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

Mark J. Rivard, Ph.D., FAAPM
Tufts University School of Medicine
Boston, Massachusetts

on behalf of the TG-167 writing team:

Ravi Nath, Mark Rivard, Larry DeWerd
Bill Dezarn, Tom Heaton, Geoff Ibbott
Ali Meigooni, Zoubir Ouhib, Tom Rusch
Frank-André Siebert, Jack Venselaar

Disclosures

Towards disclosing real or apparent conflicts of interest:

Nath serves as a research consultant to Theragenics, Corp.

Rivard served as a research consultant to CivaTech Oncology, Inc. and is a minor shareholder of Advanced Radiation Therapy, LLC.

DeWerd is principally employed by the University of Wisconsin Medical Radiation Research Center, an Accredited Dosimetry Calibration Laboratory.

Ibbott is Director of the University of Texas M.D. Anderson Cancer Center Accredited Dosimetry Calibration Laboratory.

Ouhib is on the speaker bureaus for Elekta, Inc. and Varian Medical Systems, Inc. and also serves as a consultant to Theragenics, Corp.

Rusch is a consultant and shareholder for Xoft, Inc., a subsidiary of iCAD, Inc., which develops and manufactures the Axxent® electronic brachytherapy system.

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.

§	Name	Year introduced	Primary calibration standard in the U.S.	Primary calibration standard in Europe	ADCL calibration availability	Ability to calculate patient dose distributions	Clinical experience
4.A	HDR ^{192}Ir sources/afterloaders	1964	no	yes	yes	yes	extensive
4.B	HDR ^{60}Co sources	1960s	no	yes	no	yes	moderate
4.C	LDR ^{125}I and ^{103}Pd sources	1990s	yes	yes	yes	yes	extensive
4.D	LDR ^{131}Cs sources	2004	yes	no	yes	yes	extensive
4.E	Elongated sources	1960s	yes	yes	yes	no	^{103}Pd minimal ^{192}Ir extensive
4.F	Intermediate energy sources	1987	no	yes	no	yes	minimal
4.G	Electronic brachytherapy	1992	yes	no	yes	yes	extensive
4.H	Intravascular brachytherapy	1990s	yes	no	yes	yes	extensive
4.I	Neutron-emitting ^{252}Cf sources	1965	yes	no	no	no	LDR moderate HDR minimal
4.J	^{90}Y microspheres	1980s	no	yes	no	no	moderate
4.K	Collimated applicators	1990s	N/A	N/A	N/A	yes	moderate
4.L	Breast balloon applicators	1990s	N/A	N/A	N/A	Yes	extensive
4.M	Brain balloon applicators	2001	N/A	N/A	N/A	no	moderate
4.N	Non-COMS eye plaques	1990s	N/A	N/A	N/A	yes	moderate

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

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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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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

Calibration Requirements

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.

Butler et al., *Med Phys* 35, 3860-3865 (2008)

Calibration Requirements

Number to Assay

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

Source form	Number to be assayed[a]
All loose sources, nonsterile	⩾10% of total or 10 seeds, whichever is larger.
Nonsterile cartridges	⩾10% of total via whole cartridge assay or via single sources.
Mixture of nonsterile loose sources and sterile assemblies	Loose sources amounting to ⩾10% of the total order or ten seeds, whichever is larger. ⩾10% of assemblies via sterile well chamber inserts
Sterile source assemblies	quantitative image analysis. Alternatively, order and assay nonsterile loose seeds equal to 5% of the total or five seeds, whichever is fewer.
Strands	⩾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.

[a]Each 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.

Butler et al., *Med Phys* 35, 3860-3865 (2008)

Calibration Requirements

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, ΔS_K, found between the manufacturer's source strength certificate and the assay by the physicist at the using institution.[a]

Sample size for assay of sources	ΔS_K	Action by end-user medical physicist
Individual source as part of an order of ⩾10 sources[b]	$\Delta S_K \leqslant 6\%$	Nothing further.
	$\Delta S_K > 6\%$	Consult with the radiation oncologist regarding use of the outlier source: Dependent on the radionuclide, intended target, source packaging, and the availability of extra sources.
⩾10% but <100% of order, or batch measurements of individual sterile strands, cartridges or preloaded needles	$\Delta S_K \leqslant 3\%$	Nothing further.
	$5\% \geqslant \Delta S_K > 3\%$	Investigate source of discrepancy or increase the sample size.
	$\Delta S_K > 5\%$	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.
100% of order, or batch measurements of each and every individual sterile strand, cartridge or preloaded needle	$\Delta S_K \leqslant 3\%$	Nothing further.
	$5\% \geqslant \Delta S_K > 3\%$	Investigate source of discrepancy.
	$\Delta S_K > 5\%$	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.

[a]Assay results obtained at sites other than the end-user institution should not replace the source strength value on the manufacturer's certificate. The source strength value used in planning may be either that stated on the manufacturer's certificate or the value determined by institutional medical physicist when the difference is ⩾5%.
[b]For orders consisting of < ten sources, the action threshold is $\Delta S_K > 5\%$ for individual sources.

Butler et al., *Med Phys* 35, 3860-3865 (2008)

Dosimetric Requirements

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

Outline

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.

Rivard et al., *Med Phys* 31, 633-674 (2004)

AAPM/GEC-ESTRO Rpt 229: High-Energy BT

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 applies 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 I. Physical properties of radionuclides considered in this report. Data have been taken from the NNDC (Ref. 20). Mean photon energy values are calculated with a cut-off of $\delta = 10$ keV.

	^{192}Ir	^{137}Cs	^{60}Co
Half-life	73.81 days	30.07 yr	5.27 yr
Type of disintegration	β^- (95.1%), EC (4.9%)	β^- (100%)	β^- (100%)
Maximum x-ray energy (keV)	78.6	37.5	8.3
Gamma energy-range (keV)	110.4–1378.2	661.6	1173.2–1332.5
Mean x-ray and gamma energy (keV)	350.0	613.0	1252.9
Maximum β^- ray energies (keV)	81.7 (0.103%) 258.7 (5.6%) 538.8 (41.43%) 675.1 (48.0%)	514.0 (94.4%) 1175.6 (5.6%)	318.2 (99.88%) 1491.4 (0.12%)
Mean β^- ray energy (keV)	180.7	188.4	96.5

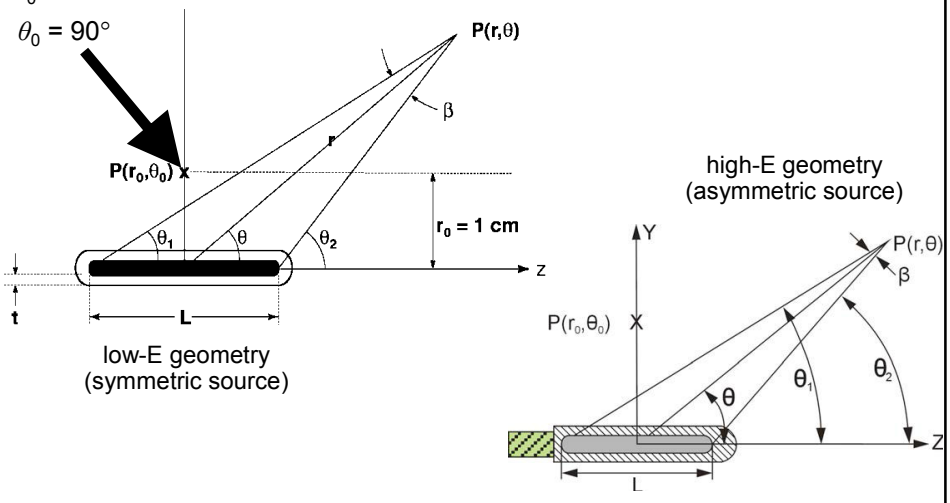
Perez-Calatayud et al., *Med Phys* 39, 2904-2929 (2012)

Brachytherapy Dose Calculation Geometry

reference position $P(r_0, \theta_0)$

r_0 = 1 cm

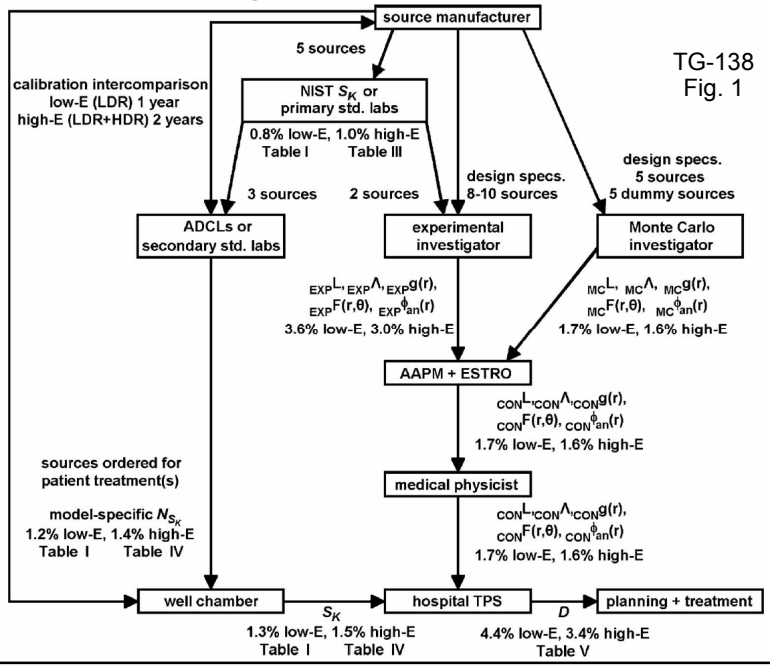
θ_0 = 90°



Rivard et al., *Med Phys* 31, 633-674 (2004)

Perez-Calatayud et al., *Med Phys* 39, 2904-2929 (2012)

Dosimetry Parameter Data Trail



TG-138
Fig. 1

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

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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

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1. Regulatory requirements and environment
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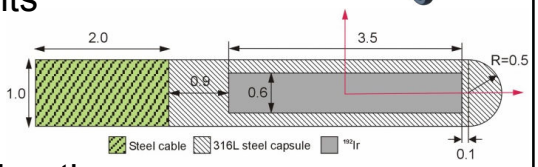
§4.A. HDR ^{192}Ir sources and afterloaders

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)

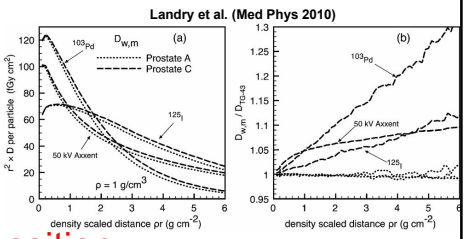
SagiNova®
Eckert & Ziegler

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}I and ^{103}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



TG-137 (full report)

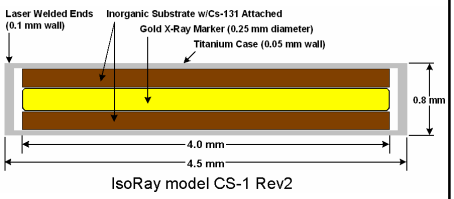
Table 5. Examples of radiobiological indices for uniform dose distributions.

Indices	Radionuclide		
	^{125}I	^{103}Pd	^{131}Cs
Dose (Gy)	145.0	125.0	120.0
BED (Gy)	101.7	112.7	115.7
TCP (%)	79.0	95.5	97.1
T_{eff} (day)	236.2	94.1	61.0

Calculated with: $\alpha = 0.15$ Gy^{-1}, $\beta = 0.05$ Gy^{-2}, $\alpha/\beta = 3.0$ Gy, $T_p = 42$ days, repair half-life of 0.27 hour, and $N_0 = 10^6$.

§4.D. LDR ^{131}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}Pd & ^{125}I)
4. Radiobiological considerations
   - 9.7 day half-life



IsoRay model CS-1 Rev2

TG-137 (full report)

Table 5. Examples of radiobiological indices for uniform dose distributions.

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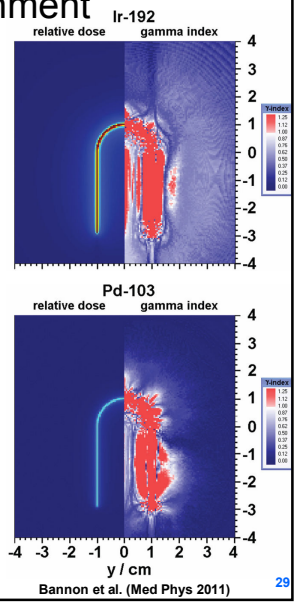
§4.E. Elongated LDR ^{192}Ir and ^{103}Pd sources

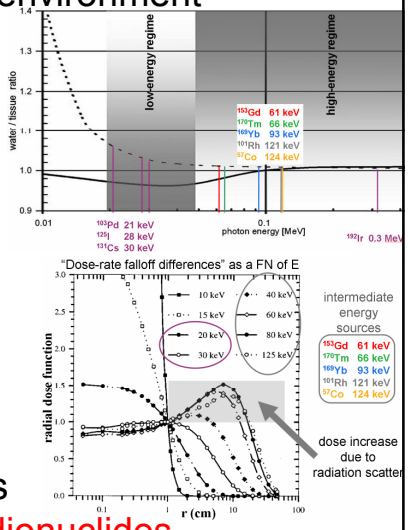
1. Regulatory requirements and environment
   - well established
2. Calibration requirements
   - need special chamber insert
3. Dosimetric requirements
   - dose superposition assumption
4. Radiobiological considerations
   - based on radionuclide



Bannon et al. (Med Phys 2011)

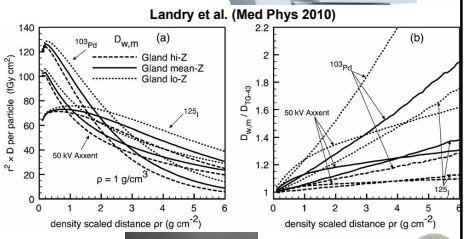
§4.F. Intermediate energy photon emitters

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



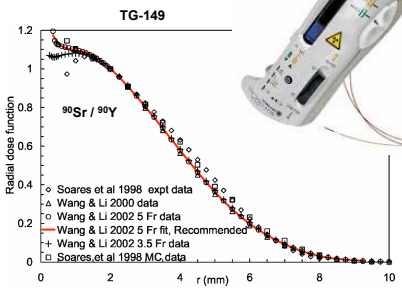
§4.G. Electronic brachytherapy sources

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



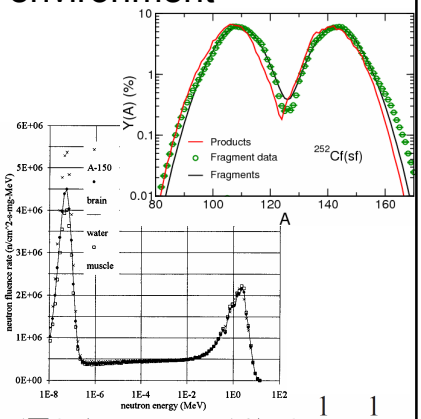
TG-60

TABLE I. Some of the possible radionuclides for intravascular brachytherapy.

Radionuclide	Emission	Maximum energy (keV)	Average energy (keV)	Half-life
^{32}P	beta	1710	695	14.28 days
^{90}Y	beta	2282	934	2.671 days
^{90}Sr	beta	546	196	28.5 yr
^{192}Ir	gamma	612	370	73.831 days
^{103}Pd	x ray	23	21	16.97 days
^{125}I	x ray	35	28	60.14 days
^{48}V	positron	696	144	15.976 days
^{106}Rh	beta	923	307	2.17 h
^{188}Re	beta	2120	765	16.98 h

§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 (γ+n)
   - custom TPS necessary
4. Radiobiological considerations
   - complicated



$$D_T = D_N + D_G = M_T(\Pi k_M)_T N_X A_{\mathrm{WALL}}(f_t)_c d_T \frac{1}{k_T}\frac{1}{1+\delta}$$

$$D_{T\text{-}EQ} = \mathrm{RBE}_{\mathrm{Cf\text{-}N}} D_{\mathrm{Cf\text{-}N}} + \mathrm{RBE}_{\mathrm{Cf\text{-}\gamma}} D_{\mathrm{Cf\text{-}\gamma}}$$

§4.J. ^{90}Y microspheres

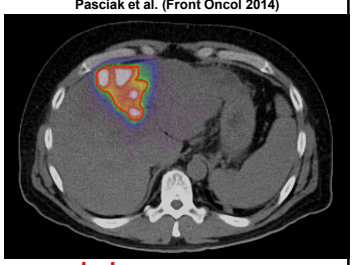
1. Regulatory requirements and environment
   - off-label, multi-disciplinary
2. Calibration requirements
   - difficult beta calibrations
   - NIST-traceable dose calibrator setting
3. Dosimetric requirements
   - infeasible pre-treatment RTP
   - need 3D dosimetry research
4. Radiobiological considerations
   - need patient-specific biokinetic models

TG-144

TABLE I. Properties of commercially available ^{90}Y microspheres.

Description item	SIR-Spheres®	TheraSphere®
Sphere material	Resin	Glass
Sphere diameter (μm)	20–60	20–30
Activity in single vial (GBq)	3	six sizes: 3, 5, 7, 10,15,20
Number of spheres per vial	$40–80 \times 10^6$	six sizes: $1.2–8 \times 10^8$
Density (g/cm^3)	1.6	3.29
^{90}Y activation mode	Carrier-free	Reactor
Activity per sphere (Bq)	50	2500
Shelf life after calibration	24 h	12 days
^{90}Y average decay energy	0.9267 MeV per disintegration	
^{90}Y half-life	2.6684 days	

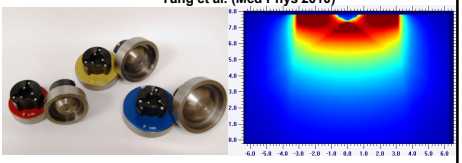
Pasciak et al. (Front Oncol 2014)



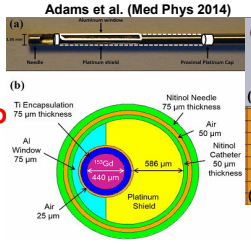
§4.K. Collimated applicators and sources

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}Ir

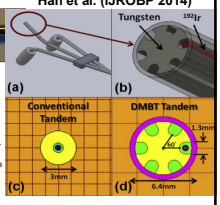
Yang et al. (Med Phys 2010)



Adams et al. (Med Phys 2014)

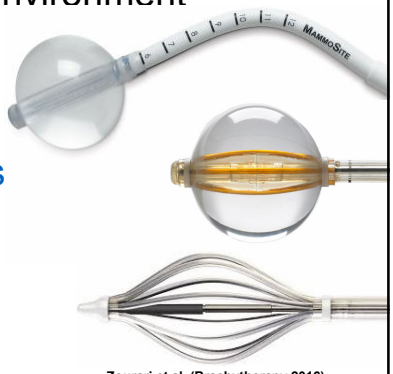


Han et al. (IJROBP 2014)

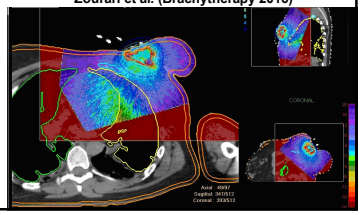


§4.L. Intracavitary breast balloon applicators

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



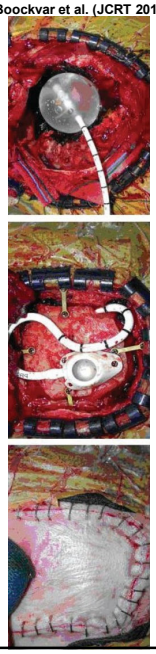
Zourari et al. (Brachytherapy 2016)



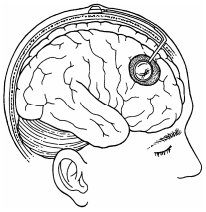
§4.M. Intracavitary brain balloon applicators

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

Boockvar et al. (JCRT 2010)



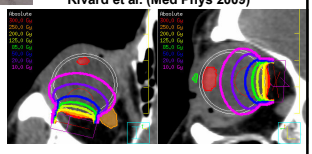
Dempsey et al. (IJROBP 1998)



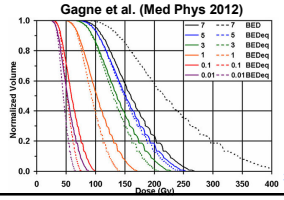
§4.N. Non-COMS eye plaques

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

Rivard et al. (Med Phys 2009)



Gagne et al. (Med Phys 2012)



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