✓ Introduction

✓ Basic science of Nuclear Medicine
  ➢ α-radiation
  ➢ β-radiation
  ➢ γ-radiation

✓ Research

✓ Report writing
Nuclear Medicine

✓ Stanford Clinical Faculty
  - Andrei Iagaru, MD
  - I. Ross McDougall, MD, PhD
  - Erik Mittra, MD, PhD
  - Andrew Quon, MD

✓ VA Clinical Faculty
  - George Segall, MD
  - Minal Vasanawala, MD
Nuclear Medicine - Goals

- To be able to sit ABNM/ABR examination and pass
- To be able to practice diagnostic and therapeutic Nuclear Medicine
- To be able to run a Department of Nuclear Medicine
- To be able to conduct research in Nuclear Medicine
- To educate physicians and students in Nuclear Medicine
What is Nuclear Medicine?

- Nuclear Medicine studies use small amounts of radioactive substances administered to the patients for detection of the radiation emitted from inside the body to produce images (scintigrams) of organs based on physiology or pathophysiology.

- Some of the studies are obtained over time for a functional evaluation.
Definitions

**Tracer:** the moiety defining the biological behavior

**Label:** the radioisotope used for detection and measurements

**Radioisotopes:** unstable elements decaying by emitting radiation
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Nucleus

Nucleus with two fewer protons and two fewer neutrons

Neutron

Proton

Alpha particle
Self-targets to bone metastases by virtue of its properties as a calcium-mimic.

223Ra (Xofigo®)

Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease

- **Phase II**: Found no significant side effects and showed 4.5 months increased OS, delayed SREs, and improvement in biochemical end points (PSA, total ALP)

- **Phase III**: Alpharadin successfully met the primary endpoint of OS in the ALSYMPCA (ALpharadin in SYMptomatic Prostate CAncer patients) study in 922 patients
ALSYMPCA Trial Results

A. Overall Survival

- Hazard ratio, 0.70 (95% CI, 0.58–0.83)
- P<0.001
- Radium-223 (median overall survival, 14.9 mo)
- Placebo (median overall survival, 11.3 mo)

B. Time to First Symptomatic Skeletal Event

- Hazard ratio, 0.66 (95% CI, 0.52–0.83)
- P<0.001
- Radium-223 (median time to first symptomatic skeletal event, 15.6 mo)
- Placebo (median time to first symptomatic skeletal event, 9.8 mo)
## ALSYMPCA Trial Results

**Table 2. Main Secondary Efficacy End Points in the Intention-to-Treat Population.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Radium-223 (N=614)</th>
<th>Placebo (N=307)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to first symptomatic skeletal event — mo</td>
<td>15.6</td>
<td>9.8</td>
<td>0.66 (0.52–0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to increase in total alkaline phosphatase level — mo</td>
<td>7.4</td>
<td>3.8</td>
<td>0.17 (0.13–0.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to increase in PSA level — mo</td>
<td>3.6</td>
<td>3.4</td>
<td>0.64 (0.54–0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patients with ≥30% reduction in total alkaline phosphatase response — no./total no. (%)</td>
<td>233/497 (47)</td>
<td>7/211 (3)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Patients with normalization of total alkaline phosphatase level — no./total no. (%)</td>
<td>109/321 (34)</td>
<td>2/140 (1)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* Only patients who had elevated total alkaline phosphatase levels at baseline are included.
**ALSYMPCA Trial Results (Continued)**

- Common non-hematologic adverse events (occurring in at least 15% of patients) included:
  - Bone pain (in 43% of $^{223}$Ra patients vs. 58% of placebo-treated patients)
  - Nausea (34% vs. 32%)
  - Diarrhea (22% vs. 13%)
  - Constipation (18% vs. 18%)
  - Vomiting (17% vs. 13%)

- The most common hematologic adverse event was anemia (in 27% of $^{223}$Ra patients vs. 27% of placebo-treated patients)

- The most common grade 3 and grade 4 adverse event was bone pain (18% of $^{223}$Ra patients vs. 23% of placebo-treated patients)
Nucleus

Beta particle

Antineutrino

Nucleus with one less neutron and one more proton

Beta particle

Antineutrino

Nucleus with one less proton and one more neutron

Neutrino

Neutron

Proton

Beta particle, Antineutrino, Neutrino
<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Physical $T_\frac{1}{2}$</th>
<th>Principal photon energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodine-131</td>
<td>8.01 days</td>
<td>364</td>
</tr>
<tr>
<td>Yttrium-90</td>
<td>64.1 hours</td>
<td>Pure $\beta$</td>
</tr>
<tr>
<td>Samarium-153</td>
<td>46.7 hours</td>
<td>103</td>
</tr>
<tr>
<td>Strontium-87</td>
<td>50.5 days</td>
<td>Pure $\beta$</td>
</tr>
<tr>
<td>Phosphorus-32</td>
<td>14.29 day</td>
<td>Pure $\beta$</td>
</tr>
</tbody>
</table>
Tg Synthesis

Tg

Thyroperoxidase

I-

I-Tg

Lysosomal Digestion

L

T4, T3

MIT, DIT

Pendrin

NIS

Na+

T4, T3

Capillary

Colloid
β radiation from $^{131}$I

- Thyroid cell average 10-20 microns
- Follicle average 100-300 microns
- Beta particles average 500 microns
- Homogeneous radiation

Courtesy of Dr McDougall
Rituximab
(Rituxan®, MabThera®)

- 1st FDA-approved monoclonal antibody for cancer (1997)
- Relapsed/refractory follicular or transformed CD20+ NHL
- Chimeric (long half life)
- ~50% ORR (pivotal trial)
  - most were PRs
  - duration 13+ months
Radioimmununotherapy for NHL

Adapted from Press. Semin Oncol. 1999;26(5 suppl 14):5:58
# Radioimmunotherapy for NHL

<table>
<thead>
<tr>
<th></th>
<th>Bexxar®</th>
<th>Zevalin®</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-emitter</td>
<td>$^{131}$I (half life: 8.01 days)</td>
<td>$^{90}$Y (half life: 2.67 days)</td>
</tr>
<tr>
<td>Anti-CD20 antibody</td>
<td>Tositumomab</td>
<td>Ibritumomab Tiuxetan</td>
</tr>
<tr>
<td>Antibody type</td>
<td>Monoclonal murine</td>
<td>Monoclonal murine</td>
</tr>
<tr>
<td>Pre-dose injection</td>
<td>Unlabeled Tositumomab</td>
<td>Unlabeled Rituximab</td>
</tr>
<tr>
<td>Pre-therapy imaging</td>
<td>Yes (for dosimetry)</td>
<td></td>
</tr>
<tr>
<td>Pre-therapy dose</td>
<td>$^{131}$I-Tositumomab (5 mCi)</td>
<td></td>
</tr>
<tr>
<td>Treatment dose</td>
<td>75 cGy (whole-body)</td>
<td>0.4 mCi/kg (up to 32 mCi)</td>
</tr>
</tbody>
</table>
60-year-old woman with NHL and complete response after \(^{90}\text{Y}\)-Ibritumomab Tiuxetan (Zevalin\textsuperscript{®}) treatment. A) pre-therapy (1 month) \(^{18}\text{F}\) FDG PET shows cervical, axillary, abdominal, pelvic and inguinal lesions (arrowheads); B) \(^{18}\text{F}\) FDG PET after therapy (3 months) is negative for active disease

65-year-old woman with NHL and complete response after \(^{131}\text{I}\)-Tositumomab (Bexxar\textsuperscript{®}) treatment. A) pre-therapy (1 month) \(^{18}\text{F}\) FDG PET shows abdominal lesions (arrowheads); B) \(^{18}\text{F}\) FDG PET after therapy (3 months) is negative for active disease
## Observed Response Rates in Patients Treated with Bexxar® vs. Zevalin®

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Bexxar®</th>
<th>Zevalin®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective responses</td>
<td>24/35 (68.6%)</td>
<td>28/36 (77.8%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>12/35 (34.3%)</td>
<td>15/36 (41.7%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>8/35 (22.8%)</td>
<td>9/36 (25%)</td>
</tr>
<tr>
<td>Mixed response</td>
<td>4/35 (11.4%)</td>
<td>4/36 (11.1%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>6/35 (17.1%)</td>
<td>4/36 (11.1%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>5/35 (14.3%)</td>
<td>4/36 (11.1%)</td>
</tr>
</tbody>
</table>
**Gamma-Ray Radiation**

Parent Nucleus: Cobalt-60  
Daughter Nucleus: Ni-60
<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Physical T½</th>
<th>Principal photon energy (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technetium-99m</td>
<td>6 hr</td>
<td>140</td>
</tr>
<tr>
<td>Iodine-123</td>
<td>13.2 hr</td>
<td>159</td>
</tr>
<tr>
<td>Gallium-67</td>
<td>78.3 hr</td>
<td>93, 185, 300, 395</td>
</tr>
<tr>
<td>Thallium-201</td>
<td>73.1 hr</td>
<td>69-83, 135</td>
</tr>
<tr>
<td>Indium-111</td>
<td>2.8 days</td>
<td>171, 245</td>
</tr>
<tr>
<td>Xenon-133</td>
<td>5.2 days</td>
<td>81</td>
</tr>
</tbody>
</table>
Inside a Gamma Camera
Functions of the Collimator

- Define Field of View
- Eliminate Scattered Photons
Collimator
Photomultiplier Tubes
Functions of the PMT Array

- Determine location of scintillation events
- Convert light to electrical pulse
Modern Cameras: CZT Detectors
Nuclear Medicine studies:

- Bone scintigraphy
- Pulmonary evaluation
- Cardiovascular imaging
- Hepatobiliary and GI scintigraphy
- Endocrine imaging
- Infection localization
- CNS imaging
- Oncology
- Renal imaging
Click Segment to Highlight

Right Upper Lobe
1. Apical
2. Posterior
3. Anterior

Right Medial Lobe
4. Lateral
5. Medial

Right Lower Lobe
6. Superior
7. Medial Basal
8. Posterior Basal
9. Lateral Basal
10. Anterior Basal

Left Upper Lobe
11. Apical Posterior
12. Anterior
13. Superior Lingual
14. Inferior Lingual

Left Lower Lobe
15. Superior
16. Anteromedial Basal
17. Lateral Basal
18. Posterior Basal
## PET Radiopharmaceuticals

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Physical $T_{1/2}$</th>
<th>Positron energy (MeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorine-18</td>
<td>110 min</td>
<td>0.635</td>
</tr>
<tr>
<td>Rubidium-82</td>
<td>1.3 min</td>
<td>3.15</td>
</tr>
<tr>
<td>Carbon-11</td>
<td>20 min</td>
<td>0.96</td>
</tr>
<tr>
<td>Nitrogen-13</td>
<td>10 min</td>
<td>1.19</td>
</tr>
<tr>
<td>Oxygen-15</td>
<td>2 min</td>
<td>1.73</td>
</tr>
</tbody>
</table>
Annihilation Photons Leave at 180°

$\gamma$ (511 keV) $\beta^+ + e^-$ $\gamma$ (511 keV)

$\beta^+$

$^{18}$F FDG
Annihilation Photon Detection

Detector A

$\gamma$ (511 keV)

$\beta^+ + e^-$

$\beta^+$

Detector B

$\gamma$ (511 keV)
Attenuation Correction
• 32 rings of detectors
• 576 crystals per ring (BGO)
• Blocks of 8 x 8 crystals coupled to 4 PMT’s
$^{18}\text{F FDG}$

D–Glucose

2–Fluoro–2–Deoxy–D–Glucose
PLASMA

FDG → Glucose
Transporter

FDG

TISSUE

Hexokinase
Glucose-6-phosphatase

FDG-6-PO₄
Glycolysis

FDG
What Went Wrong?
Penetrating Distances

- Alpha
- Beta
- Gamma and X-rays
- Neutron

Paper - Plastic - Lead - Concrete
✓ Introduction

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  - $\alpha$-radiation
  - $\beta$-radiation
  - $\gamma$-radiation

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✓ Report writing
Clinical Trials in Nuclear Medicine

1. $^{99m}$Tc MDP Bone Scintigraphy, $^{18}$F NaF PET/CT, $^{18}$F FDG PET/CT and Whole Body MRI for Cancer Detection

2. Combined $^{18}$F NaF and $^{18}$F FDG PET/CT for Initial Cancer Staging

3. $^{18}$F NaF PET/CT vs. $^{99m}$Tc MDP Bone Scintigraphy for Detection of Bone Metastases: A Randomized Multi-Center-Trial

4. $^{18}$F FPPRGD$_2$ PET/CT Prediction of Response to Anti-Angiogenesis Therapy in NSCLC, Breast Cancer and GBM

5. $^{64}$Cu-DOTA-Rituximab PET/CT Imaging of NHL Patients

6. $^{18}$F FSPG PET/CT in Oncology Patients
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Definition:

- To give an account
- To write an account
- To make known
- To give a formal statement
- To make a charge
- Loud resounding noise
The report describes the performance of the test

The report interprets the test

The report reflects on the resident or fellow, the attending, the division and the medical center

The report is a permanent record and should be crafted so that it is a pleasure to read after days, weeks, months, or years

The report can be used in court
Use of Words

- **Try to avoid:**
  - “Suggestive of”
  - “Clinical correlation recommended”
  - “Unknown significance”
  - “If clinically indicated”

- **Ambiguity should be reduced/eliminated**
Importance of the Test

➢ To the referring physician
  ✔ Answer first the question asked in the request
  ✔ Decide what is the appropriate test
  ✔ Don’t send back a longer list of questions instead of answers

➢ To the patient
- Identification
- Indication/Clinical history (relevant)
- Comparison/Correlating studies
- Procedure
  - Radiopharmaceutical
  - Dose
  - Route
  - Protocol
- Findings
- Impression
Findings and Interpretation

- Avoid describing everything seen but not giving an interpretation
- Avoid rambling description of findings without a reasonable conclusion
- Avoid language that pushes referring MD into inaction

ACR Standard for Communication in “Standards 2002-2003”:

“Precise diagnosis...wherever possible. Differential diagnosis when appropriate and follow-up or additional studies when appropriate”
Impression

- This is often all that is read
- Start with statement normal or abnormal
- Answer the clinical question asked by referring physician
Good Reports

- Clear
- Concise (brief)
- Complete
- Consistent
- Clinically relevant
- Communication (documented)
Radiologists are understandably cautious and generally fearful of missing lesions, and to be sure, certain serious findings demand follow-up action in many instances.

However, there seems to be a culturally ingrained inclination on the part of radiologists to get more and more imaging, frequently without an appreciation of the implications that such imaging will have on the patient and his or her family and referring physician.

These include economic and psychologic ramifications (e.g., additional expense, inconvenience, fear, risk of complications) and the risk that such imaging might lead to further potentially unnecessary risky and/or costly tests and biopsies.
THANK YOU!

http://nuclearmedicine.stanford.edu

http://mips.stanford.edu