
<tr>
<td>ECOG</td>
<td>0.077</td>
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<tr>
<td>Wt loss some/none</td>
<td>0.96</td>
</tr>
<tr>
<td>Stage</td>
<td>0.46</td>
</tr>
<tr>
<td>CT Response</td>
<td>0.066</td>
</tr>
<tr>
<td>Evaluable CT Response</td>
<td>0.033</td>
</tr>
<tr>
<td>PET Response</td>
<td>0.0005</td>
</tr>
<tr>
<td>PET Response per Category</td>
<td>&lt; 0.0001</td>
</tr>
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</table>

- Survival by PET response in 88 patients receiving rRT

PET for Therapy Monitoring
Post-Treatment FDG in Breast Cancer

Cachin et al. *J Clin Oncol* 2006;24:3026-3031
PET for Therapy Monitoring
Post-Treatment FDG in Breast Cancer

Cachin et al. *J Clin Oncol* 2006;24:3026-3031
PET for Therapy Monitoring

Esophageal Cancer

Results

Survival by PET response post-CRT

Resection of tumor site

No Resection

In 53 patients with locally-advanced disease

Duong et al. 2006;33:770-778
Flouroethyltyrosine FET
PMCC FET PET Pilot Study in Brain Tumours
Therapeutic Monitoring

Baseline FET

Post-CRT FET

• Left frontal grade II WHO oligoastrocytoma
• Treated by chemo-radiation following debulking surgery
PET in Therapeutic Monitoring

• Standardisation required to;
  – interpret results in clinical trials
  – Compare different trials
  – Implement prospective evaluation

• Initial criteria of Young et al. EJC 1999
  – CMR - disappearance
  – PMR Decrease of 15-25% after 1 cycle, >25% after 2
    or more cycles
  – PMD - Increase of >25% or new lesion
  – SD, neither PMR or PMD

“Committee- a group of men who individually can do nothing
but as a group decide that nothing can be done.”

Fred Allen (American Humorist), 1894-1956
PET for Therapy Monitoring
FDG Methodology

Beaulieu et al. JNM 2003:44:1044-50

Change in SUV over time in breast cancer
PET for Therapy Monitoring

FDG Methodology

Change in SUV between median 70 (range 47-112) and 98 (range 77-142) minutes post-injection of FDG

Hustinx et al. EJNM 1999:26:1345-8
Imaging of Cancer
Importance of Disease Biology

Rate of cell depopulation and repopulation determines survival advantage of PET responders versus non-responders.
THERE IS NEW AMMUNITION IN THE WAR AGAINST CANCER. THESE ARE THE BULLETS.

Revolutionary new pills like GLIVEC combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
The New Molecular Paradigm

A new era of personalised “molecular medicine”!
The Power of Metabolic Imaging
FDG PET for Therapeutic Monitoring

Before Imatinib            One day after Imatinib
Gastrointestinal stromal tumor (GIST)
Discordance in Metabolic and Anatomic Response

Clinical response in GIST treated with imatinib concordant with metabolic response but not RECIST
PET-CT of GIST

- Poor therapeutic response to imatinib
PET for Therapy Monitoring

The Prognostic Significance of Metabolic Response in GIST

![Graph showing cumulative proportion surviving over time for PET responders and non-responders.]

FDG PET for Therapeutic Monitoring

Discordance between metabolic and structural responses in GIST tumour treated with imatinib (Sustained CMR but never achieved PR)
FDG PET for Therapeutic Monitoring

Discordance between metabolic and structural responses in GIST tumour treated with imatinib (Relapsed despite progressive PR)
KIT and PDGFRA Mutations in 950 GISTs

KIT (78.5%) Exon 11 Exon 17 (Imatinib binding domain)

PDGFRA (7.5%)
Key role of oncogenes and hypoxia link FDG uptake to poor prognosis

Why is FDG response to imatinib so rapid?

**PET For Therapeutic Monitoring**

**Availability of *Ex Vivo* Biomarker Validation**

<table>
<thead>
<tr>
<th>Baseline FDG PET</th>
<th>pVEGFR2</th>
<th>Ki67</th>
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<tbody>
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<td><img src="image1.png" alt="Baseline FDG PET" /></td>
<td><img src="image2.png" alt="pVEGFR2" /></td>
<td><img src="image3.png" alt="Ki67" /></td>
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<table>
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<th>Week 4</th>
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<tbody>
<tr>
<td><img src="image4.png" alt="Week 4 FDG PET" /></td>
<td><img src="image5.png" alt="Week 4 pVEGFR2" /></td>
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- Metastatic thyroid cancer treated with an anti-angiogenesis agent
- Excellent clinical and radiological response predicted by early qualitative response but not by SUVmax response
PET for Therapy Monitoring

FDG PET - Role in Novel Therapies

• Metastatic renal cell carcinoma
• Novel anti-angiogenesis agent in phase I development
• FDG PET used for assessment of drug activity
PET For Therapeutic Monitoring
Comparison of FDG and FLT Response

- Metastatic malignant melanoma
- Bone and liver mets better seen on FDG PET
Evaluating New Treatments

Malignant melanoma

New targeted therapy for mutant gene expressed in >40% of cases

"Why not go out on a limb? Isn't that where the fruit is?"

Frank Scully, American writer
Evaluating New Treatments

Lung cancer

New targeted therapy for a mutant gene (ALK fusion gene) expressed in <5% of cases
PET for Therapy Monitoring
New Targets Require New Tracers

FDG (Glucose)

2 tumour sites

FMISO (Hypoxia)

Only 1 site lacks oxygen

Lack of oxygen limits effectiveness of current therapies but provides a target for new drugs!
Concept of Clonal De-Differentiation

FDG

Fused Ga-68 octreotate (colour) and FDG
Future Directions

More specific biological probes
- Receptor ligands, e.g.
  somatostatin receptor
  ligands (Ga-68 octreotate)
- Hypoxia, e.g. FMISO
PET for Therapy Monitoring

Summary

• Treatment options are becoming more complex

• Better treatment selection is required

• Early monitoring of response can identify non-responders sparing further futile toxicity

• Optimum timing of monitoring scan is probably disease and therapy dependent

• Molecular biology and molecular imaging are complementary tools in the new era of molecular medicine
Now we only need to convince the regulators!