TG-167: Clinical recommendations for innovative brachytherapy devices and applications

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Disclosures
Towards disclosing real or apparent conflicts of interest:

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The other authors (Dezarn, Heaton, Meigooni, Siebert, and Venselaar) have no real or apparent conflicts of interest.
Learning Objectives

1. Understand necessary considerations for clinical implementation (including calibrations, dose calculations, and radiobiological aspects) to comply with existing societal dosimetric prerequisites for sources in routine clinical use.

2. Evaluate risks/benefits from regulatory/safety perspectives.

3. Identify necessary resources and create a plan for clinical introduction of innovative brachytherapy device or applications.

AAPM/GEC-ESTRO TG-167: Innovative BT

Medical Physics

Guidelines by the AAPM and GEC-ESTRO on the use of innovative brachytherapy devices and applications: Report of Task Group 167

It is critical that physicists be actively involved in the quantitative evaluation of the dosimetric characteristics of an innovative BT device or application. The physicist’s role (along with physician colleagues) in this process is highlighted for innovative products or applications and includes evaluation of: 1) dosimetric considerations for clinical implementation (including calibrations, dosimetry, and radiobiology) to comply with existing societal dosimetric prerequisites for sources in routine clinical use, 2) risks and benefits from a regulatory and safety perspective, and 3) resource assessment and preparedness.

<table>
<thead>
<tr>
<th>S</th>
<th>Name</th>
<th>Year introduced</th>
<th>Primary calibration standard in the U.S.</th>
<th>Primary calibration standard in Europe</th>
<th>ADCL calibration availability</th>
<th>Ability to calculate patient dose distributions</th>
<th>Clinical experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.A</td>
<td>HQR ¹²⁵S sources/afterloaders</td>
<td>1964</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>extensive</td>
</tr>
<tr>
<td>4.B</td>
<td>LDR ¹⁵³Gm sources</td>
<td>1960s</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>moderate</td>
</tr>
<tr>
<td>4.C</td>
<td>LDR ¹³⁷Cs and ¹⁵³Gm sources</td>
<td>1990s</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>extensive</td>
</tr>
<tr>
<td>4.D</td>
<td>LDR ¹⁵³Cs sources</td>
<td>2004</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>extensive</td>
</tr>
<tr>
<td>4.E</td>
<td>Elongated sources</td>
<td>1960s</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>minimal</td>
</tr>
<tr>
<td>4.F</td>
<td>Intermediate energy sources</td>
<td>1967</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>extensive</td>
</tr>
<tr>
<td>4.G</td>
<td>Electronic brachytherapy</td>
<td>1992</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>extensive</td>
</tr>
<tr>
<td>4.H</td>
<td>Intravascular brachytherapy</td>
<td>1990s</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>extensive</td>
</tr>
<tr>
<td>4.I</td>
<td>Neutron-emitting ²³⁵Cf sources</td>
<td>1965</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>LDR moderate</td>
</tr>
<tr>
<td>4.J</td>
<td>¹⁹²Ir microsources</td>
<td>1960s</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>moderate</td>
</tr>
<tr>
<td>4.K</td>
<td>Collimated applicators</td>
<td>1990s</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>yes</td>
<td>moderate</td>
</tr>
<tr>
<td>4.L</td>
<td>Breast balloon applicators</td>
<td>1990s</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>yes</td>
<td>extensive</td>
</tr>
<tr>
<td>4.M</td>
<td>Brain balloon applicators</td>
<td>2001</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>no</td>
<td>moderate</td>
</tr>
<tr>
<td>4.N</td>
<td>Non-COMS eye plaques</td>
<td>1990s</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>yes</td>
<td>moderate</td>
</tr>
</tbody>
</table>

Nath et al., Med Phys 43, 3178-3206 (2016)
# Outline

1. Regulatory requirements and environment
2. Calibration requirements
3. Dosimetric requirements
4. Radiobiological considerations
5. Team organization and training
6. Practical examples
Regulatory Requirements and Environment

- perform/document safety/efficacy analysis
  consider ISO 2919 (U.S. DOT special form)

- prefer sources on NSSDR of NRC
  (National Sealed Source and Device Registry)
  if not, institutional RSC should perform NSSDR safety analysis

- perform human-use research on clinical trial
  trial/procedures review/approval by institutional RSC+IRB

- TG-167 describes components of clinical trial

- < 5% total dose from radio-impurities

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1. Regulatory requirements and environment
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Calibration Requirements

- determine absolute dose-rate at ref. position
- evaluate source strength ($S_K$ or RAKR)
- measurement traceable to calibration lab
- primary calibration: NIST, ADCL, or NMI (or DI)
- validate vendor value with measured result
- develop research-cal std when no other choice

AAPM Report 98: Low-Energy Calibrations

*Medical Physics*

3rd party brachytherapy source calibrations and physicist responsibilities: Report of the AAPM Low Energy Brachytherapy Source Calibration WG

This document presents the findings on the responsibilities of the institutional medical physicist and clarifies existing AAPM recommendations on the assay of brachytherapy sources.

Responsibility for the performance and attestation of source assays rests with the institutional medical physicist, who must use calibration equipment appropriate for each source type used at the institution. Such equipment and calibration procedures shall ensure secondary traceability to a national standard.

For each multi-source implant, 10% of the sources or 10 sources (whichever is greater) are to be assayed. Procedures for presterilized source packaging are outlined. The mean source strength of the assayed sources must agree with the manufacturer's stated strength to within 3%, or action must be taken to resolve the difference. The AAPM leaves it to the discretion of the institutional medical physicist whether the manufacturer's or institutional physicist's measured value should be used in performing dosimetry calculations.

Third party assays do not absolve the institutional physicist from the responsibility to perform the institutional measurement and attest to the strength of the implanted sources.

Calibration Requirements

Number to Assay

TABLE I. Quantities of brachytherapy sources to be assayed by the end-user physicist.

<table>
<thead>
<tr>
<th>Source form</th>
<th>Number to be assayed^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>All loose sources, nonsterile</td>
<td>≥10% of total or 10 seeds, whichever is larger.</td>
</tr>
<tr>
<td>Nonsterile cartridges</td>
<td>≥10% of total via whole cartridge assay or via single sources.</td>
</tr>
<tr>
<td>Mixture of nonsterile loose sources and sterile assemblies</td>
<td>Loose sources amounting to ≥10% of the total order or ten seeds, whichever is larger, ≥10% of assemblies via sterile well chamber inserts quantitative image analysis. Alternatively, order and assay nonsterile loose seeds equal to 5% of the total or five seeds, whichever is fewer.</td>
</tr>
<tr>
<td>Sterile source assemblies</td>
<td></td>
</tr>
<tr>
<td>Strands</td>
<td>≥10% of total or two strands, whichever is larger, using single-seed calibration coefficient (see Ref. 15). Alternatively, order and assay nonstranded loose seeds equal to 5% of the total or five seeds, whichever is fewer.</td>
</tr>
</tbody>
</table>

^aEach source-strength grouping in an order should be sampled.
If the number of sources in a strength group is <10, the entire group should be assayed.

Actions to Take

TABLE II. Actions to be taken by the physicist at the end-using institution based on sample size assayed and relative difference, ΔSx, found between the manufacturer’s source strength certificate and the assay by the physicist at the using institution.^b

<table>
<thead>
<tr>
<th>Sample size for assay of sources</th>
<th>ΔSx</th>
<th>Action by end-user medical physicist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual source, as part of an order of ≥10 sources</td>
<td>ΔSx ≤6%</td>
<td>Nothing further. Consult with the radiation oncologist regarding use of the outlier source.</td>
</tr>
<tr>
<td></td>
<td>ΔSx &gt;6%</td>
<td>Nothing further.</td>
</tr>
<tr>
<td>≥10% but &lt;100% of order, or batch measurements of individual sterile strands, cartridges or preloaded needles</td>
<td>ΔSx ≤3%</td>
<td>Investigate source of discrepancy or increase the sample size. Consult with manufacturer to resolve differences or increase the sample size. For assays performed in the operating room, consult with the radiation oncologist regarding whether to use the measured source strength or average with manufacturer’s value.</td>
</tr>
<tr>
<td></td>
<td>5% ≥ΔSx &gt;3%</td>
<td>Nothing further.</td>
</tr>
<tr>
<td></td>
<td>ΔSx &gt;5%</td>
<td>Nothing further.</td>
</tr>
<tr>
<td>100% of order, or batch measurements of each and every individual sterile strand, cartridge or preloaded needle</td>
<td>ΔSx ≤3%</td>
<td>Investigate source of discrepancy. Consult with manufacturer to resolve differences. For assays performed in operating room, consult with radiation oncologist regarding consequences of proceeding with the implant using measured source strength.</td>
</tr>
<tr>
<td></td>
<td>5% ≥ΔSx &gt;3%</td>
<td>Nothing further.</td>
</tr>
<tr>
<td></td>
<td>ΔSx &gt;5%</td>
<td>Nothing further.</td>
</tr>
</tbody>
</table>

^aAssay results obtained at sites other than the end-user institution should not replace the source strength value on the manufacturer’s certificate. If the difference is >5%, consult with the radiation oncologist regarding whether to use the measured source strength or average with manufacturer’s value.
^bFor orders consisting of < ten sources, the action threshold is ΔSx >5% for individual sources.
Dosimetric Requirements

- only air-kerma strength \( (S_K) \) is traceable to a calibration standards laboratory (i.e., NIST)
- \( S_K \) defined \textit{in vacuo}, no air attenuation/scatter
- \( S_K \) defined on transverse-plane for \( E_\gamma > \delta \)
  - \( \delta \) threshold dependent on calibration protocol
- mg Ra, mgRaEq, mCi (apparent activity), Bq \textbf{are not traceable quantities}
- obsolete units: mg Ra, mgRaEq, mCi, Bq

Outline

1. Regulatory requirements and environment
2. Calibration requirements
3. Dosimetric requirements
4. Radiobiological considerations
5. Team organization and training
6. Practical examples
Dosimetric Requirements

- well characterized dose distribution
dosimetry investigators or robust in-house analysis

- reference parameters used in TPS
(TG-43 dose calculation formalism)
preference for societal consensus datasets

- validate/document source or applicator compatibility and workflow with CT, TPS, etc

- establish RTP standards: common expectations
treatment planning goals and constraints
uniform inputs/outputs for consistent high-quality results

AAPM TG-43U1 Report: Low-Energy BT

Medical Physics
Update of AAPM Task Group No. 43 Report:
A revised AAPM protocol for brachytherapy dose calculations

Since publication of the TG-43 protocol in 1995, significant advances have taken place in the field of permanent source implantation and brachytherapy dosimetry. To accommodate these advances, the AAPM deemed it necessary to update this protocol for the following reasons:

(a) eliminate minor inconsistencies and omissions in the original TG-43 formalism and its implementation.

(b) incorporate subsequent AAPM recommendations, addressing requirements for acquisition of dosimetry data as well as clinical implementation. These recommendations, e.g., elimination of $A_{app}$ (see Appendix E) and description of minimum standards for dosimetric characterization of low-energy photon-emitting brachytherapy sources, needed to be consolidated in one convenient document.

(c) critically reassess published brachytherapy dosimetry data for the $^{125}$I and $^{103}$Pd source models introduced both prior and subsequent to publication of the TG-43 protocol in 1995, and to recommend consensus datasets where appropriate.

(d) develop guidelines for determination of reference-quality dose distributions by experimental and Monte Carlo methods, and promote consistency in derivation of parameters used in TG-43 formalism.

Medical Physics

Dose calculation for photon-emitting brachytherapy sources with average energy higher than 50 keV: Report of the AAPM and ESTRO

Purpose: Recommendations on dose calculations for high-energy (>50 keV) sources are presented, including physical characteristics of specific $^{192}$Ir, $^{137}$Cs, and $^{60}$Co source models.

Methods: This report includes applications of the TG-43U1 formalism to high-energy sources with particular attention to phantom size effects, interpolation accuracy dependence on dose calculation grid size, and dosimetry parameter dependence on source active length.

Results: Consensus datasets are provided, with discussion on uncertainty analyses.

<table>
<thead>
<tr>
<th></th>
<th>$^{192}$Ir</th>
<th>$^{137}$Cs</th>
<th>$^{60}$Co</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>73.81 days</td>
<td>30.07 yr</td>
<td>5.27 yr</td>
</tr>
<tr>
<td>Type of disintegration</td>
<td>$\beta^-$ (95.1%), EC (4.9%)</td>
<td>$\beta^-$ (100%)</td>
<td>$\beta^-$ (100%)</td>
</tr>
<tr>
<td>Maximum x-ray energy (keV)</td>
<td>78.6</td>
<td>37.5</td>
<td>8.3</td>
</tr>
<tr>
<td>Gamma energy-range (keV)</td>
<td>110.4-1378.2</td>
<td>661.6</td>
<td>1173.2-1332.5</td>
</tr>
<tr>
<td>Mean x-ray and gamma energy (keV)</td>
<td>350.0</td>
<td>613.0</td>
<td>1252.9</td>
</tr>
<tr>
<td>Maximum $\beta^-$ ray energies (keV)</td>
<td>81.7 (0.103%)</td>
<td>514.0 (94.4%)</td>
<td>318.2 (99.88%)</td>
</tr>
<tr>
<td></td>
<td>258.7 (5.6%)</td>
<td>1175.6 (5.6%)</td>
<td>1491.4 (0.12%)</td>
</tr>
<tr>
<td>Mean $\beta^-$ ray energy (keV)</td>
<td>675.1 (61.9%)</td>
<td>188.4 (5.6%)</td>
<td>96.5 (0.12%)</td>
</tr>
</tbody>
</table>


Brachytherapy Dose Calculation Geometry

reference position $P(r_0, \theta_0)$

$r_0 = 1$ cm

$\theta_0 = 90^\circ$

Outline

1. Regulatory requirements and environment
2. Calibration requirements
3. Dosimetric requirements
4. Radiobiological considerations
5. Team organization and training
6. Practical examples
Radiobiological Considerations

- evaluate linear energy transfer (LET)
- evaluate relative biological effectiveness (RBE)
- utilize the linear-quadratic (LQ) model
- derive EQD2 for EBRT comparisons
- acceptable range of doses and dose-rates

Outline

1. Regulatory requirements and environment
2. Calibration requirements
3. Dosimetric requirements
4. Radiobiological considerations
5. Team organization and training
6. Practical examples
Team Organization and Training

• evaluate whether clinic is ready to safely introduce a new BT modality
• define clinic team, defined qualifications
• vendor-specific training for new modality
  FDA requires training (case proctoring) for their approval
• advantages of offsite and onsite training
• set local standards to evaluate quality care
• require/document periodic retraining

Outline

1. Regulatory requirements and environment
2. Calibration requirements
3. Dosimetric requirements
4. Radiobiological considerations
5. Team organization and training
6. Practical examples
§4.A. HDR $^{192}$Ir sources and afterloaders

1. Regulatory requirements and environment
   • well established

2. Calibration requirements
   • well established with ADCLs

3. Dosimetric requirements
   • well established
   • scatter importance

4. Radiobiological considerations
   • established in the 1990s

§4.B. HDR $^{60}$Co sources and afterloaders

1. Regulatory requirements and environment
   • recently established (K142986)

2. Calibration requirements
   • in process with ADCLs

3. Dosimetric requirements
   • established for some models (Ralston/FlexiSource/SagiNova)
   • scatter importance

4. Radiobiological considerations
   • similar to HDR $^{192}$Ir
§4.C. LDR $^{125}\text{I}$ and $^{103}\text{Pd}$ seeds

1. Regulatory requirements and environment
   • well established

2. Calibration requirements
   • NIST WAFAC + ADCLs

3. Dosimetric requirements
   • well established
   • sensitive to tissue composition

4. Radiobiological considerations
   • not typically addressed

§4.D. LDR $^{131}\text{Cs}$ seeds

1. Regulatory requirements and environment
   • well established

2. Calibration requirements
   • NIST WAFAC + ADCLs

3. Dosimetric requirements
   • well established
   • less tissue composition sensitivity (c.f. $^{103}\text{Pd}$ & $^{125}\text{I}$)

4. Radiobiological considerations
   • 9.7 day half-life
§4.E. Elongated LDR $^{192}$Ir and $^{103}$Pd sources

1. Regulatory requirements and environment
   • well established

2. Calibration requirements
   • need special chamber insert

3. Dosimetric requirements
   • dose superposition assumption

4. Radiobiological considerations
   • based on radionuclide

§4.F. Intermediate energy photon emitters

1. Regulatory requirements and environment
   • well established

2. Calibration requirements
   • no NIST traceability
   • no ADCL calibrations

3. Dosimetric requirements
   • scatter:attenuation
   • manufacturing consistency

4. Radiobiological considerations
   • assumptions from other radionuclides
§4.G. Electronic brachytherapy sources

1. Regulatory requirements and environment
   • easier than radionuclide-based BT

2. Calibration requirements
   • need standardization

3. Dosimetric requirements
   • Xoft (TG-43 formalism)
   • Intrabeam (radiance)
   • esteya (hand calc)

4. Radiobiological considerations
   • not typically addressed

§4.H. Intravascular brachytherapy sources

1. Regulatory requirements and environment
   • PMA, multi-disciplinary

2. Calibration requirements
   • NIST traceability

3. Dosimetric requirements
   • beta dosimetry
   • cylindrical formalism
   • no image-guided RTP

4. Radiobiological considerations
   • assumptions from HDR
§4.I. Neutron emitting $^{252}$Cf sources

1. Regulatory requirements and environment
   • PMA and special shielding

2. Calibration requirements
   • NIST traceability (NBS-1)
   • no ADCL calibrations

3. Dosimetric requirements
   • mixed-radiation field ($\gamma+n$)
   • custom TPS necessary

4. Radiobiological considerations
   • complicated

\[ D_T = D_N + D_G = M_1 (1 + k_M) \frac{N_A A_{WALL}}{f_t} d_i \frac{1}{K_T} \frac{1}{1 + \delta} \]

$D_{T-\text{eq}} = \text{RBE}_{\text{CXT}} D_{\text{CXT}} + \text{RBE}_{\text{CF-\gamma}} D_{\gamma}$

§4.J. $^{90}$Y microspheres

1. Regulatory requirements and environment
   • off-label, multi-disciplinary

2. Calibration requirements
   • difficult beta calibrations
   • NIST-traceable dose calibrator setting

3. Dosimetric requirements
   • infeasible pre-treatment RTP
   • need 3D dosimetry research

4. Radiobiological considerations
   • need patient-specific biokinetic models
§4.K. Collimated applicators and sources

1. Regulatory requirements and environment
   • well established

2. Calibration requirements
   • need NIST traceability
   • many possibilities

3. Dosimetric requirements
   • need image-guided RTP
   • not TG-43 compatible

4. Radiobiological considerations
   • similar to HDR $^{192}\text{Ir}$

§4.L. Intracavitary breast balloon applicators

1. Regulatory requirements and environment
   • well established

2. Calibration requirements
   • well established with ADCLs

3. Dosimetric requirements
   • image-guided RTP
   • TG-43 formalism
   • scatter importance

4. Radiobiological considerations
   • 14-year standardized fraction
### §4.M. Intracavitary brain balloon applicators

1. Regulatory requirements and environment  
   - established, multidisciplinary

2. Calibration requirements  
   - need NIST traceability

3. Dosimetric requirements  
   - need image-guided RTP  
   - determine dose-to-brain  
   - not TG-43 compatible

4. Radiobiological considerations  
   - temporary LDR

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### §4.N. Non-COMS eye plaques

1. Regulatory requirements and environment  
   - no FDA 510(k), multidisciplinary

2. Calibration requirements  
   - individual seeds  
   - beta calibrations

3. Dosimetric requirements  
   - Plaque Simulator®  
   - TG-43 hybrid technique

4. Radiobiological considerations  
   - MDR domain
Summary

* TG-167 covers investigational BT sources and applications
  a) regulatory requirements and environment
  b) team organization and training
  c) calibration requirements
  d) dosimetric requirements
  e) radiobiological considerations

* guidelines issued for AAPM + GEC-ESTRO physicist members, BT source vendors/manufacturers, and regulatory agencies

* practical examples \((n=14)\) are examined