Richard Wahl, MD

“Imaging as a Predictor of Therapeutic Response”

11:10 - 11:40 AM
Imaging as a Predictor of Treatment Response

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Contributions of Anthony Shields, M.D., Ph.D gratefully noted

Predicting Treatment Response

Oncology
Neurologic/Psychiatric Diseases
Cardiovascular Disease
Surgical Interventions
Infectious Diseases

Predict possibility of response of disease
Predict possibility of toxicity response induced by treatment

Limited time for presentation: Emphasis on Oncology

P-4 Healthcare

New Horizons Lecture to Address Evolution of Imaging

Predictive
Personalized
Pre-Emptive

Patients are Individuals

• Variability in drug pharmacokinetics in whole body, organs and tumors
• Varying receptor status in tumors, brain heart
• Varying proliferative/apoptotic rates in tumors
• Varying in many characteristics
• Current cancer treatments are substantially based on the “Average Patient” not the individual patient
• Goal is to individualize treatments to optimize responses and minimize toxicity
• Imaging shows the phenotype in the physiological milieu

Disclosure Information

2011 RSNA: Richard L. Wahl, M.D.

I have the following financial relationships to disclose:
Consultant for: Cellectar, Nihon Medi-Physics, MDS, Marqullon Pharmaceuticals
Speaker’s Bureau for GSK
Grant/Research support from: NIH
Stockholder in: Threshold Pharmaceuticals
Honoraria from: GSK
Employee of: Johns Hopkins University
Royalties and Patents licensed to: Glaxo Smith Kline, Naviscan PET, Spectrum Pharmaceuticals; Intramedical Diagnostics

- and -

I will discuss the following off label use and/or investigational use in my presentation: I-124, FLT, FES, (PET Agents)
How is Cancer Treatment Personalized—Or is it?

• Predictors of efficacy—non-imaging and imaging
• Early markers or response—non-imaging or imaging

Roles of Imaging in Predicting Response

• Prior to treatment
  – Diagnosis (disease/cancer or not?)—including directing biopsy
  – Staging before therapy or assessing extent of disease
    • Pre surgical
    • Pre Radiation therapy (planning)
    • Pre Radionuclide therapy (dosimetry)
  – Predicting Response*
• After treatment initiated
  – Assessment of response after completing therapy
  – Intra-therapy monitoring
  – Assessment at end of Rx to predict pathological outcome
  – Response Adaptive Approaches

Roles of PET/CT and SPECT/CT in Cancer Management

• Prior to treatment
  – Diagnosis (cancer or not?)—including directing biopsy or enriching population
    – Staging before therapy
      • Pre surgical
      • Pre Radiation therapy (planning)
      • Pre Radionuclide therapy (dosimetry)
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PET/CT, SPECT/CT, DCE MRI, DWMRI, CT, CT Volume are Qualitative and a Quantitative Methods

• Most applications to date have been Qualitative
• In treatment response assessment, especially if looking for small treatment induced changes, Quantitation will be needed
• Quantitation requires greater attention to technical details than qualitative imaging
• Standardization of methods—including Analytical Methods is required

Personalised medicine today

1. Pharmacogenomics to predict the potential for disease or response of a patient on a one time, but whole body basis. Unacceptable metabolism leading to lack of effect or toxic effect.

2. Targeted oncology drugs for use in patients who have been demonstrated to have the target in excised tumor tissue.

Spatially Normalized DVR Images Generated from [18F]AV45 PET Dynamic Studies

AD Patient (78 yrs, Male)
Healthy Control (83 yrs, Male)
Dynamic Rb-82 PET-CT for Quantification of Myocardial Bloodflow

Rb Flow vs Microsphere

Dog Model of Myocardial Ischemia

Dept. of Nuclear Medicine / PET Center, Zentralklinik Bad Berka

Ga-68 DOTA-NOC PET/CT

Metastasis of neuroendocrine carcinoma in the heart (pericard)

Ga-68 SMS:
- fast clearance
- low background
- high specificity
  = high contrast

FDG vs FAZA
courtesy R. Hicks, M.D
Purpose: validate biopsy tool trajectory

Roles of PET/CT and SPECT/CT in Cancer Management

- Prior to treatment
  - Diagnosis (cancer or not?)—including directing biopsy
  - Staging before therapy
    - Pre surgical vs. medical
    - Pre Radiation therapy (planning)
    - Pre Radionuclide therapy (dosimetry)
  - Predicting Response
- After treatment initiated
  - Assessment of response after completing therapy
  - Intra-therapy monitoring
  - Response Adaptive Approaches

Example of Stage Change Implications

- PET can identify CA lesions < 1 cm diameter
- Patients thought to have “isolated metastases” may have more extensive disease present and be excluded vs a group not selected with PET—i.e. entering patient populations may vary

Survival Post Resection of Liver Metastases

- Longer in patients staged by PET
- Shorter in patients not staged by PET
- True benefit, stage migration
- Better segregation of Rx with prevention of unneeded procedures
Roles of PET/CT and SPECT/CT in Cancer Management

- Prior to treatment
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*Predicting Response*
Post-therapy PET

- Multiple studies demonstrating superior prognostic value of PET vs CT at therapy completion
  - Can differentiate viable tumor from fibrosis
  - Can detect residual disease in context of radiographic CR
- Relapse up to 100% if PET+, 5-17% if PET-

Jerusalem et al, Blood 1999; 94:420-433
Spaepen K et al, JCO 2001; 19: 414-419

Qualitative vs Quantitative or Both?

- Visual assessments can be used to assess response
- Strengths: No special instrumentation, integration of all data.
- Weaknesses: Tendency to be binary, perhaps not reproducible
- Quantitative: Ignores qualitative data, can be erroneous due to technical factors, Standardized is not so standard after all

IWG response criteria

<table>
<thead>
<tr>
<th>Original</th>
<th>Revised (includes Hodgkin’s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Normal size</td>
</tr>
<tr>
<td></td>
<td>FDG-avid tumor: mass of any size, as long as PET “negative”</td>
</tr>
<tr>
<td></td>
<td>Variably FDG-avid or unknown: normal size</td>
</tr>
<tr>
<td>CRu</td>
<td>If nodes &gt; 1.5 cm, &gt; 75% decrease</td>
</tr>
<tr>
<td>PR</td>
<td>&gt; 50% decrease</td>
</tr>
<tr>
<td></td>
<td>FDG-avid tumor: &gt; 50% decrease, but at least one PET positive focus</td>
</tr>
<tr>
<td></td>
<td>Variably FDG-avid or unknown: regression in size</td>
</tr>
</tbody>
</table>

PET/CT Appearance of Lung Malignancies Following Radiofrequency Ablation

Robert P. Liddell, MD¹, Richard L. Wahl, MD², Stephen Yang, MD², David Mason, MD², Leo P. Lawler, MD², Stephen B. Solomon, MD²

The Johns Hopkins Medical Institutions
Baltimore, MD.
¹ The Russell H. Morgan Department of Radiology and Radiological Science
² Department of Surgery, Division of Thoracic Surgery

Post Treatment PET

• Head and Neck Cancer
• Colon Cancer
• Lung Cancer
• Lymphoma
• Esophageal Cancer
• Hepatoma and liver metastases

PFS determinations

• If PET is used to determine duration of response, it may be able to detect earlier recurrences than if standard anatomic imaging or simply clinical follow up for symptoms is used
• Example: Ovarian carcinoma and use of CT, CA-125 clinical exam etc.
• How does one deal with these findings when detected? (some may be FP).

Comparative Analysis of FDG PET/CT and Serum CA-125 in the Surveillance of Recurrent Ovarian Cancer - Initial Assessment

Mehrbod S Javadi, Aditi Shruti, Robert Bristow, Richard L. Wahl

Division of Nuclear Medicine
Department of Radiology
Johns Hopkins University
There was a significant difference between the two tests for diagnosis of recurrence (p < 0.0001)

Roles of PET/CT and SPECT/CT in Cancer Management

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Baseline 5/03 2 cycles chemo 6/03 4 cycles chemo 7/03 63 days post chemo start, 48% decline in FDG uptake in responders

Wahl et al. JCO 11:2101-2111, 1993

PET Monitoring of Chemotherapy

63 days post chemo start, 48% decline in FDG uptake in responders

No significant decline in FDG uptake in non responders, n=11

Wahl et al. JCO 11:2101-2111, 1993

Why might mid-treatment PET be superior to post-treatment?

Early PET result implies a certain rate of tumor kill
**First-order kinetics**

With 6 cycles, need at least 1.5 logs of cell kill per cycle

**Usual size at diagnosis**

**Cure**

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**Practical Considerations:**

- Consistent Protocol Essential
- Same time from injection to imaging
- Same fasting
- Same Imaging sequence (caudal to cranial)
- Variability in estimates of SUV of 10-20%
- Changes in SUV under 20% may be chance
- Normalization to liver can help
**Mid-treatment PET strongly predicts PFS in aggressive lymphoma**

- Median time to treatment failure
  - PET+: 1.5 mo
  - PET-: 1 yr

- Stronger predictor than IPI

Spaepen K et al, Ann Oncol 2002;13: 1356-63

**NHL: PET during first-line therapy**

<table>
<thead>
<tr>
<th>Cycle before PET</th>
<th>N</th>
<th>PET+</th>
<th>PPV</th>
<th>NPV</th>
<th>EFS, PET+</th>
<th>EFS, PET-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mikhaeel 2000</td>
<td>2-4</td>
<td>23</td>
<td>35%</td>
<td>88%</td>
<td>100%</td>
<td>--</td>
</tr>
<tr>
<td>Spaepen 2002</td>
<td>2-4</td>
<td>70</td>
<td>47%</td>
<td>100%</td>
<td>84%</td>
<td>4% (2 yr)</td>
</tr>
<tr>
<td>Mikhaeel 2005</td>
<td>2-3</td>
<td>102</td>
<td>51%</td>
<td>71%</td>
<td>90%</td>
<td>16% (5 yr)</td>
</tr>
<tr>
<td>Haun 2006</td>
<td>2</td>
<td>90</td>
<td>40%</td>
<td>--</td>
<td>--</td>
<td>43% (2 yr)*</td>
</tr>
</tbody>
</table>

- Event rate: 78-100% if PET+, 8-16% if PET-

- * 40% of all pts got upfront BMT, irrespective of PET

**Summary of in Vitro Studies**

- Chemotherapy transiently “stuns” cancer cells and drops FDG uptake vs. viable cell number
- The stunning effect is short lived, less than 2 days
- mRNA for Glut 1 rises, but Glut 1 protein falls
- Even after chemotherapy, FDG uptake remains reasonably well correlated with cell viability, especially after period of “stunning”

**“Metabolic” Flare Reaction: Protocol**

- Women with locally advanced, recurrent, or metastatic estrogen-receptor-positive breast cancer
- Baseline FDG-PET and FES-PET
- Start tamoxifen
- Repeat FDG-PET and FES-PET at 7-10 days
- Follow-up until disease progression (by oncologist blinded to PET results)
FLT Lung Cancer Response

- FLT-PET images of the thorax were obtained before and 7 days after the start of gefitinib (250 mg/d) therapy in non-smokers with new or recurrent NSCLC.
- SUV_{max} and ¾ decline in SUV_{max} were assessed in tumor at baseline and 7 days. Compared with CT after 6 weeks of therapy.
- 31 patients of whom 28 had complete data.
- CT at 6 weeks showed PR in 14 (50%), SD in 4 (14%), and PD in 10 (36%) after 6 weeks of treatment.
- Pretreatment SUV_{max} of the tumors did not differ between responders and nonresponders.


Roles of PET/CT and SPECT/CT in Cancer Management

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  - Intra-therapy monitoring
  - Response Adaptive Therapy
Response-adapted therapy

**J0348: rationale**
- Early $^{18}$F FDG-PET (after 2-4 cycles) is highly predictive and more individualized than the IPI
  - Event rates of 78-100% if PET+ midtreatment, versus 8-16% if PET-, consistently seen
- Benefit of early BMT most pronounced in poor-risk pts
- **HYPOTHESIS**: Early PET can identify those pts who most stand to benefit from early treatment intensification
- **PRIMARY ENDPOINT**: 25% absolute improvement in 2-yr EFS (from 20% to 45%) of PET+ pts, compared with historical outcomes, through early BMT

**Study design**
- Aggressive NHL, any stage, any IPI
- (R)CHOP for 2 or 3 cycles
- PET -
  - complete conventional therapy
- PET +
  - if no disease progression (R)ESHAP or (R)ICE x 2
  - High dose therapy and ABMT

**PET assessment**
- **NEGATIVE**
  - 0 no abnormal activity (tumor cold compared with background)
  - 1+ minimal activity (tumor less than background)
  - 2+ equivocal (tumor = background)
- **POSITIVE**
  - 3+ moderate activity (tumor greater than background)
  - 4+ strong activity (tumor much greater than background)

**J0348**
- **Primary endpoint**: 25% absolute improvement in 2-yr EFS (from 20% to 45%) of PET+ pts, compared with historical outcomes, through early BMT
- **Goal**: 55 pts, expect 50% PET + and 19 transplants

**Response Adaptive Therapy**
- Fifty-nine newly diagnosed patients, 98% with B cell lymphoma, had PET/CT performed after 2 or3 cycles of first-line chemotherapy.
- Mid-treatment PET was positive in 33 (56%).
- 28 received ASCT with an actuarial 2-year EFS of 75% (95% confidence interval, 60%-83%).
- On intention-to-treat analysis, 2-year EFS was 67% (53%-86%) in all PET-positive patients and 89% (77%-100%) in PET-negative patients. (overlapping CI)
Conclusions:

- PET/CT after initial therapy is complete has prognostic value in lymphomas > CT alone.
- PET/CT after 1-2 cycles appears predictive of effectiveness of treatment in several tumor types. Will allow for response adaptive therapy.
- PET/CT with non FDG ligands, eg. FES, may be predictive before treatment is begun.

EORTC Response Criteria

<table>
<thead>
<tr>
<th>CR</th>
<th>Complete Disappearance of all Metabolically Active Tumor (i.e. decreased to background levels)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>&gt;15% decline in SUV after 1 cycle, &gt;25% decline after 2 or more cycles. Reduction in extent (size) of FDG uptake is not required</td>
</tr>
<tr>
<td>SD</td>
<td>Increase in FDG SUV of &lt;25% or decrease of &lt;15% in SUV and no increase in extent of uptake (&lt;20% in longest dimension)</td>
</tr>
<tr>
<td>PMD</td>
<td>Increase in SUV of over 25%, Increase in extent of FDG uptake by &gt;20%, New FDG positive metastases</td>
</tr>
</tbody>
</table>

If there were RECIST Criteria for PET, It Would be Defined as…

“PERCIST”

- Positron
- Emission
- Response
- Criteria in
  - Solid
  - Tumors

From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors

Blesovsky L, Wohldt A, Heisterkamp C, van Leeuwen, and Martin S. Lodge.  


![Graphs depict the relationships between patient body weight and blood SUVs: (a) SUVbw, (b) SUVibw, (c) SUVlbm, or (d) SUVbsa.](image)
What is Measured?

- SUL Peak
- In Hottest Tumor Focus

Introduction

- A number of different ROI definitions have been employed including:
  - Mean within an irregular ROI defined by isocontours.
  - Mean within a fixed size ROI centered on the most metabolically active region.

Normalization for Quality Control

- Normal liver SUL must be within 20% (and <0.3 SUL mean units) for baseline and follow up study to be assessable. If liver is abnormal, blood pool SUL must be within 20% (and <0.3 SUL mean units) for baseline and follow up study to be assessable.
- Uptake time of baseline study and follow up study 2 must be within 15 minutes of one another to be assessable. Typically, these are at a mean of 60 minutes post injection, but not less than 50 min post injection.
- Same scanner, or same scanner model at same site, injected dose, acquisition protocol (2D vs. 3D), and software for reconstruction should be used. Scanners should provide reproducible data and be properly calibrated.

Complete Metabolic Response

- Complete metabolic response (CMR) complete resolution of [18F]-FDG uptake within the measurable target lesion so that it is less than mean liver activity and indistinguishable from surrounding background blood pool levels.
- Disappearance of all other lesions to background blood pool levels. % decline in SUL should be recorded from measurable region as well as (ideally) time in weeks after treatment was begun (i.e. CMR -90, 4).
- No new FDG avid lesions in a pattern typical of cancer. If progression by RECIST must verify with follow up.
Continued declines out to 24 weeks

CT PET FUSED

Partial metabolic response (PMR)
- Reduction of a minimum of 30% in target measurable tumor FDG SUL peak.
- Absolute drop in SUL must be at least 0.8 SUL units, as well.
- Measurement is commonly in the same lesion as the baseline, but can be another lesion if that lesion was previously present and is most active lesion after treatment. ROI does not have to be in precisely the same area as baseline scan, though typically it is.
- No increase, >30% in SUL or size of target or non target lesions (i.e. no PD by RECIST or IWC). If PD anatomically, must verify with follow up). A reduction in the extent of the tumor FDG uptake is not a requirement for partial metabolic response. % decline in SUL should be recorded as well as (ideally) time in weeks after treatment was begun (i.e. PMR - 40, 3). No new lesions.

Stable Metabolic Disease
- Stable metabolic disease (SMD) Not CMR, PMR nor PMD. Note, the SUL peak in metabolic target lesion should be recorded as well as (ideally) time from start of most recent therapy in weeks (i.e. SMD - 15, 7). No new lesions

Progressive metabolic disease (PMD)
- >30% increase in FDG SUL peak, with >0.8 SUL unit increase in tumor SUV peak from the baseline scan in pattern typical of tumor and not of infection/treatment effect.
- OR. Visible increase in the extent of [18F]-FDG tumor uptake (75% in TLG volume with no decline in SUL).
- OR - new [18F]-FDG avid lesions which are typical of cancer and not related to treatment effect or infection. PMD other than new visceral lesions should be confirmed on follow up study within 1 month unless PMD also is clearly associated with progressive disease by RECIST 1.1. PMD should be reported to include % change in SUV peak, (ideally time post treatment in weeks) and whether new lesions are present/absent and their number (i.e. PMD, +35, 4, New-5).
PERCIST Continuous Response Scale

- Because SUL is a continuous variable, dividing response criteria into a limited number of somewhat arbitrary response categories loses much data.

- For this reason PERCIST preserves percent declines in the SUV peak in each reported category. Because the rapidity with which a scan normalizes is important (faster appears better), PERCIST asks for the time from start of treatment as part of the reporting.

- For example, a CMR 90, 1 is probably superior to a CMR 90, 10, especially if the latter patient were SMD 20,1. More than one measurement of PET response may be needed at differing times and it may be treatment type dependent.

Number of Lesions

- PERCIST 1.0 only evaluates the SUL peak of the hottest tumor. This is a possible limitation of the approach, but lesions and their responses are highly correlated in general.

- Additional data are required to determine how many lesions should be assessed over 1.

- A suggested option is to include the 5 hottest lesions, or the 5 observed on RECIST 1.1 which are the most measurable. % change in SUL can be reported for the single lesion with the largest increase in uptake or the smallest decline in uptake. Additional studies will be needed to define how many lesions are optimal for assessment.

Key Issue in Response Criteria is reproducibility of the metric

- SUV is reproducible to about 20% in carefully controlled settings

- Probably less reproducible in practice

- Do not want NOISE to confuse with real change in tumor metabolism

Changing Paradigms on How and When to Assess Response

- Standard Anatomic Read outs are “too slow” and too crude to individualize therapy-- bye to RECIST—minor anatomic changes may still be useful

- Newer Metrics, continuous readouts such as SUV on FLT or FDG as reported in “PERCIST” criteria (in development)—or DCE MRI will allow faster readout of drug effects.

Personalized Therapy in the Future?

- Initial therapy selection based on tumor characteristics at biopsy, scan

- PET/CT at baseline

- PET/CT after one cycle of Rx

- Responding group, continue Rx

- Non responding group-begin alternative therapy, potentially dose intensive or clinical trial.

- This will be response adaptive therapy
Acknowledgements

- Heather Jacene, M.D.
- Eric Frey, Ph.D.
- Bin He, Ph.D.
- George Sgouros, Ph.D.
- Martin Lodge, Ph.D.
- Wayne Kasecamp, CNMT
- Ken Zasadny, Ph.D.
- James Engles, M.S., MBA.
- Ian Flinn, M.D.
- Yvette Kasamon, M.D.
- Dan Mollura, M.D., MBA
- Frank Bengel, M.D.
- Igal Madar, Ph.D.