Advisory Committee on the Medical Uses of Isotopes

June 25, 2009

Overview

- Dr. William Van Decker
  Perspectives on the Clinical Benefit of Diagnostic Nuclear Medicine
- Mr. Steve Mattmuller
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- Dr. Bruce Thomadsen
  Cesium-137 Chloride Irradiators
- Dr. Darrell Fisher
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- Dr. James Welsh
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National Council on Radiation Protection and Measurements Report 160: Perspectives on the Clinical Benefit of Diagnostic Nuclear Medicine

William A. Van Decker, MD

Advisory Committee on the Medical Uses of Isotopes

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NCRP Report 160: Ionizing Radiation Exposure of Population 2006

- Compared to the National Council on Radiation Protection and Measurements (NCRP) Report 100 in 1980/82 – about 1.7 times increase
- On average, 50% ubiquitous background, 48% medical diagnostics
- Medical diagnostic (about 3 millisievert) increased 5-6 times from 1980/82
- Increase appears due to increased care utilization of Computed Tomography (CT) scanning and diagnostic nuclear medicine

NCRP Report 160: Ionizing Radiation Exposure of Population 2006

- Attributed average exposure does not account for the fact that diagnostics may be correctly and disproportionately performed on the elderly and those with more serious medical problems.
- The report does not “attempt to quantify the associated health risks nor specify the actions that should be taken in light of these latest data”.
- The report does not include data on the enormous benefit of medical imaging to patient care nor on the intense efforts of the provider community to practice As Low As Reasonably Achievable (ALARA).

HEALTHCARE OUTCOMES 1980 - 2005

	1980	2005	Change
Life Expectancy (years)	70.0 (male)	75.4 (male)	+8%
	77.7 (female)	80.7 (female)	+4%
Death Rates (Age adjusted, per 100,000)			
• Myocardial Ischemia	345.2	144.4	-58%
• Total Cardiac Deaths	412.1	211.1	-48%
• Malignant Neoplasms	207.9	183.8	-12%
Cancer Incidence Rates (per 100,000)	475.4	442.7	-7%

Clinical Benefit of Diagnostic Nuclear Medicine – Nuclear Cardiology Example

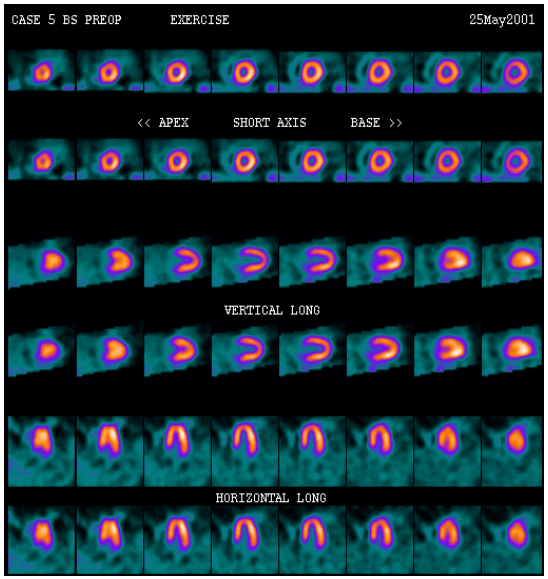
- Myocardial perfusion imaging is the most reliable, reproducible measure of physiologic flow perfusion.
- Images are obtained rest and then compared to changes in flow perfusion during stress (treadmill or medication).
- Test serves as a gatekeeper for higher risk downstream procedures (e.g. invasive angiography).
- Test stratifies for appropriate revascularization by cardiac stents and open heart bypass surgery

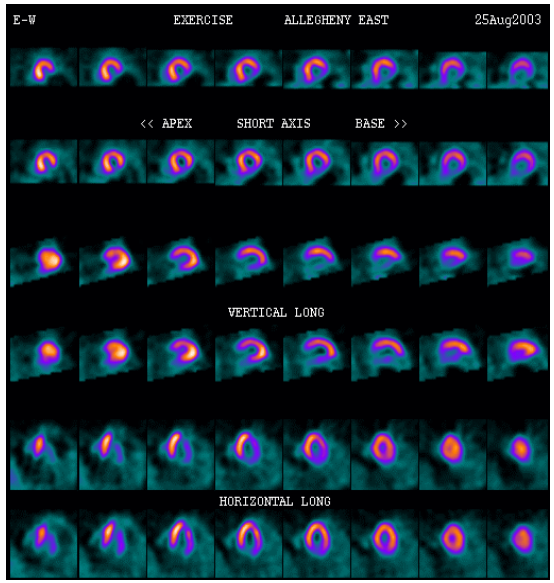
(Shaw, etal, Circulation 2007;116:2628)

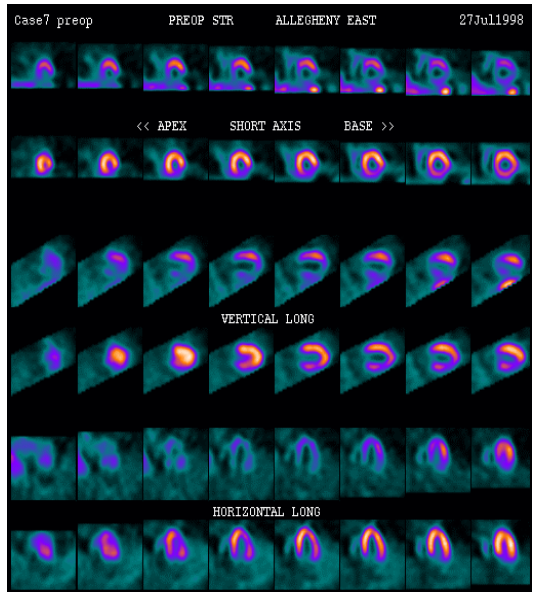
Clinical Benefit of Diagnostic Nuclear Medicine – Nuclear Cardiology Example

- Regardless of coronary anatomy, patients with “normal scans” often do relatively well with medical therapy
- Scans which are very abnormal are predictors of poorer outcomes

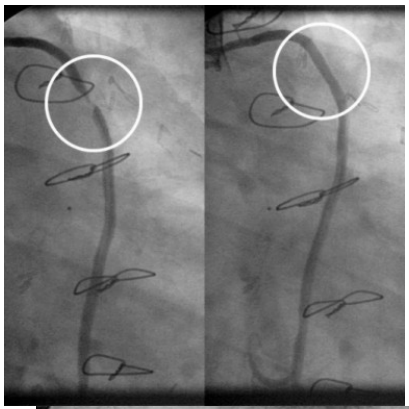
Nuclear Stress Testing
Exercise vs. Resting Images

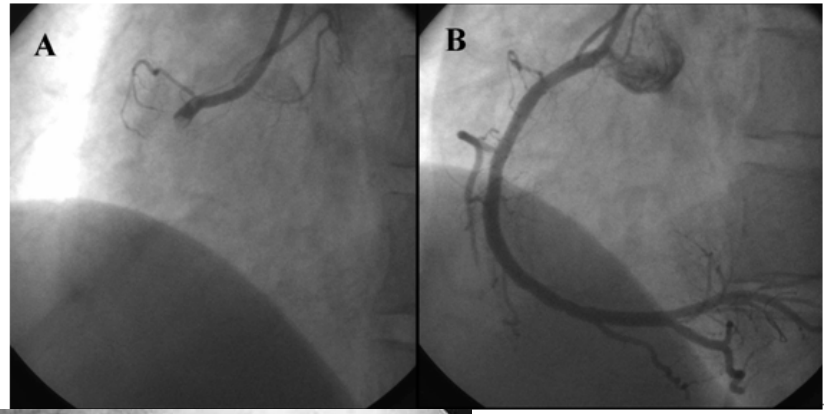






Correlated Coronary Angiographic Findings Before and After Therapy





Provider ALARA Response

- Appropriateness Criteria

  (Hendel, etal, JACC 46:8, 155-1605, 2005)

  (Updated, Hendel, etal, Circulation 2009:119)
- Imaging Acquisition Guidelines

  (Depuey, etal, Journal of Nuclear Cardiology, Jan/Feb 2001)(Updated, Depuey, etal, Journal of Nuclear Cardiology, Nov/Dec 2007)
- New Hardware

  (Slomka, etal, Journal of Nuclear Cardiology 2009, 16:255-76)
- Lab Accreditations

Conclusion

- NCRP Report 160 appreciated and noted by medical community.
- Clinical benefits of imaging are great and driven by physician-patient discussion.
- Broad medical community already involved in ALARA activities.
- The Advisory Committee on the Medical Uses of Isotopes recommends that the U.S. Nuclear Regulatory Commission retain the current policy.

Acronyms

ALARA	As Low As Reasonably Achievable
CT	Computed Tomography
NCRP	National Council on Radiation Protection and Measurements

Medical Isotope Shortages Molybdenum-99

Steve Mattmuller, MS, RPh, BCNP
Advisory Committee on the Medical Uses of Isotopes

June 25, 2009

Overview

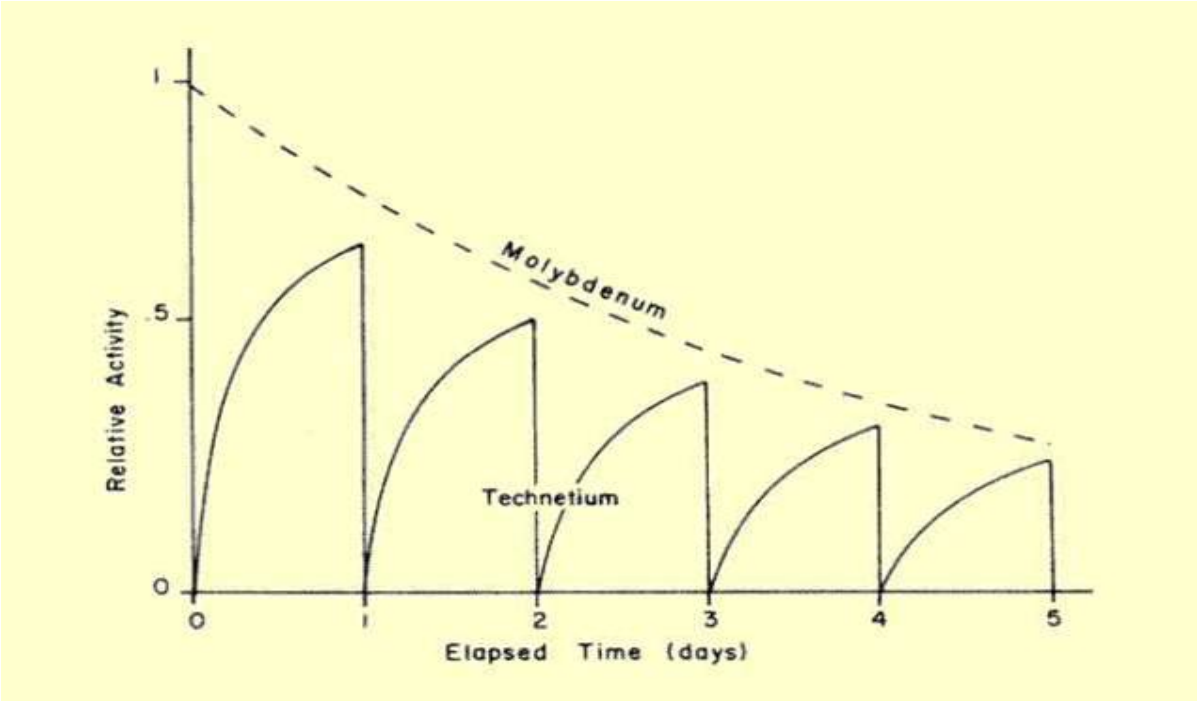
- Need for Molybdenum-99 (Mo-99)
- Causes of shortage
- Effects of shortage
- Solutions

Need: Mo-99 for Patient Care

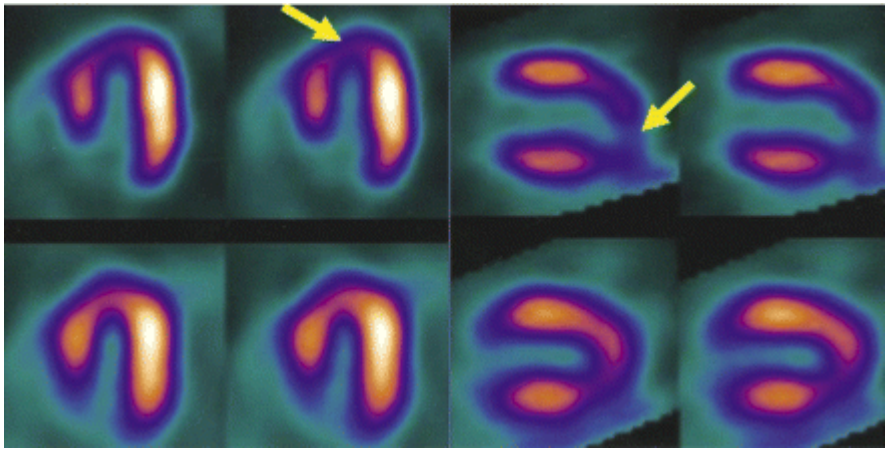
More than 34,000 Nuclear Medicine (NM) procedures each day in the United States depend on Mo-99.

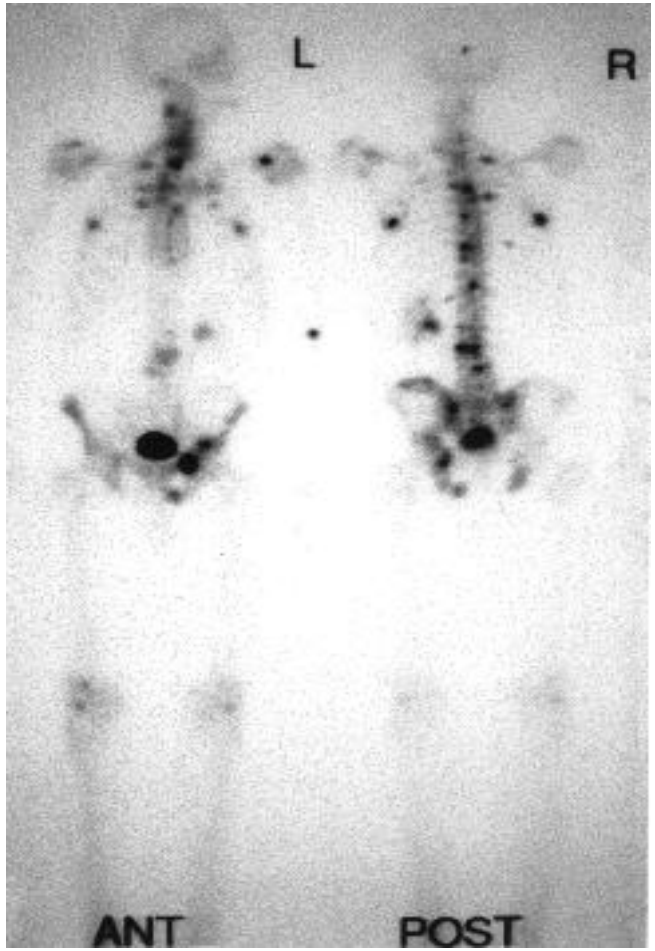
Need: Mo-99 every week

Decay of Mo-99 over time and decreasing yields of Technetium-99m (Tc-99m)



Need: Patient Care





Causes: Fragile Supply Chain

Uranium-235 Targets Irradiated

Targets Processed, Purify Mo-99

Generator Produced

Tc-99m Doses to NM Department

Causes: Fragile Supply Chain

- National Research Universal (NRU) Reactor Canadian, 52 years old
  Responsible for shortage started in 5/2009, due to leak in the aluminum tank liner

- High Flux Reactor (HFR), Dutch, 47 years old
  Responsible for shortage started in 8/2008, due to corrosion problem in cooling system

- Both reactors use highly enriched uranium (HEU) targets

Effects: Diminished Patient Care

Since January 2007, ~~five~~ SIX periods of supply disruptions.
Latest started 5/2009

Society of Nuclear Medicine (SNM) Survey

	2008*	2009**
Postponed a procedure:	49%	60%
Cancelled a procedure:	19%	32%
Changed a procedure:	25%	44%
Percent fewer procedures:	18%	TBD

*final results published 11/2008 based on 479 respondents
**preliminary results based on 1900 respondents

Effects: Diminished Patient Care

Referring physicians are frustrated by these interruptions and some have chosen alternate procedures.

- inferior in accuracy
- usually more expensive
- may have a higher radiation dose

Solution: New Mo-99 Suppliers

Missouri University Research Reactor (MURR) Needs a Mo-99 processing facility

Cost of 40-50 million dollars.

Babcock & Wilcox; partner with Covidien

Different reactor design

Aqueous Homogenous Reactor (AHR).

BUT Both are 5-7 years away!

Mo-99 for Patient Care

Two patients at Kettering, who, along with others, benefit from the 34,000 procedures performed each day with Mo-99.

Acronyms

AHR	Aqueous Homogenous Reactor
HEU	Highly Enriched Uranium
HFR	High Flux Reactor
Mo-99	Molybdenum Mo99
MURR	Missouri University Research Reactor
NM	Nuclear Medicine
NRU	National Research Universal
SNM	Society of Nuclear Medicine
Tc-99m	Technetium-99m

U.S.NRC
UNITED STATES NUCLEAR REGULATORY COMMISSION
Protecting People and the Environment

Cesium-137 Chloride Irradiators

Bruce Thomadsen, PhD
Advisory Committee on the Medical Uses of Isotopes

June 25, 2009

Purpose of Subcommittee

- The National Research Council's report suggesting elimination of Cesium-137 Chloride (^{137}CsCl) units made several assumptions that seemed questionable to the Advisory Committee on the Medical Uses of Isotopes (ACMUI).

- The ACMUI created a subcommittee to investigate the need for sources, alternatives and security:
  - Ms. Debbie Gilley
  - Mr. Ralph Lieto
  - Dr. Orhan Suleiman
  - Dr. Bruce Thomadsen (chair)
  - Dr. Richard Vetter
  - Dr. James Welsh

Need for Irradiators

Blood Irradiation

- 15% - 40% of transfusion blood irradiated – mostly for oncology/hematology patients.
- Original report assumed 10%.
- Without access to irradiated blood, patients may die.

Animal Irradiation

- Suppress immune system for transplant or stem cell work. (Chemical suppression leaves residues.)
- Cancer treatment experiments.

Alternatives to ^{137}CsCl Irradiators

- The alternatives are conventional x-ray units or linear accelerators.
- Both have been and are used for blood, animal and material irradiation.

X-ray Units: Blood Irradiation

- The only U.S. Food and Drug Administration (FDA)-approved unit costs $250,000 with $33,000/year for the service contract, not $180,000 and $10,000/year, as stated in the National Research Council report.
- Extra expenses include: replacement tubes, calibration, and quality management.
  - With 48,000 blood-product units per x-ray tube, a 50-unit per day operation would require tube replacement every 3.7 years.
- Throughput is lower for the x-ray unit.

X-ray Units: Animal Irradiation

- Few units provide beams $\geq$ 200 kilovolts (kV), which limits use with animals due to lack of penetration and Relative Biological Effectiveness.
- Prices range from $146,000 - $250,000 plus the service contract ~10%/year.
- Low dose rate hard for anesthesia.

Medical Linear Accelerators

- If the radiotherapy department's accelerator is used, time available for blood or animal irradiation becomes a problem.
- If not using a radiotherapy department's accelerator, price becomes a problem
  - Example: $1.5 million to start, plus ~$150,000/year service.

Security Enhancements since the National Research Council Report

- The security of the users through required background checks.
- The security of the facility following directives of the Nuclear Regulatory Commission (sometimes at great costs to the facility).
- The security of the units through a program of the Department of Energy and Department of Homeland Security.

Alternative Forms for ^{137}Cs

- Possibly fused glass or other chemical forms.
- Manufacturers have no interest in making these expensive changes.
- No American manufacturer of the sources.

Summary

- Irradiation facilities are essential for irradiation of blood and in research.
- Forced replacement of ^{137}CsCl units will result in facilities stopping irradiations due to expense.
- There are problems and/or large expenses associated with x-ray animal irradiation.
- Enhanced security for the ^{137}CsCl units mitigates much of the concern.
- Without a domestic source for ^{137}Cs, newer and safer forms are unlikely.

Acronyms

- ^{137}CsCl – Cesium-137 Chloride
- ACMUI – Advisory Committee on the Medical Uses of Isotopes
- FDA – Food and Drug Administration
- kV – kilovolt

Cobalt-60 for Stereotactic "Gamma Knife®" Radiosurgery Systems

Darrell R. Fisher, PhD
Advisory Committee on the Medical Uses of Isotopes

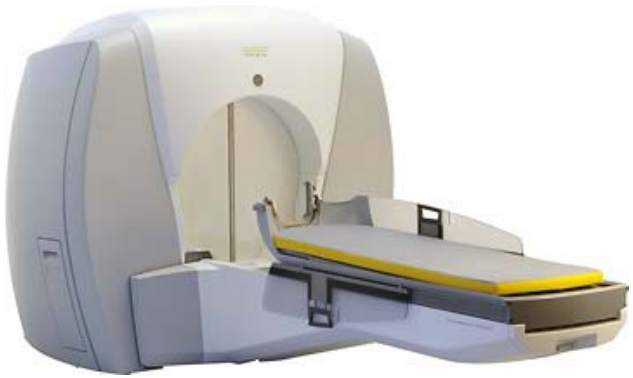
June 25, 2009

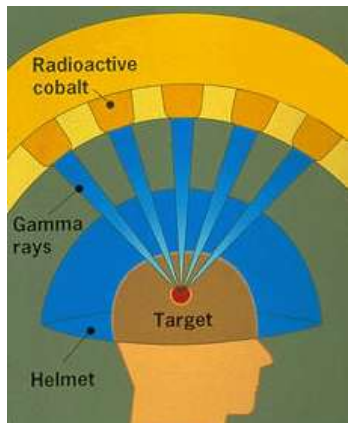
Overview

- Need
- Supply
- Transportation
- Security
- Other

Importance to medical practice

- Gamma Knife® stereotactic radiosurgery represents the standard of care for treating brain tumors using Cobalt-60 (^{60}Co) sources while minimizing dose to healthy brain tissues





Images Courtesy of Elekta

Cobalt-60 supply

- Produced by International Isotopes, Incorporated at the Advanced Test Reactor (ATR), Idaho Falls
- High specific-activity ^{60}Co sources are used for medical therapy and cargo imaging
  - Two to three-year production cycles
- Low specific-activity ^{60}Co sources are used in radiation sterilizers
- Supply and availability are currently adequate to meet international needs---as long as the ATR continues to operate

The major ^{60}Co issues

- Availability of Department of Transportation (DOT) and Nuclear Regulatory Commission (NRC)-approved transportation containers and casks
- Security initiatives implemented with little or no industry input
- Arduous and costly import/export licensing requirements for U.S. licensees
- Excessive state transportation permit fees (in some cases $5,000 per shipment)

Shipping containers

- DOT withdrew approval of all specification packages on October 1, 2008 after a 4-year transition period.
- The availability of new replacement package designs has not kept up with the need to make shipments
- Approval of a new replacement package design can take approximately 18 – 24 months and can cost up to $750,000
- NRC is working with industry and has approved the use of discontinued specification package designs on a case-by case basis based on demonstrated need.
- The use of foreign package designs can be revalidated by DOT for import/export shipments, whereas package designed for domestic shipments must have a specific NRC or DOT approval.

Shipping containers (continued)

- The container revalidation process is burdensome due to the need to interact with foreign regulatory bodies.
- DOT/NRC should streamline the approval process for packages approved by other countries under international standards (UK, Canada, France, Australia)

Security initiatives

- Industry supports the concept of source security
- Fundamentally, source-tracking is a good idea, but industry reports that the current NRC system is not working well in practice
  - Under current requirements, the 200 sources shipped to replace aging ^{60}Co sources for a Gamma Knife® have to be tracked individually, rather than as a unit
- If Category 3 sources are also tracked, the current system will not be able to handle the large number of individual sources

Import/export licensing

- Import authorizations should be included in the Possession and Use license to reduce the financial burden on industry
- Export license fees and expirations should be based on the U.S. licensee and not the importing country (a fee uniformity issue)
- Identification of specific facilities on the import/export licensee requires U.S. companies to list all possible customers---complicating the review and authorization process

Other

State Fee Regulation

- Some states require excessive Radioactive Materials in Quantities of Concern (RAMQC) shipment permits to transport ^{60}Co
  - Shippers and carriers often bypass these states whenever possible, which increases transportation costs and in-route times
- Unlike the DOT, the NRC does not have preemption authority over the states for transportation

Recovery & Recycling

- The recovery and recycling program element works well

Summary

- ^{60}Co availability is good
- Approved container shortages, complex transportation regulations, and costly import/export licensing requirements have made it difficult and costly to supply cancer therapy devices with ^{60}Co

Acronyms

- ^{60}Co – Cobalt-60
- ATR – Advanced Test Reactor
- DOT – Department of Transportation
- NRC – Nuclear Regulatory Commission

Multiple Medical Events Involving Permanent Prostate Brachytherapy within the Department of Veterans Affairs Medical System

James S. Welsh, MS, MD
Advisory Committee on the Medical Uses of Isotopes

June 25, 2009

Synopsis

- U.S. Nuclear Regulatory Commission (NRC) received reports from Veterans Affairs (VA) Medical Center, Philadelphia of multiple medical events involving permanent prostate iodine-125 seed implants
- NRC inspected 13 medical facilities (of the same permittee) to assess the brachytherapy programs
- Numerous medical events were identified at multiple locations
- Prostate brachytherapy at the Philadelphia VA has been suspended along with 3 other programs
  - (Cincinnati, Jackson, and Washington, D.C.)
- Corrective actions taken
- The VA will not restart its suspended cancer treatment programs until these commitments have been met

Additional Actions Taken
(beyond the corrective actions)

- For patient care concerns at one facility, the licensee:
  - Performed verification Computed Tomography (CT) scans on all patients that received prostate implants
  - Re–evaluated the dose delivered to the treatment area
  - Re–implanted some patients at a different facility

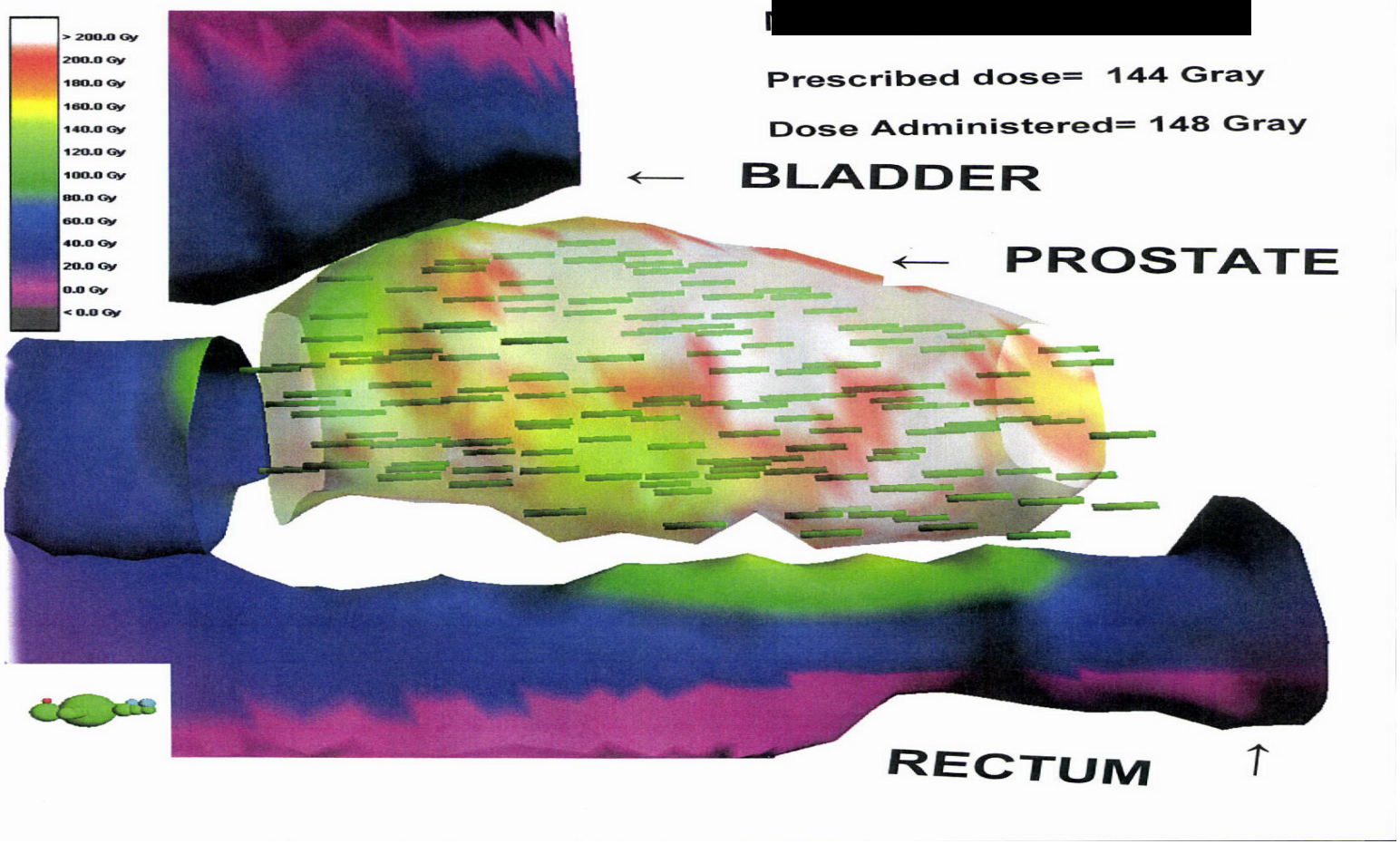
[redacted]

VariSeed: 3D View Report [Page 1]

VAMC Rad Onc · 1 · 1 · 11/18/2008 10:52:16 AM

	Study: **POST PLAN** Variation: **Default** Images: **37**	Source: **I-125 (IAI-125A) [NIST 00]** Comment: Sources: **152** Anisotropy: **Function (Line Model)** Source Activity: **0.394 U [0.310 mCi]** Total Activity: **59.888 U [47.156 mCi]**
Procedure Date: **7/2/2008**	Prescription Dose: **144.0 Gy**	

[redacted]



Caveats and Pitfalls cont.

- Are the criteria for medical events too low?
  - Are there too many “medical events” being reported that are not truly of clinical significance?

- Were the medical event criteria used by the VA medically appropriate?
  - Phase I: ± 20% of prescribed dose
  - Phase II: Rectum - dose to 1.33 cubic centimeter (cc) volume exceeds 150% of pre-treatment plan dose
  - External Tissue - 5 or more seeds located beyond 1 centimeter (cm) exterior, and inferior, to the surface of prostate
  - Bladder - 3 or more seeds located in bladder wall

Caveats and Pitfalls cont.

- NRC staff used the current criteria for determining those events that met the medical event definition
  - There is a proposed rule on new criteria for permanent implant brachytherapy
  - Proposed rule has been postponed to allow consideration of the impacts of medical events like those under investigation

- Normal practice is to have a post-implant CT scans to verify seed placement.
  - CTs were done; however, the software program was not functioning properly
  - Comparisons could not be really made

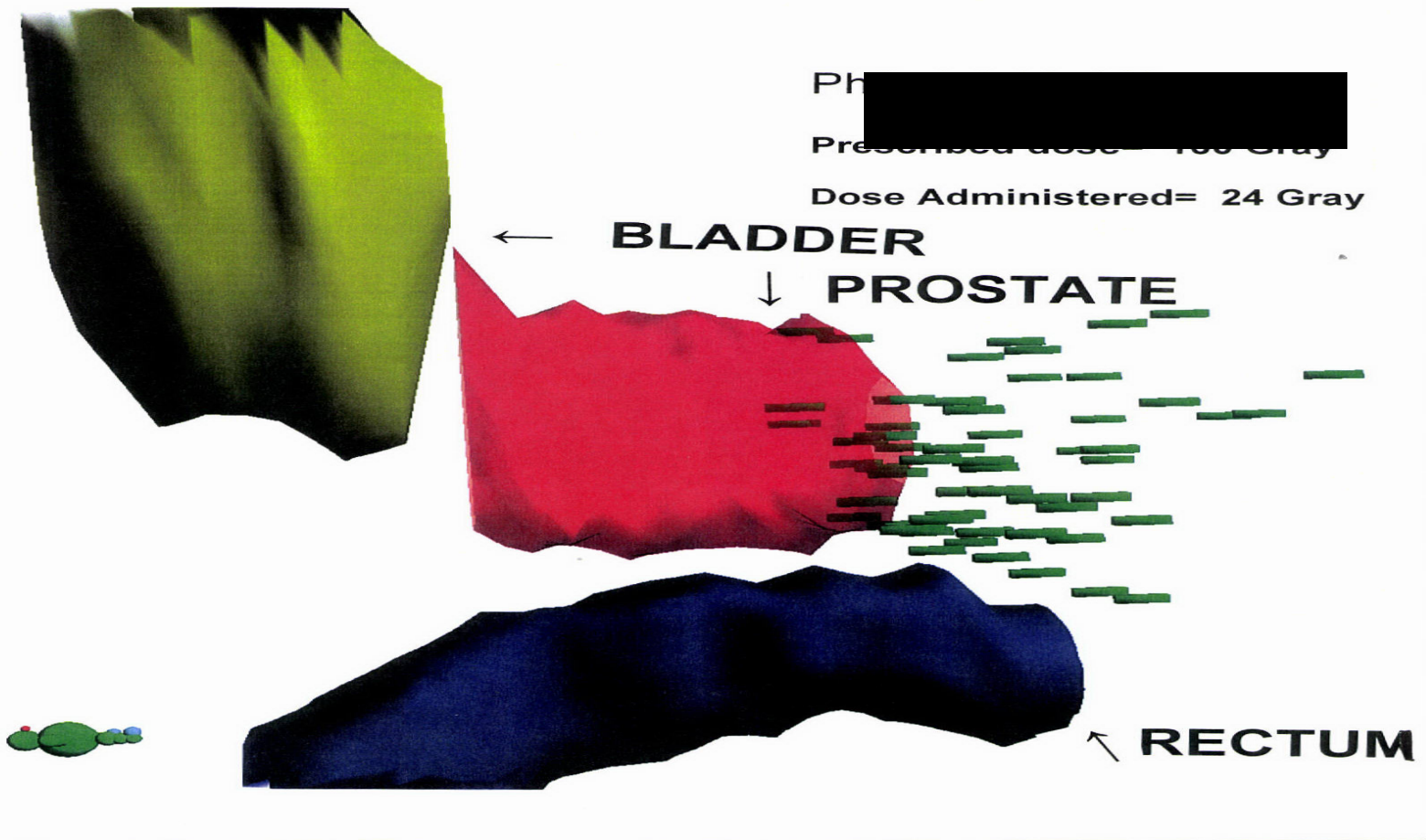
Caveats and Pitfalls cont.

- Can a Radiation Safety Officer or Medical Physicist really determine if an implant looks right?
  - "Instruction to the Radiation Safety Officer (RSO) and quality management staff to immediately report all deviations that exceed ten percent of the prescribed dose or dose fraction"
- Can we really determine this late if a medical event truly happened?
  - "…for patient care, the licensee:
    1) Performed verification CT scans on all patients that received prostate implants between 2002 and May 2008;
    2) Re-evaluated the dose delivered to the treatment area;
    3) Re-implanted brachytherapy seeds at a different VA location for at least four individuals.."

VariSe[redacted]1]

VariSeed 7.0 (Build 1955) [redacted] 9/9/2008 4:54:55 PM

Study: followupEval_062408 Variation: Default # Scans: 54	Isotope: I-125 (2301) [NIST 00] # Seeds: 58 Prescription Dose: 160.000 Anisotropic Correction: Fac	U/mCi: 1.270 U/Seed: 0.483 mCi/Seed: 0.380



Caveats and Pitfalls

- It is known that the prostate may shrink following brachytherapy seed implantation
- ACMUI is concerned about determination of medical events based on CTs performed approximately a year post-implantation

The Future

- The goal is to prevent such events from happening again
  - “Instituted a medical center peer-review system for radiation oncology services and post-treatment evaluations”
  - ACMUI supports the idea of performing peer reviews for permanent implant brachytherapy procedures
- Should an Authorized Medical Physicist participate in the procedure?
- Should post-implant dosimetry be mandatory?
- ACMUI is awaiting further information from NRC before making any formal recommendations

Acknowledgements & Acronyms

Special Thanks to:

Patricia Pelke, Chief, Materials Licensing Branch, Region III; Darrel Wiedeman, Senior Health Physicist, Region III and Cassandra Frazier, Senior Health Physicist, Region III for their presentation at the recent ACMUI meeting and for many of these slides.

ACMUI – Advisory Committee on the Medical Uses of Isotopes

CT – Computed Tomography

NRC – U.S. Nuclear Regulatory Commission

RSO – Radiation Safety Officer

VA – Veterans Affairs

Summary

- ACMUI recommends maintaining the current NRC policy for patient exposures and notes improvements in longevity with regard to cardiovascular disease.
- There is a crisis with medical isotope shortages, and the situation is worsening.
- ACMUI believes $^{137}CsCl$ is critical for patient care, and there is no practical substitute.
- The supply and availability of ^{60}Co is adequate; however, transportation issues exist.
- ACMUI is following the issues regarding the medical events at the Veteran's Affairs facilities and will advise the NRC staff of any policy implications.