Dosimetry in Radionuclide Therapy

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Food and Drug Administration

- The Food and Drug Administration sets standards for the use of lasers (21CFR) and other non-ionizing radiations, food irradiation, and pharmaceuticals. Medical imaging agents are submitted for approval in:
  - Investigational new drug applications (INDs)
  - New drug applications (NDAs)
  - Biologics license applications (BLAs)
  - Abbreviated NDAs (ANDAs)
  - Supplements to NDAs or BLAs.
• Radiation safety assessment associated with the approval of use of medical imaging agents shall:

  – “...allow a reasonable calculation of the radiation absorbed dose to the whole body and to critical organs upon administration to a human subject ...”

  – At a minimum, ...radiation absorbed dose estimates be provided for all organs and tissues in the standardized anthropomorphic phantoms established in the literature...

  – For diagnostic radiopharmaceuticals...[one should calculate] the effective dose as defined by the International Commission on Radiological Protection (ICRP) in its ICRP Publication 60 (this quantity is not meaningful for therapeutic radiopharmaceuticals)
– the amount of the radiation absorbed dose delivered by internal administration of diagnostic radiopharmaceuticals be calculated by standardized methods [should be provided]...

– the methodology used to assess radiation safety [should] be specified including reference to the body models that were used...

– the mathematical equations used to derive the time activity curves and the radiation absorbed dose estimates [should] be provided along with a full description of assumptions that were made....
– sample calculations and all pertinent assumptions [should] be listed and submitted...
– the reference to the body, organ, or tissue model used in the dosimetry calculations [should] be specified, particularly for new models being tested. If a software program was used to calculate the radiation doses...
– [one should provide]
  • a full description of the code, including official name, version number, and computing platform;
  • a literature citation for the code; and
  • photocopies of the code’s output, preferably showing all of the user input data and model choices.”
• Approval of a new medical imaging agent includes several phases:
  – A preclinical phase, in which studies in an appropriate animal species are carefully planned and executed, to provide a preliminary assessment of the possible radiation doses expected in human subjects.
  – Phase 1 studies of medical imaging agents, which are designed to obtain pharmacokinetic and human safety assessments, based on a single mass administration and escalating mass administrations of the drug or biological product.
Phase 2 studies of medical imaging agents include:

- “refining the agent's clinically useful mass dose and radiation dose ranges or dosage regimen (e.g., bolus administration or infusion) in preparation for phase 3 studies,
- answering outstanding pharmacokinetic and pharmacodynamic questions,
- providing preliminary evidence of efficacy and expanding the safety database,
- optimizing the techniques and timing of image acquisition,
- developing methods and criteria by which images will be evaluated, and
- evaluating other critical questions about the medical imaging agent.”
• *Phase 3 studies* are designed to confirm the principal hypotheses developed in earlier studies, demonstrating the efficacy of the compound and method employed, verify the safety of the use of the medical imaging agent, and validate the necessary instructions for use of the compound and for imaging in the population for which the agent is intended.
Figure 1: 10-Year Trends in Biomedical Research Spending

The figure shows 10-year trends in biomedical research spending as reflected by the NIH budget (Budget of the United States Government, appendix, FY 1993-2003) and by pharmaceutical companies’ research and development (R&D) investment (PAREXEL's Pharmaceutical R&D Statistical Sourcebook 2002/2003).
Figure 2: 10-Year Trends in Major Drug and Biological Product Submissions to FDA

The figure shows the number of submissions of new molecular entities (NMEs) — drugs with a novel chemical structure — and the number of biologics license application (BLA) submissions to FDA over a 10-year period. Similar trends have been observed at regulatory agencies worldwide.
The figure shows one estimate of the total investment required to "launch" (i.e., market) a successful drug in two time periods. Most of the recent cost increases are within the "critical path" development phase, between discovery and launch.

The overall increase between 1995 - 2000 and 2000 - 2002 is estimated to be 55 percent.
Radioactive Drugs: Collect sufficient data from animal or human studies to allow a reasonable calculation of radiation absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.

G. Mills, Soc. Nucl. Med meeting, 2004
Goals for Dosimetry
(characterization dosimetry)

• Estimate radiation exposures to all organs/tissues (MIRDose 3/OLINDA) for a typical individual for the specific radiolabeled drug/biologic

• Provide a “roadmap” of radiation exposures to monitor potential adverse events

• Dosimetry is not intended for prospective or retrospective “dose optimization”

G. Mills, Soc. Nucl. Med meeting, 2004
CARDIOLITE®
Kit for the Preparation of
Technetium Tc99m Sestamibi for Injection

FOR DIAGNOSTIC USE

DESCRIPTION: Each 5 mL vial contains a sterile, non-pyrogenic, lyophilized mixture of:
- Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate—1.0 mg
- Sodium Citrate Dihydrate—2.6 mg
- L-Cysteine Hydrochloride Monohydrate—1.0 mg
- Mannitol—20 mg
- Stannous Chloride, Dihydrate, minimum (SnCl$_2$·2H$_2$O)—0.025 mg
- Stannous Chloride, Dihydrate (SnCl$_2$·2H$_2$O)—0.075 mg
- Tin Chloride (stannous and stannic) Dihydrate, maximum (as SnCl$_2$·2H$_2$O)—0.086 mg

Prior to lyophilization the pH is 5.3 to 5.9. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection. The pH of the reconstituted product is 5.5 (5.0—6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is Tc99m[MIBI]$_6^+$ where MIBI is 2-methoxy isobutyl isonitrile.
PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours.¹ Photons that are useful for detection and imaging studies are listed in Table 1.

<table>
<thead>
<tr>
<th>Radiation</th>
<th>Mean %/</th>
<th>Mean Energy (KeV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma -2</td>
<td>89.07</td>
<td>140.5</td>
</tr>
</tbody>
</table>


EXTERNAL RADIATION

The specific gamma ray constant for Tc99m is 5.4 microcoulombs/Kg-MBq-hr (0.78R/mCi-hr) at 1 cm. The first half value layer is 0.017 cm of Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb is shown in Table 2. ² To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25 cm thickness of Pb will attenuate the radiation emitted by a factor of 1,000.

<table>
<thead>
<tr>
<th>Shield Thickness (Pb) cm</th>
<th>Coefficient of Attenuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.017</td>
<td>0.5</td>
</tr>
<tr>
<td>0.08</td>
<td>$10^{-1}$</td>
</tr>
<tr>
<td>0.16</td>
<td>$10^{-2}$</td>
</tr>
<tr>
<td>0.25</td>
<td>$10^{-3}$</td>
</tr>
<tr>
<td>0.33</td>
<td>$10^{-4}$</td>
</tr>
</tbody>
</table>

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.
<table>
<thead>
<tr>
<th>Organ</th>
<th>2.0 hour void</th>
<th></th>
<th>4.8 hour void</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rads/30 mCi</td>
<td>mGy/1110 MBq</td>
<td>rads/30 mCi</td>
<td>mGy/1110 MBq</td>
</tr>
<tr>
<td>Breasts</td>
<td>0.2</td>
<td>2.0</td>
<td>0.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Gallbladder Wall</td>
<td>2.0</td>
<td>20.0</td>
<td>2.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>3.0</td>
<td>30.0</td>
<td>3.0</td>
<td>30.0</td>
</tr>
<tr>
<td>Upper Large Intestine Wall</td>
<td>5.4</td>
<td>55.5</td>
<td>5.4</td>
<td>55.5</td>
</tr>
<tr>
<td>Lower Large Intestine Wall</td>
<td>3.9</td>
<td>40.0</td>
<td>4.2</td>
<td>41.1</td>
</tr>
<tr>
<td>Stomach Wall</td>
<td>0.6</td>
<td>6.1</td>
<td>0.6</td>
<td>5.8</td>
</tr>
<tr>
<td>Heart Wall</td>
<td>0.5</td>
<td>5.1</td>
<td>0.5</td>
<td>4.9</td>
</tr>
<tr>
<td>Kidneys</td>
<td>2.0</td>
<td>20.0</td>
<td>2.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Liver</td>
<td>0.6</td>
<td>5.8</td>
<td>0.6</td>
<td>5.7</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.3</td>
<td>2.8</td>
<td>0.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Bone Surfaces</td>
<td>0.7</td>
<td>6.8</td>
<td>0.7</td>
<td>6.4</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.7</td>
<td>7.0</td>
<td>0.7</td>
<td>2.4</td>
</tr>
<tr>
<td>Ovaries</td>
<td>1.5</td>
<td>15.5</td>
<td>1.6</td>
<td>15.5</td>
</tr>
<tr>
<td>Testes</td>
<td>0.3</td>
<td>3.4</td>
<td>0.4</td>
<td>3.9</td>
</tr>
<tr>
<td>Red Marrow</td>
<td>0.5</td>
<td>5.1</td>
<td>0.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>2.0</td>
<td>20.0</td>
<td>4.2</td>
<td>41.1</td>
</tr>
<tr>
<td>Total Body</td>
<td>0.5</td>
<td>4.8</td>
<td>0.5</td>
<td>4.8</td>
</tr>
</tbody>
</table>
Patient-Individualized Medicine

• Using a fixed activity or activity/body size gives very different therapeutic benefit to different patients.
• Individual kinetics and body morphologies are highly variable.
Cumulative excretion of Ho-166 DOTMP in twelve subjects (6 ♀, 6 ♂) with multiple myeloma. Breitz et al. J Nucl Med 2006
Individuals with a rapid clearance rate require a higher dose of radiation (in mCi).

Rapid Clearance:
- Treatment dose, mCi:
  - Days: 1
  - 100 mCi
  - 75 cGy

Slow Clearance:
- Treatment dose, mCi:
  - Days: 1
  - 50 mCi
  - 75 cGy

Targeted total body radiation dose 75cGy for patients with platelet counts 150,000/mm³ or 65cGy for patients with platelet counts between 100,000 and 150,000/mm³.


FIGURE 3. Total absorbed dose to bone marrow of 200 patients for a single therapy cycle.

FIGURE 7. Maximum tolerable number of cycles with respect to absorbed doses to bone marrow and kidneys for 200 patients.

Sandstrom et al. JNM 2013:54:33-41
“Treating all nuclear medicine patients with a single, uniform method of activity administration amounts to consciously choosing that these patients be treated with a lower standard of care than patients who receive radiation externally for cancer treatments.”
**Phantom organ masses (g) for the Adult Male**

<table>
<thead>
<tr>
<th><strong>Next Phantom</strong></th>
<th><strong>Previous Phantom</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>16.3</td>
<td>Adrenals</td>
</tr>
<tr>
<td>1420.0</td>
<td>Brain</td>
</tr>
<tr>
<td>351.0</td>
<td>Breasts</td>
</tr>
<tr>
<td>10.5</td>
<td>Gallbladder Wall</td>
</tr>
<tr>
<td>167.0</td>
<td>LLI Wall</td>
</tr>
<tr>
<td>677.0</td>
<td>Small Intestine</td>
</tr>
<tr>
<td>158.0</td>
<td>Stomach Wall</td>
</tr>
<tr>
<td>220.0</td>
<td>ULI Wall</td>
</tr>
<tr>
<td>316.0</td>
<td>Heart Wall</td>
</tr>
<tr>
<td>299.0</td>
<td>Kidneys</td>
</tr>
<tr>
<td>1910.0</td>
<td>Liver</td>
</tr>
<tr>
<td>1000.0</td>
<td>Lungs</td>
</tr>
<tr>
<td>28000.0</td>
<td>Muscle</td>
</tr>
<tr>
<td>8.71</td>
<td>Ovaries</td>
</tr>
<tr>
<td><strong>Alpha Weight Factor</strong></td>
<td><strong>Beta Weight Factor</strong></td>
</tr>
<tr>
<td>5.0</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Multiply all masses by:</strong></td>
<td><strong>Reset organ values</strong></td>
</tr>
</tbody>
</table>

**Modified by user**

Hit <ret> to see changes immediately, or just DONE at end

- Pancreas
- Red Marrow
- Osteogenic Cells
- Skin
- Spleen
- Testes
- Thymus
- Thyroid
- Urinary Bladder Wall
- Uterus
- Fetus
- Placenta
- Total Body
Organ Mass Scaling

• For electrons, the scaling is:

\[ DF_2 = DF_1 \frac{m_1}{m_2} \]

• For photons, the scaling is:

\[
\begin{align*}
\phi_2 &= \phi_1 \left( \frac{m_2}{m_1} \right)^{1/3} \\
\Phi_2 &= \Phi_1 \left( \frac{m_1}{m_2} \right)^{2/3}
\end{align*}
\]
Patient-Specific Modifications

• Traino, DiMartino et al. – adjustment for change in thyroid mass during dose delivery

\[ D_T = \frac{\sigma A_m T}{2m_0} + \frac{\sigma}{k} \left[ m_0 - \left( m_0^2 - \frac{2kA_m}{c} \right)^{\frac{1}{2}} \right] \]
Radioiodine Therapy

• Jonsson and Mattsson, Graves disease, (n=200) (2004) compared theoretical levels of activity that could be given to patients using patient-specific dose calculations and actual practice to a fixed-activity approach.

• “…most of the patients were treated with an unnecessarily high activity, a mean factor of 2.5 times too high and in individual patients up to eight times too high, leading to an unnecessary radiation exposure both for the patient, the family and the public.”
Radioiodine Therapy

• Kobe et al. (2007), Graves disease:
  • 571 subjects, target dose 250 Gy.
  • Relief from hyperthyroidism was achieved in 96% of patients who received more than 200 Gy, even for those with thyroid volumes > 40 mL.
<table>
<thead>
<tr>
<th>Study</th>
<th>Radionuclide</th>
<th>System</th>
<th>Reconstruction</th>
<th>Absolute quantification accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeintl et al., 2010 (18)</td>
<td>$^{99m}$Tc</td>
<td>SPECT/CT</td>
<td>OS-EM, CDR, CT-derived AC, energy window-based SC, PVC</td>
<td>&lt;6.8% error for 0.5- to 16-mL spheres</td>
</tr>
<tr>
<td>Dewaraja et al., 2010 (37)</td>
<td>$^{131}$I</td>
<td>SPECT/CT</td>
<td>OS-EM, CDR, CT-derived AC, energy window-based SC</td>
<td>&lt;17% error for 8- to 95-mL spheres; 31% for 4-mL sphere</td>
</tr>
<tr>
<td>Assie et al., 2010 (23)</td>
<td>$^{111}$In</td>
<td>SPECT and CT separate</td>
<td>OS-EM, CT-derived AC, energy window-based SC, PVC</td>
<td>&lt;20% error for organs and 2- to 32-mL spheres; 48% error for 0.5-mL sphere</td>
</tr>
<tr>
<td>Shcherbinin et al., 2008 (49)</td>
<td>$^{99m}$Tc, $^{111}$In, $^{123}$I, $^{131}$I</td>
<td>SPECT/CT</td>
<td>OS-EM, CDR, CT-derived AC, analytic scatter modeling</td>
<td>3%–5% error for 32-mL bottles</td>
</tr>
<tr>
<td>Minarik et al., 2008 (95)</td>
<td>$^{90}$Y</td>
<td>SPECT/CT</td>
<td>OS-EM, CDR, CT-derived AC, ESSE</td>
<td>&lt;11% error for liver and 100-mL sphere</td>
</tr>
<tr>
<td>Willowson et al., 2008 (19)</td>
<td>$^{99m}$Tc</td>
<td>SPECT/CT</td>
<td>OS-EM, CT-derived AC, transmission-dependent SC, PVC</td>
<td>&lt;4% error for liver and cardiac chambers</td>
</tr>
<tr>
<td>de Wit et al., 2006 (59)</td>
<td>$^{166}$Ho</td>
<td>SPECT</td>
<td>OS-EM, CDR, $^{153}$Gd transmission source-derived AC, Monte Carlo scatter modeling</td>
<td>16% average error for 220-mL bottles</td>
</tr>
<tr>
<td>Du et al., 2006 (62)</td>
<td>$^{123}$I</td>
<td>SPECT/CT</td>
<td>OS-EM, CDR, CT-derived AC, ESSE, PVC</td>
<td>&lt;2% error for putamen and caudate regions of brain phantom</td>
</tr>
<tr>
<td>He et al, 2005 (52)</td>
<td>$^{111}$In</td>
<td>SPECT/CT</td>
<td>OS-EM, CDR, CT-derived AC, ESSE, PVC</td>
<td>&lt;12% error for organs and 8- to 23-mL spheres</td>
</tr>
<tr>
<td>Koral et al., 2005 (50)</td>
<td>$^{131}$I</td>
<td>SPECT and CT separate</td>
<td>OS-EM, CDR, CT-derived AC, energy window-based SC, PVC</td>
<td>&lt;7% average error for 100-mL sphere</td>
</tr>
</tbody>
</table>

AC = attenuation correction; SC = scatter correction.
FIGURE 4. One slice of RIT patient CT image, SPECT image, and corresponding dose-rate map.

FIGURE 3. (A) Summed coronal $^{124}$I PET image slices obtained on day of $^{124}$I administration (day 0) and on subsequent 2 days are depicted using same intensity level. Cross-hairs show plane of intersection for corresponding transverse slices through tumor 2, shown immediately below coronal images. (B) Image of absorbed dose distribution in tumor 2, magnified to highlight spatial distribution of absorbed dose within this tumor. Color-coded isodose contours are superimposed as follows: yellow = 75%, red = 50%, blue = 25%, and green = 10% of maximum absorbed dose to tumor (400 Gy). Three different foci of enhanced absorbed dose are observed and designated 1–3 as shown. Kolbert et al. J Nucl Med Vol. 45 No. 8 1366-1372.
Strigari et al.: Tumor control probability in systemic radiotherapy
Medical Physics, Vol. 33, No. 6, June 2006

Fig. 7. Calculated dose distribution after administration of $^{131}$I-MIBG superimposed on axial CT scan.

Fig. 8. Differential dose volume histogram for normal liver and metastasis of the case presented in this study.
Figure 1. Data for Patient A with CTV, PTV, spinal cord and kidneys outlined. a) CT image of corresponding slice; b) XBT isodose plot showing dose levels in Gy; c) XBT dose distribution; d) XBT BED distribution; e) TRT dose distribution; f) TRT BED distribution; g) Combined BED distribution; h) Equivalent external beam isodose plot for the combined therapy showing dose levels in Gy.
STRATOS Dosimetry Solution is an advanced research software package for 3-dimensional dose calculation in nuclear medicine, allowing you to calculate and visualize patient-specific dose maps for targeted therapeutic radionuclide agents based on antibodies or peptides. STRATOS Dosimetry Solution optimally supports research focussed on image-based dosimetry using SPECT/CT and PET/CT data.
**FIGURE 2.** Axial (A), coronal (B), and sagittal (C) views of isodose curves superimposed on patient-specific voxel phantom obtained for evaluation E3 with an injected activity of 1 GBq. LL = left lung; RL = right lung.
FIGURE 2. 3D dosimetry results for patient 1. (A) Transverse slice of 3D dose map fused with CT. (B) Isodose curves superimposed on transverse slice of CT. Blue curve = isodose 1% of maximum dose; green curve = isodose 5% of maximum dose; yellow curve = isodose 10% of maximum dose; orange curve = isodose 30% of maximum dose; red curve = isodose 50% of maximum dose.

FIGURE 3. DVH in TL for each patient. Patients 6 and 7 had 2 tumor sites.
Figure IV.2: Modification of NURBS surface by moving control points. (a) NURBS representation of a plane with controls points (*) aligned on the surface. (b) Surface with shaped altered by translating two of the center control points in the z-axis.

Figure IV.11: Overlap of lungs at base before deforming structures to match patient (a) and after modification (b). The white area is the left diaphragm that is voxelized as body and replaced by other organs including spleen (red), stomach and heart (pink).
Figure V.1: Fused SPECT/CT images for (a) Patient 1 and (b) Patient 2 with matching 3D dose maps overlaid on CT for (c) Patient 1 and (d) Patient 2. The dose maps are displayed in units of Gy.
Do Calculated Doses Predict Biological Effects?
Shen et al. JNM 43 No. 9 1245-1253, 2002
Figure 6. Tumor dose-response characterized by Pauwels et al.\textsuperscript{48} with $^{90}$Y-DOTATOC. Reprinted with permission of the Society of Nuclear Medicine.

$R^3 = 0.4962$

Figure 7. Plot from Barone et al.\textsuperscript{51} showing prediction of kidney toxicity from patient-individualized dose calculations in the use of $^{90}$Y (DOTATOC). (Larger and smaller dots on the plot were used to indicate the number of treatment cycles received by different patients.) Reprinted with permission of the Society of Nuclear Medicine.

$R = 0.93$
$p < 0.0001$
Dose rates and renal toxicity

**TABLE 2**
Comparisons of Absorbed Doses and Dose Rates to Kidneys with Radionuclide Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>$N_{frac}$</th>
<th>$A$ (GBq)</th>
<th>$D$ (Gy)</th>
<th>$R_0$ (Gy/h)</th>
<th>RE</th>
<th>BED (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{90}$Y-DOTA-octreotide</td>
<td>3</td>
<td>13.3</td>
<td>27</td>
<td>0.15</td>
<td>1.2</td>
<td>32</td>
</tr>
<tr>
<td>$^{111}$In-DTPA-octreotide</td>
<td>8</td>
<td>83</td>
<td>34</td>
<td>0.07</td>
<td>1.1</td>
<td>37</td>
</tr>
<tr>
<td>$^{177}$Lu-DOTA-octreotate</td>
<td>4</td>
<td>29.6</td>
<td>26</td>
<td>0.04</td>
<td>1.1</td>
<td>29</td>
</tr>
<tr>
<td>$^{166}$Ho-DOTMP</td>
<td>1</td>
<td>167</td>
<td>7.5–15</td>
<td>4.2–8.4</td>
<td>2.4–3.7</td>
<td>18.0–55.5</td>
</tr>
<tr>
<td>External-beam irradiation</td>
<td>16</td>
<td>NA</td>
<td>23</td>
<td>NA</td>
<td>1.6</td>
<td>37</td>
</tr>
<tr>
<td>Total-body irradiation</td>
<td>6</td>
<td>NA</td>
<td>12</td>
<td>NA</td>
<td>1.8</td>
<td>22</td>
</tr>
</tbody>
</table>
% CLR loss versus BED (open circles/dashed line) or TDF (solid circles/solid line) for the combined Barone and Bodei data sets. (A) All patients. (B) All patients without risk factors. (C) All patients with risk factors.
SPECT/CT based 3D Tumor Dosimetry

Day 0 post-tracer

Day 2 post-therapy

Day 8 post-therapy

Tumor time-activity

Iso-dose contours
PFS Stratified by Tumor Dose

- Longer PFS for mean tumor absorbed dose >200 cGy
- Median PFS
  - 13.6 mo (>200 cGy)
  - 1.9 mo (<200 cGy)

p<0.0001
Bystander Effects

*In Vitro Studies*

- Medium transfer:
  - Irradiated cells secreted one or more molecules into the culture medium that is capable of killing cells when that medium is transferred onto unirradiated cells.
  - Depends on cell number and time of irradiation - as soon as 30 min post irradiation, up to 60 h after irradiation.
  - Doses as low as 0.25 mGy and is not significantly increased up to doses of 10 Gy.
Bystander Effects

*In Vitro Studies*

• Microbeam Irradiation
• Irradiated human fibroblasts - cells of one population were lightly stained with cyto-orange, a cytoplasmic vital dye, while cells of another population were lightly stained blue with a nuclear vital dye.
• The two cell populations were mixed and allowed to attach to the culture dish, and the computer controlling the accelerator was programmed to irradiate only blue-stained cells with 10 alpha particles directed at the centroid of the nucleus.
• The cells were fixed and stained 48 h later, at which time micronuclei and chromosome bridges were visible in a proportion of the nonhit (i.e., orange-stained) cells!
Bystander Effects

*In Vivo Studies*

- Irradiation of the lung base in rats, marked increase in the frequency of micronuclei in the shielded lung apex.

- However, radiation of the lung apex did not result in an increase in the chromosome damage in the shielded lung base.

- This suggests that a factor was transferred from the exposed portion of the lung to the shielded part and that this transfer has direction from the base to the apex of the lung.
Bystander Effects

• In another experiment, exposure of the left lung resulted in a marked increase in micronuclei in the unexposed right lung.

• Experiments suggest that bystander effects are limited to the organ irradiated, and have been demonstrated primarily in experiments with alpha particles.

• These results challenge the traditional notion of the relationship of dose and effects.
- Cells do not respond to radiation, tissues do.

- Cells are signaling one another in reaction to radiation damage.
Philosophical Point

- When is a Gy a Gy? Almost never!
- 1 Gy of gamma whole body...
- 1 Gy of alpha?
- 1 Gy of beta or gamma in therapy?

• Medium transfer bystander effects? Dose is zero!
• 0 $\otimes$ anything = 0
Bystander effect shown by Hall\textsuperscript{20} in V79 cells in which all cells or 10% of cells were struck by 1-16 alpha particles.
Sawant et al. Radiation Research, 156, 177–180 (2001)
In Vivo Bystander Effects: $^{123}$IUDr and $^{125}$IUDr

Human LS174T adenocarcinoma (s.c.)

- **Live**
- **Dead**
- $^{123}$IUDr-labeled
- $^{125}$IUDr-labeled

**123I** → sBE (Stimulatory Bystander Effect)

**Control**

**125I** → iBE (Inhibitory Bystander Effect)

* Freeze-defrost 3 times