Anniversary Paper: Past and current issues, and trends in brachytherapy physics

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Brachytherapy began at the turn of the 20th century, contemporary with external-beam radiotherapy. Physicists and physicians together developed the field. There has not been a period since the beginning that has not witnessed innovations and progress in brachytherapy. At the time of this article, the pace of change in the field has never been more rapid, particularly in image-guided brachytherapy and the development of unconventional sources and treatment techniques. © 2008 American Association of Physicists in Medicine. DOI:10.1118/1.2981826

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I. MAJOR TRENDS AND CHALLENGES IN BRACHYTHERAPY

Since its inception in the early 20th century, brachytherapy and its evolution have had a close association with medical physics. The 50 year history of the American Association of Physicists in Medicine (AAPM) has coincided not only with the emergence of medical physics as a mature profession, but with truly revolutionary innovations in radiological physics, including nuclear reactors, new particle accelerators, three-dimensional (3D) imaging, and computer-assisted treatment planning. Along with conceptual advances in radiation transport and modulation of clinical response, these developments have dramatically altered the practice of brachytherapy.

Through fortunate intersections of technological opportunity and clinical need, brachytherapy has continued to serve an important, if rapidly changing, role in cancer management despite challenges to its survival from surgery and other treatment modalities. A recently published review and a 50th anniversary article have thoroughly covered the history of brachytherapy technology and dosimetry, an area in which the AAPM has had a major impact as an organization. Rather than duplicate or summarize these excellent reviews, we propose to focus this article on current trends and challenges in brachytherapy, particularly those that fall within the scope of medical physics practice or research activities.

Probably the highest impact technological advances in the last half century were the introduction of artificial radionuclides and afterloading into clinical brachytherapy. These advances significantly lowered cost, reduced personnel exposure, and increased technical flexibility. They also set the stage for the renaissance of low dose-rate (LDR) temporary brachytherapy techniques beginning in the early 1960s in spite of the rapid penetration and development of megavoltage beam therapy, which made curative external-beam therapy feasible. Other important advances, reviewed elsewhere, were computer-assisted treatment planning/dose evaluation and advances in dosimetry. Together, these advances set the stage for dramatic shifts in both clinical indications and technical practice that have occurred in the last 15 years.

I.A. New and evolving clinical applications

One remarkable trend has been the nearly exponential growth of transrectal ultrasound (TRUS)-guided brachytherapy for treatment of low and intermediate risk prostate cancer using low-activity $^{103}$Pd or $^{125}$I. Perhaps due to the attraction of a 1 day procedure along with a favorable profile of normal tissue complications, the number of procedures has grown from less than 5000 in 1995 to between 40 000 and 60 000 in 2002. This is approximately 30% to 40% of all eligible patients diagnosed annually in the United States, challenging radical prostatectomy as the standard of treatment. A second major growth area is breast conservation therapy, in which lumpectomy is followed by fractionated high dose-rate (HDR) brachytherapy (34 Gy in ten fractions administered over 5 days) using either interstitial brachytherapy or a balloon applicator in place of 6 weeks of external-beam therapy. A third clinical indication for a
new brachytherapy application is intravascular brachytherapy (IVBT), which was introduced in the late 1990s with much excitement in the radiation oncology community. Randomized clinical trials soon showed that IVBT dramatically lowered the incidence of restenosis following percutaneous coronary angioplasty relative to unirradiated controls. As many as 40,000 intravascular brachytherapy procedures were performed annually as its utilization peaked in 2002. Perhaps due to unequivocally positive results only for in-stent restenosis, late stent thrombosis, and recurrent restenosis at the edge of the treated field, IVBT was abandoned as rapidly as it was developed in favor of rapamycin- and paclitaxel-eluting stents. This remarkable phenomenon illustrates how vulnerable specialized surgical procedures practiced by nonsurgeons, e.g., brachytherapists, are to competing surgical technologies.

Growth in the areas of permanent prostate brachytherapy and HDR \(^{192}\)Ir accelerated partial breast irradiation has been accompanied by a reduction in the use of temporary LDR brachytherapy at other sites. This reduction is due, in part, to migration of traditional LDR brachytherapy procedures, e.g., intracavitary brachytherapy for gynecological malignancies, to fractionated HDR. At least in the United States, use of definitive brachytherapy for sites such as early stage head and neck has failed to compete effectively with other therapeutic options, including intensity-modulated radiation therapy (IMRT) and surgery.

I.B. Physics and technical innovations in brachytherapy

I.B.1. Integration of 3D medical imaging into brachytherapy

Throughout most of its long life, brachytherapy has evolved as a surgical art, in which seed or applicator positioning was guided by palpation or visualization of the target tissue. Treatment planning consisted of calculating dose relative to the source positions derived from orthogonal radiographs, not the underlying anatomy. While a number of pioneering publications investigated the registration of dose distributions to 3D medical images throughout the 1980s and 1990s, only with the rise of prostate seed brachytherapy did image-guided source placement or image-based planning achieve widespread use in brachytherapy. TRUS-guided seed placement and post-implant x-ray and computer-aided tomography (CT) imaging, used to evaluate the final dose distribution, are now standards of practice. CT-based catheter guidance and dose evaluation is commonplace for partial breast brachytherapy, and magnetic resonance imaging is emerging as the planning image modality of choice for gynecological tumors. These exciting developments offer many potential advantages, including a planning process conceptually similar to that of teletherapy, less dependence on surgical skill, and most importantly, enhanced targeting accuracy, target conformality, and normal tissue avoidance. Associated developments include intraoperative planning (planning and delivery integrated into a single procedure) and intraoperative adaptive planning (intraoperative dose re-planning used to correct source position).

On the horizon, positron emission tomography and other biological imaging modalities should work their way into brachytherapy treatment planning as it has in external-beam radiotherapy.

I.B.2. Improved dosimetry and treatment planning

The rapidly growing utilization of low-energy interstitial sources has motivated intensive investigation of dosimetry techniques for more accurately estimating clinical dose distributions, a development that has greatly benefited from AAPM’s leadership and consensus building. Parallel developments in computational and experimental dosimetry have reduced physical dose specification uncertainty to the 3% to 5% level (\(k=1\)) for \(^{125}\)I brachytherapy. Another emerging development is the application of Monte Carlo-based dose calculations to treatment planning, which will eliminate major uncertainties in clinical dose specification due to tissue heterogeneities, interseed attenuation, and applicator shielding effects.

I.C. Scientific and clinical challenges facing brachytherapy

While brachytherapy usually is an invasive procedure limited to surgically accessible tumor sites, it is able to safely deliver much higher biological equivalent doses than IMRT. HDR brachytherapy is able to deliver very large fraction sizes safely while, at the other end of the spectrum, permanent seed brachytherapy (the ultimate form of hyperfractionation) supports delivery of very high physical doses due to repair of normal tissue sublethal damage. Credit is often given to brachytherapy’s superior targeting accuracy and conformality (direct insertion of sources into target tissue versus external fiducial alignment and minimum impact of tissue motion), which is widely assumed to make planning target volume (PTV) expansions unnecessary. For brachytherapy to retain these competitive advantages, the following scientific issues require urgent attention.

I.C.1. Improved understanding and exploitation of geometric and radiobiological uncertainties

Geometric uncertainty, and its role in determining PTV margins, has been extensively studied in external-beam radiation therapy in contrast to brachytherapy, where relatively little data is available. Image-guided radiotherapy (IGRT) techniques have markedly improved external-beam precision. Brachytherapy-like hypofractionated regimens have been successfully delivered to patients with lung and prostate cancers using external beam IGRT. To use brachytherapy safely for highly conformal treatment of well-defined target volumes, a better understanding of the interplay between organ delineation errors, seed and applicator positioning uncertainties, and intrafractional tissue motion are needed. For permanent brachytherapy, a better understanding of normal and target-tissue response to the ultralow dose rates, along with the modulating effects of geometric uncer-
tainties, are required to be able to extend permanent seed brachytherapy to new treatment sites without mounting dose-seeking phase I and II clinical trials.

**I.C.2. Improved management of tissue deformation**

Since brachytherapy is a surgical intervention, it deforms and displaces tissues in a highly localized and nonlinear fashion. These problems hinder accurate registration of pre-treatment biological images onto intraoperatively available images or preclude accurate summation of biological doses from individual brachytherapy fractions. Deformable image registration is a promising solution to this problem and has been demonstrated in both prostate\(^{27}\) and gynecological\(^{28}\) brachytherapy applications. However, many challenging problems remain to be solved, including general and patient-specific validation of such registrations.\(^{29}\)

**I.C.3. More realistic dose-computation techniques**

Despite substantial progress in single-source brachytherapy dosimetry, current table-based dose computation algorithms model patients as uniform water spheres of water, neglecting tissue density and composition heterogeneities and applicator- and source-shielding effects. This approximation results in large differences between the dose distribution actually delivered to the patient and that calculated by the treatment planning system, particularly for low-energy sources. This topic is discussed below.

**II. BRACHYTHERAPY DOSIMETRY**

**II.A. Brachytherapy treatment planning calculation algorithms**

One of the greatest contributions of the AAPM to radiotherapy physics has been the development of brachytherapy source dosimetry. Based on work by Meisberger and Dale,\(^{30-32}\) the current established method for brachytherapy treatment planning uses the formalism introduced by the Intersitial Collaborative Working Group\(^{33}\) and refined by AAPM Task Group No. 43 report.\(^{34}\) In 2004, this protocol was updated to eliminate shortcomings due to the lack of information when the original protocol was published.\(^{19}\) The TG-43 formalism has been applied to dose calculations around the intravascular brachytherapy sources,\(^{35,36}\) elongated brachytherapy sources,\(^{37}\) and \(^{137}\)Cs sources.\(^{38}\) In the TG-43 protocol, the dose rate distribution around a sealed brachytherapy source can be determined in two dimensions (2D) using the following formalism:

\[
\bar{D}(r, \theta) = \frac{S_f A G(r, \theta)}{G(r_o, \pi/2)} g_L(r) F_L(r, \theta)
\]

or without knowledge of the source orientation, a one-dimensional (1D) version

\[
\bar{D}(r) = \frac{S_f A}{r^2} g_p(r) \phi_{\text{iso}}(r).
\]

where \(r\) is the distance from the source center to the point of interest, and \(\theta\) is the angle with respect to the source axis.

Although discussed briefly here, the reader is directed to the references cited for discussions of each of the parameters.

The 2D formalism tends to reproduce actual dose distributions more realistically than the 1D formalism, especially for points located near the source long-axis. As of this writing, the 2D formalism is used almost exclusively for HDR brachytherapy treatment planning, where a single source is used and confined to a route defined by a catheter or needle, or temporary LDR interstitial implants. The 1D formalism is used most frequently for permanent LDR brachytherapy treatment planning, where the active source length is less than about 0.5 cm and the orientation of individual sources cannot be determined accurately. Practical considerations often prohibit the use of the 2D formalism in permanent implant cases.

**II.A.1. Source Strength \(S_f\)**

Currently the recommendation for expressing source strength is in terms of air-kerma strength, equal to the product of the air-kerma rate for a small mass of air in vacuum and the distance squared, in units of \(\mu\text{Gy h}^{-1}\text{m}^2\)\(^{-2}\).\(^{39}\) For convenience, the units are abbreviated as “U.” Considerable improvements have been made in reducing the uncertainties of source calibrations over recent years, and continue through the time of writing (see, for example, Rasmussen \textit{et al.}\(^{30,41}\)). While most of the efforts have been directed toward improving the determination of \(S_f\), calorimetric approaches have also been investigated that would yield the power emitted by a source or the dose rate to a point.\(^{42,43}\)

**II.A.2. Dose rate constant \(\Lambda\)**

The dose rate constant \(\Lambda\) is defined as the dose rate per unit air-kerma strength at a reference point along the transverse axis, \((r_o=1\text{ cm and } \theta=90^\circ \text{ or } \pi/2 \text{ radians})\) of the source:

\[
\Lambda = \bar{D}(r_o, \pi/2)/S_f.
\]

where \(r_o\) customarily falls at 1 cm for photon sources, or 2 mm for beta emitters. Predicting the value for the dose rate constant from spectroscopic measurements has proven reliable for many sources and shows some promise for replacing direct measurement.\(^{44}\)

**II.A.3. Radial dose function, \(g(r)\) and the geometry function \(G(r, \theta)\)**

The radial dose function \(g(r)\) represents the attenuation of the radiation in tissue, defined as

\[
g(r) = \frac{\bar{D}(r, \pi/2) \cdot G(r_o, \pi/2)}{\bar{D}(r_o, \pi/2) \cdot G(r, \pi/2)},
\]

where \(G(r, \theta)\) is the geometry function which accounts for the effect of the distribution of radioactive material inside the source on the dose distribution at a given point. The geometry function is defined as\(^{34}\).
where \(x\) and \(y\) are the coordinates of the point of interest relative to the longitudinal and transverse axes of the source, and \(L\) is the active length of the source. As seen in Eq. (3), the value of the radial dose function is equal to 1 at the reference point along that source’s transverse bisector, \((r_0, \pi/2)\). An update to the TG 43 report clarified the “length” of the source when the construction consists of spheres or pellets instead of a linear carrier as an effective “length” \((L_{\text{eff}})\) equal to the number of pellets times the center-to-center distance between the sources.  

II.A.4. 2D Anisotropy Function \(F(r, \theta)\)

The 2D anisotropy function \(F(r, \theta)\) represents the variation of the dose distribution around a brachytherapy source due to the distribution of radioactivity within the source, self-absorption, and oblique filtration of the radiation in the capsule material. The TG-43 report defines the anisotropy function as

\[
F(r, \theta) = \frac{\hat{D}(r, \theta) \cdot G(r, \pi/2)}{\hat{D}(r, \pi/2) \cdot G(r, \theta)}.
\]  

II.A.5. 1D Anisotropy Function \(\phi_{an}(r)\)

The 1D anisotropy function, or anisotropy factor \(\phi_{an}(r)\) for a given radial distance comes from integrating the dose rates over the polar angle (assuming a cylindrical source) at a given radial distance:

\[
\phi_{an}(r) = \frac{\int_0^\theta \hat{D}(r, \theta) \sin(\theta) d\theta}{2 \hat{D}(r, \theta_0)}.
\]  

II.B. Clinical dose calculations

Clinical use of computerized systems has permitted dosimetry data obtained by researchers to overlay source dose distributions, via the superposition principle, onto patient-specific geometries. Use of this principle becomes inappropriate when the interactions between sources become significant, when the geometry used by the dosimetry investigator does not approximate well that of the patient, and when differences between the patient’s tissue and the water medium used with TG-43 tables become pronounced. Dose distributions obtained by researchers for a single source at specific points are fitted to mathematical functions for entry into a radiotherapy treatment planning system and subsequent derivation of clinical dose distributions. This data fitting is most typically performed for the radial dose function where it is impossible for the brachytherapy dosimetry researcher to determine the dose distribution at all possible clinical locations. There is a wide assortment of possible techniques for clinical dose calculations. Some planning systems utilize a polynomial fit while others prompt the clinical physicist to enter data with a given bin size or spatial resolution, sometimes requiring specification of dose at the source origin or within the source capsule! Clearly, differences in dose distributions can arise when there are differences in the choice of fitting functions between the dosimetry investigator and the clinical treatment planning system. To minimize the likelihood of this occurrence, the AAPM has in place a mechanism for issuing consensus datasets for brachytherapy source dose distributions.

The AAPM Low- and High-Energy Brachytherapy Source Dosimetry Working Groups under the Brachytherapy Subcommittee perform this function and typically publish recommended consensus datasets and dosimetry formalisms in the journal Medical Physics. These datasets include the following source-model specific dosimetry parameters: effective \((L_{\text{eff}})\) or active source length \(L\); dose rate constant \(\Lambda\); radial dose function for the point- \(g_P(r)\), or line-source \(g_L(r)\), approximation; the 2D anisotropy function \(F(r, \theta)\); and 1D anisotropy function \(\phi_{an}(r)\).

The range of data specified by the dosimetry investigator is often inadequate to cover all clinical possibilities. Consequently, and to promote uniform brachytherapy source delivery and patient treatment, the AAPM has further recommended interpolation and extrapolation techniques to facilitate brachytherapy dose calculation beyond the range published by the dosimetry investigator. Not all vendors of brachytherapy treatment planning systems have incorporated the AAPM recommendations. The largest dose differences may arise at locations close to the source, near the source long-axis, or in between researcher-specified points.

In addition to concerns with dosimetry parameters, brachytherapy physicists should be concerned with the grid size used for dose calculation—both upon initial source characterization and subsequent treatment planning. Some planning systems permit the physicist to set grid size, and detrimental effects can result if it is set too large. For example, Fig. 1 shows the impact of setting 0.1, 1, 2, and 5 mm grid size during treatment planning for the same \(^{125}\)I source. The planning systems did not change the dose calculated to the 15 circular points or to dose volume histograms when changing the grid size, but visualization of isodose rate distribu-
tions became perturbed as grid size increased. The physicist must know the limitations of the planning system before setting out to calculate clinical dose distributions and deciding on the optimal grid size to balance dose calculation time with dose calculation accuracy.

II.C. Measurement of dosimetric parameters

Due to high dose gradients and small dose rates around brachytherapy sources, measurement of dose distribution is labor intensive, particularly for low-energy photon-emitting sources. A detector with a wide dynamic range, flat energy response, small geometric dimensions, and high sensitivity is a suitable device for these measurements. The low signal-to-noise ratio in this field limits application of ionization chambers in these measurements. Currently, LiF thermoluminescent dosimeters (TLDs) are the most commonly used detectors in this application. Silicon diodes, radiochromic film, and diamond detectors also have been used. In this section, the main emphasis is on measurement of the dose distribution around brachytherapy sources with LiF TLDs because most measurements of the dosimetric parameters for brachytherapy sources have been made using these dosimeters.

LiF TLDs are available in various forms and shapes; however, chips of $3.1 \times 3.1 \times 0.8$ mm$^3$ and $1.0 \times 1.0 \times 1.0$ mm$^3$ are the two most commonly used. For dose measurements with these detectors, slabs of water equivalent phantom material can be machined accurately to accommodate the source and the TLD. Care must be taken to avoid dosimeters eclipsing more distant dosimeters during the measurements. Responses of the irradiated TLD in a given measurement are converted to absorbed dose using the following formalism, described by Meigooni et al.,$^{45}$ and Williamson and Rivard,$^3$

$$\hat{D}(r, \theta) = \frac{R_{\text{net}}(r, \theta)}{S_k E(r) dT F_{\text{lin}} T},$$

(7)

where $\hat{D}(r, \theta)$ is the dose rate at a point $(r, \theta)$, $R_{\text{net}}(r, \theta)$ is the net response of the TLDs placed at $(r, \theta)$ as corrected for background and the physical differences among TLD chips using predetermined chip calibrations.$^{45}$ $T$ is the irradiation duration, $S_k$ is the measured source air-kerma strength at the time of measurement, and $e$ is the calibration factor for the TLD response (e.g., nC/Gy) usually using a calibrated Co-60, 4 MV, or 6 MV photon beam. Occasionally superficial x-ray beams are used for TLD calibration. $E(r)$ is a correction factor for the energy dependence of the TLD between the calibration beam and the brachytherapy source; for instance, a value of 1.4 for both $^{125}$I and $^{103}$Pd source dosimetry if the TLDs are calibrated with a megavoltage beam.$^{3,46}$ $dT$ is a correction factor used to account for the decay of the source during the experiment, and $F_{\text{lin}}$ accounts for TLD nonlinearity.

For measurement of the dose rate constant, TLDs are placed 1 cm from the axis of the source on the perpendicular bisector at a number of angles around the source. TLD measurements of radial dose function are normally performed at distances ranging from 0.5 to 10 cm at 0.5 and 1 cm increments. The measured value at each distance is obtained from the average of several TLD chips to achieve an uncertainty (one standard deviation) of about $\pm 4\%$. Determination of the anisotropy function requires measurements at many angles and distances with the measurements taken several times to allow averaging to achieve the 4% uncertainty.$^{19}$

Because the use of TLDs, or any point dosimeter, requires so many individual measurements, planar detectors such as radiochromic film become attractive. The calibration, use, and reading of the film all pose potential problems and require consideration of details.$^{37-39}$ While gel dosimetry looks appealing because it conceptually could provide an entire set of three-dimensional data with a single exposure, characteristics such as the high dose required for adequate signals and a marked gradient effect pose challenges for widespread use.$^{51-55}$

II.D. Monte Carlo simulations for estimating brachytherapy dosimetry

In the first half of the 20th century up until the early years of the AAPM in the 1960s, clinical brachytherapy dose distributions were generally determined using lookup tables (i.e., along-away tables) based on ionization measurements and Sievert integrals.$^{56-58}$ Based on modeling brachytherapy source dose distributions in solid-state media using radiation transport, one of the earliest publications using Monte Carlo methods to simulate a geometrically realistic cylindrically symmetric brachytherapy source was by Krishnaswamy in 1971.$^{59}$ This work and subsequent efforts set the stage for modern brachytherapy dosimetry simulations using Monte Carlo methods. Given Moore’s Law for exponential increase.
in computer processor speed, the $5 \times 10^7$ histories for the $^{252}$Cf applicator tube source performed in 1997 by Rivard et al. closely followed the expected increase in comparison to the $5 \times 10^7$ histories performed in 1970 by Krishnaswamy over a timeframe of about three decades. Based on the Monte Carlo simulations by Krishnaswamy, over a decade passed before other investigators simulated brachytherapy sources to the same level of detail as Krishnaswamy. For example, isotropic point-source build-up factor-based approximations were performed by Berger, Webb and Fox, and in the famous paper by Meisberger et al. More sophisticated approaches using 3D modeling were pursued later, and were largely spearheaded by Williamson.

Various Monte Carlo codes for radiation (i.e., 0.03 to $\sim 1$ MeV photon) transport had been used since the 1950s, but medical physicists transcended the gap between basic physics and the needs of the clinic, often by developing homemade radiation transport codes. Once brachytherapy source dose distributions were calculated, these results were readily integrated into then-modern approaches for treatment planning. In fact, the first president of the AAPM, Gail Adams, was involved, along with other groups (Nelson, Hope, Shalek) in developing computer-assisted dose calculations based upon precomputed Sievert integral single-source dose distributions and the superposition principle. A detailed summary of this era was prepared by Stovall and Shalek.

With increases in processor speed, accessibility of operating systems, and more widespread use across medical research, Monte Carlo methods for simulating brachytherapy dose distributions reached a critical threshold in the 1990s. A key event was the publication of the 1995 AAPM TG-43 report. This report significantly advanced the standard brachytherapy dosimetry formalism, required separate brachytherapy dosimetry parameters for different source models of the same radionuclide, promoted consistent use of brachytherapy dosimetry parameters at separate institutions, and through its popularity, informed medical physicists far and wide of the possibilities of Monte Carlo methods for simulating brachytherapy source dose distributions. Monte Carlo methods for brachytherapy dosimetry were further popularized by Williamson using his PTRAN code, where different source types and aspects of brachytherapy were examined.

Monte Carlo codes are products of humans, and are consequently subject to a variety of errors. For example, some studies published on Monte Carlo-derived brachytherapy dosimetry methods accidentally utilized photon cross-section libraries based on antiquated data. DeMarco and colleagues first noticed this problem for the MCNP code. Subsequently, modern cross-section libraries have been adopted by groups using established Monte Carlo codes. The AAPM methodologically examined the role of Monte Carlo codes for simulating brachytherapy source dose distributions. Specifically, Monte Carlo radiation transport codes were identified that have been well benchmarked for brachytherapy dosimetry. These included EGS, MCNP, PTRAN, GEANT4, MCNPX, and EGSnrc. Only EGS, MCNP, and Williamson’s PTRAN code were mentioned in the TG-43U1 report as examples of well-benchmarked codes.

The field of Monte Carlo simulation of brachytherapy source dose distributions is mature; however, there is room for improvement towards better simulating the clinical environment. Since Krishnaswamy, it has been shown that improved dose simulation accuracy, determined through comparisons with measurements, are obtained through accurate modeling of the brachytherapy source and capsule. This approach has been extended to investigation of interseed interactions and motion of internal components. In fact, the principal equipment used to produce calibration results, i.e., the wide-angle free-air chamber at the National Institute of Standards and Technology, has been simulated for direct comparison with experimental measurements. Further advances include simulations of material heterogeneities, scatter conditions, and localization in the patient through image-guidance. With the introduction of HDR brachytherapy sources having relatively low-energy photon emissions, distant prescription points are more likely to cause dosimetric changes if accounting for material heterogeneities in comparison to assuming a liquid water environment. One must exercise caution, however, since a feature unique to Monte Carlo methods in comparison to measurement techniques is the capability to simulate unreal circumstances, for example, using water with a mass density of 10 g/mm$^3$. In addition, Monte Carlo results, unlike experimental measurements, cannot account for modeling errors, e.g., contamination of radionuclide spectrum, errors in implementing calibration standards, etc. Comparison of Monte Carlo and limited experimental results is needed to detect unanticipated discrepancies between the assumed and actual properties of the system under investigation.

Efforts are underway to incorporate Monte Carlo methods into clinical brachytherapy treatment planning systems due to their proven utility to simulate radiation scatter conditions and account for material heterogeneities. Other approaches not using Monte Carlo methods, such as the collapsed cone employing superposition of primary and scatter dose, may also account for dosimetric effects not modeled by the AAPM TG-43 dosimetry formalism. Thus, it remains to be seen whether or not Monte Carlo methods for brachytherapy dosimetry will transition from a research tool to the backbone of the treatment planning algorithm. Investigation of a similar shift occurred a few years ago for external beam treatment planning. However, the competing standard treatment planning algorithms for external beam radiotherapy provide much better agreement with measurements than the TG-43 dosimetry formalism for measurements of brachytherapy dose under challenging scatter and material heterogeneity conditions.

II.E. Accounting for heterogeneities in dose calculations

It is widely recognized that current dose-specification and -calculation practices introduce significant dose-
calculation errors by failing to adequately account for applicator attenuation, tissue heterogeneities, and intersource shielding. Some applicators containing local shielding to spare bladder and rectal tissues can produce dose reductions as large as 50% \cite{103,104} that most treatment planning systems still continue to ignore. The perturbing effects of partial transmission shielding have been shown \cite{13,105,106} to vary rapidly with cross-sectional area and location of shielding materials, especially for sources with energies at or below that of 192Ir. Only for 137Cs shielded sources can one-dimensional pathlength algorithms (available on some commercial planning systems), e.g., generalizations of the Sievert integral model \cite{107} be used reliably. \cite{108} These studies also document that Monte Carlo simulations accurately predict such effects. Seed-to-seed attenuation effects have been shown to produce moderate but potentially significant systematic dose overestimates (2% to 4% average errors, and up to 15% local errors) for 103Pd and 125I volume implants. \cite{90,109}

For 125I and 103Pd sources, tissue-composition heterogeneities are known to have a high impact on theoretical grounds, as the photoelectric effect dominates energy deposition. Dose rates in adipose and fat-like tissues can deviate from water-equivalent calculations by as much as 50%. \cite{109,111} whereas in bony tissues, or soft tissues with significant mineral content, conventional calculations underestimate true dose by as much as a factor of 2. \cite{112} On the other hand, replacement of as little as 1% of soft tissue mass by calcified tissue has been shown to reduce prostate doses by 8%. \cite{20} Maughan’s combustion analysis measurements show that mineral ash content of excised tumors ranges from 0.9% to 3%, leading to dose estimation errors as large as 15% at 28 keV. \cite{113} For higher energy sources, there is evidence that air-tissue boundaries forming the breast and lung contours can perturb HDR breast implant doses by 5% to 10% at lower doses (<60% of D90) for 192Ir while for lower energy 169Yb, D90 is lower than predicted by conventional dose planning by 5% and as much as 25% at lower doses. \cite{87} No studies systematically assessing the impact of compositional (in contrast to density) heterogeneities on higher energy sources are available. For 192Ir, Anagnostopoulos found that bony structures perturbed doses by up to 15% at low doses while Ye found that a 5% variation in contrast-agent concentration in the MammoSite applicator reduced dose by as much 7%. \cite{114,115}

1D pathlength and other heuristic algorithms have been reviewed elsewhere. \cite{108} A more general approach is the superposition/convolution algorithm. \cite{2,116} Tedgren’s algorithm, which adapts the “collapsed cone” methodology from external beam dose calculation, is being considered for implementation in the Nucletron PLATO planning system. Preliminary results suggest that superposition is quite accurate but computationally intensive. Another and more general deterministic algorithm is discrete ordinates, which rigorously solves the Boltzmann transport equation on a systematically discretized phase-space grid. \cite{117,118} These solutions approach the complexity, rigor, and computational efficiency of Monte Carlo simulation. Daskalov et al. \cite{118,120} have shown that single-processor 2D and 3D discrete ordinates calculations are one to two orders of magnitude faster than general purpose Monte Carlo code calculations of equivalent dimensionality, while Gifford’s code required 20 min of computing time for 3D dose distributions from a shielded colpostat. \cite{119} Both Daskalov and Gifford required analytic or Monte Carlo computation of the first collision source to avoid ray effects characteristic of discrete point sources.

Several groups are investigating direct application of Monte Carlo simulation for dose computation on clinically realistic multiple-source implants. Early studies required several hours or even days of computing time. \cite{90,121,122} However, two groups have reported Monte Carlo codes especially designed to facilitate efficient and more accurate planning in brachytherapy with 20 s to 1 min computation times for clinical implants. \cite{20,88} Because Monte Carlo calculations can be parallelized using PC clusters with distributed memory in a cost effective manner, in contrast to more expensive shared-memory multiple processors needed for discrete ordinates, the authors predict that Monte Carlo simulation may be the dominant brachytherapy dose-calculation algorithm of the future.

Lack of voxel-by-voxel knowledge of the photoelectric-effect and scattering cross sections versus photon energy limits its implementing any realistic dose-calculation algorithm for low-energy seeds. Although average compositions of human tissues and organs have been estimated, \cite{123} no data on variations within individual organs or from patient to patient are available. Quantitative dual-energy CT imaging is one possibility that has been investigated for bone-mineral assay \cite{124,125} and, early in the history of CT, for estimation of human tissue composition. \cite{125} While preliminary data suggest that dual-energy CT cross-section imaging is feasible, \cite{26,127} the high quality images required by this demanding application are difficult to achieve at reasonable patient doses on commercial scanners with currently available data preprocessing and reconstruction algorithms.

II.F. Optimization

Treatment planning for brachytherapy consists mostly of determining the catheter, needle, applicator or source locations, and the strength or dwell time for the sources used. Systems such as the Manchester \cite{128} or Paris \cite{129} give good suggestions for needle placement, as does the work of Kwan et al. \cite{130} and of Zwicker et al. \cite{131} Some general principles help guide needle location selection for interstitial implants:

1. To achieve the most uniform dose distributions, the concentration of sources or dwell positions near the periphery needs to be higher than in the interior. For many configurations, this approximates 75% of the source material or dwell weight being on the periphery, as suggested by the Manchester System \cite{132–135} The actual percentage that should reside on the periphery depends on the shape of the CTV and the source positions.

2. Needles in corners of implants should be moved inward to avoid breaks in the prescription isodose surface between sources. \cite{136} Reducing the distance to each of the nearest needles to about two-thirds of what it would be
for a regular geometric pattern usually suffices. While most useful for uniformly loaded needles or catheters, moving the catheters inward in implants that will be optimized reduces the potential for large high dose volumes.

3. When using small sources (such as iridium “seeds” as opposed to wire), the strength at the ends of needles should be roughly twice that of each of the rest of the sources in the needle. Such loading helps prevent the prescription dose distribution from dipping into the treatment volume between the catheters.

Differential loading of implants can create a more uniform dose distribution, while a more uniform loading produces a higher dose in the center of the implanted volume. Either pattern may be consistent with the desired goals of the treatment.

Intracavitary brachytherapy presents less opportunity to control the dose distribution, but the design of the applicators has a great impact on the resultant dose distribution. Some general principles for source distribution for intracavitary applications include the following:

1. When the goal is to project the dose to points distant from the treatment appliance, the source locations should be far from the applicator-tissue interface. Just as in external-beam radiotherapy, a greater source-to-surface distance gives a greater fractional depth dose, so also with brachytherapy.

2. If possible, the applicator should place sources distributed around the target (such as using tandem and ovoids rather than a tandem and cylinders.)

3. Recognize that the dose distribution will not be uniform, but continually decreasing with distance from the sources.

Determining the source strengths at each location for an LDR implant, or the source dwell times for an HDR Ir applicator, forms one of the problems most often identified as optimization. The LDR problem may be a quantized problem, such as which of eight source strength options should be placed at each source location, or a binary selection, for example in prostate implants, whether a source occupies a given location or not. The HDR problem is almost continuous, where the dwell times could assume any value between 0 and 999 min in 0.1 s increments. For a comprehensive discussion on optimization, see Ezzell and also Ezzell and Luthmann.

Many techniques for optimization have found their way into brachytherapy, but because of space limitations, only those most commonly encountered or offering some unique advantage will be discussed here. The classifications carry considerable arbitrariness, and several approaches sometimes could be listed under more than one classification. The list below only considers the approaches applied in brachytherapy in commercial systems or in recurring research articles. Many of the techniques use objective functions which evaluate how closely the solution matches the desired distribution. The functions often consider the dose coverage of the target, target dose homogeneity, and doses to organs at risk, possibly in nonlinear combinations.

II.F.1. Deterministic

This class of optimization approaches refers to methods that produce the same result each time they run on the same case. Several deterministic approaches have been used for brachytherapy optimization, but the most successful and practical for permanent implants is branch and bound.

In this technique, the strength of sources at all possible positions is solved in an analytical manner, giving an idyllic solution but with fractional sources at each position. One by one, the process considers each position and changes the fraction to a source present or absent, and reevaluates the objective function. The pattern of the changes guarantees a relatively efficient search (not having to consider every option), and guarantees finding the absolute optimum solution. If simply satisfactory solutions are needed, the process becomes very rapid.

A subset of deterministic approaches falls under the classification of “analytical techniques.” Used mostly for HDR applications, an analytical approach sets up a set of simultaneous equations where each equation expresses the dose at a point as a function of all the source dwell times that form the variables. For implants with a few hundred dwell positions and a similar number of points defining the dose to a target surface, the problem becomes very time consuming, and polynomial models and approximations are common. Because it solves for a particular set of constraints (the doses to a set of points), this approach is not truly “optimization,” but satisfaction.

II.F.2. Stochastic

Stemming originally from permanent implants, simulated annealing and genetic simulation are the most common stochastic approaches. The techniques start with any potential binary loading pattern, then make changes and evaluate whether the new pattern is better than the original. At first, the changes are major, but as the process progresses, the changes become more refined. Occasionally large random changes help prevent the solution from settling into local optima. While not necessarily finding the global minimum of the objective function in a finite computing time, the stochastic approaches are likely to find satisfactory solutions. The methodology now applies to HDR brachytherapy as well as permanent implants.

II.F.3. Heuristics

Instead of trying to find optimal solutions, heuristics use very fast methods to find useful solutions, often using surrogates for the dose distribution to guide the search. Geometric “optimization,” used mostly for HDR applications, weights each dwell time inversely to the sum of the distances between a given dwell position and all other dwell positions. The adjoint/greedy heuristic uses the adjoint sensitivity function to determine the most efficacious positions for source strength to provide a uniform dose to a target and minimize
the dose to sensitive structures.\textsuperscript{143} The heuristics’ speed comes from the absence of iteration.

One of the current challenges for optimization is “live-time reoptimization” guidance intraoperatively.\textsuperscript{16} This process would update the dose distribution as sources are placed, usually in a permanent implant, and recalculate the positions of the remaining sources. Such a process requires extremely fast computations and high quality imaging.

Limitations on the length for this article prevent consideration of evaluation procedures for the quality of brachytherapy plans. Thomadsen has presented detailed discussion of plan evaluation.\textsuperscript{144}

III. BRACHYTHERAPY PROCEDURES: APPLICATIONS, APPROACHES, AND APPLICATORS

III.A. Cervix brachytherapy

Reports of brachytherapy for cancer of the uterine cervix trace back to at least 1903, and it soon became the preferred treatment modality.\textsuperscript{145} The early techniques varied greatly, mostly specifying treatment in terms of mg-h. The practice at the Holt Radium Institute in Manchester developed a system for treating patients designed to deliver the same dose to the control point, called Point A, a fixed distance 2 cm superior to the vaginal fornices and 2 cm lateral to the uterine canal. This system found great acceptance throughout the world and formed the basis for much of cervical intracavitary brachytherapy to this day. At M.D. Anderson, Fletcher developed an approach calling for loading the radioactive material in the applicators based on the size of the applicator accommodated and on the stage of the disease.\textsuperscript{146} For the given combination of stage and applicator, the treatment would be specified as a particular number of hours, although limited to a specified total number of mg-h or dose to the bladder, rectum, or vaginal surface. In Paris, a different approach evolved particularly for preoperative brachytherapy, matching the 60 Gy isodose surface (the “reference isodose”) to the dimensions of the cervix and lower uterus.\textsuperscript{129}

The introduction of HDR brachytherapy for cervical brachytherapy improved the accuracy of radiation delivery through optimization of the treatment plan and reduction in applicator movement during the treatment time. The HDR technique also reduced the unnecessary radiation exposure to medical staff, reduced the treatment duration time, and eliminated the mandatory hospitalization.

All these methods used radiographs to determine the geometry of the applicator and visual inspection and palpation to establish the diameter of the cervix. The tumor played little or no role in defining the treatment. The advent of CT enabled better dosimetry for the bladder and rectum, but failed to visualize the tumor as distinct from the rest of the cervix. MRI, on the other hand, distinguishes between a tumor and normal cervix. The Group Européen de Curiethérapié of the European Society for Therapeutic Radiology and Oncology has developed a protocol for three-dimensional, target-based intracavitary brachytherapy founded on MR images.\textsuperscript{14} While the use of MRI for treatment planning does present challenges, the future of cervical brachytherapy lies in this direction.

III.B. Prostate implants

Brachytherapy for treatment of prostate cancer has been used for about 100 years.\textsuperscript{147} Since those first investigations with \(^{226}\text{Ra}\) needles, there have been many variations on implant technique and radionuclides implanted. Significant advances since then include transperineal implantation using transrectal guided ultrasound, use of hormones to decrease gland size, widespread use of prostate-specific antigen testing to assist staging and treatment modality choice, use of radionuclides having lower photon energies than \(^{226}\text{Ra}\), and the treatment planning advances described above. Since an excellent review of the current status of prostate brachytherapy is given in Chapters 28 through 33 of the 2005 joint AAPM/ABS Summer School text,\textsuperscript{148-153} this section will focus on steps medical physicists are taking towards advancing this treatment technique.

In this decade, there have been substantial advances to brachytherapy source dosimetry. These advances have come about in part due to increasing choices of source types and configurations. It is understood that some sources have dynamic internal components which can vary prostate dose depending on patient positioning/orientation.\textsuperscript{10} There are now seeds having nonmetallic plastic capsules,\textsuperscript{154,155} unencapsulated \(^{103}\text{Pd}\) wires,\textsuperscript{156-158} seeds which may be connected together like LEGO®s,\textsuperscript{159} and seeds not having cylindrically symmetric dose distributions that provide directional emissions for preferentially protecting critical structures.\textsuperscript{160} Further, seeds may now be purchased already contained in strands or needles, complicating direct calibration.\textsuperscript{161} This feature makes it difficult for medical physicists to assay sources preceding clinical implantation. The AAPM has issued preliminary guidance on this topic,\textsuperscript{162,163} and is in the process of preparing a report updating prior AAPM recommendations on medical physicist responsibilities\textsuperscript{164,165} and source assay criteria.\textsuperscript{166}

HDR \(^{192}\text{Ir}\) for prostate brachytherapy has been a treatment choice for two decades, with a role primarily for large glands.\textsuperscript{167,168} A recent possible alternative is HDR \(^{169}\text{Yb}\), which has lower photon energies than \(^{192}\text{Ir}\) and a potentially more advantageous dose distribution for localized treatment.\textsuperscript{98,169} Similarly, LDR \(^{131}\text{Cs}\) sources, commercially available since 2004, emit photon energies slightly higher than those of \(^{125}\text{I}\).\textsuperscript{170,171} Due to the different dose distributions because of photon energy for HDR \(^{169}\text{Yb}\) versus HDR \(^{192}\text{Ir}\), and due to different half-lives for LDR \(^{131}\text{Cs}\) versus LDR \(^{125}\text{I}\), there will be different biological responses with these new radiotherapy modalities. Part of the physicist’s job is to know the science supporting radiation therapy treatment modalities, and to guide the radiation oncologist towards meaningful programmatic decisions regarding choice of treatment modalities.\textsuperscript{12} This ethical mandate becomes clouded when referral patterns rather than evidence-based medicine guide treatment modality choice, such as has been
observed for prostate cryotherapy and radiofrequency ablation.172–174 Significant long-term advances for prostate cancer therapy will come only through clinical results obtained via randomized trials without physician financial conflicts.

Once in the operating room (OR), after the treatment modality has been decided, there are still many choices on how to proceed. Surprisingly, there is still ambiguity regarding the necessary margin to apply for adequate prostate coverage, even though a collaboration of academically oriented prostate brachytherapy teams endeavored to resolve this issue.175,176 Additional areas under investigation or development are intra-operative treatment planning or IORT where knowledge obtained about seed placement in the OR guides decisions about subsequent seed placement to obtain an optimal plan.15 As medicine becomes more automated, robotic seed implantation may have a significant role in the future.177–179 This technique could potentially improve standardization of the actual seed implantation process and minimize the impact of physician-to-physician technique variations. As in the case of treatment margins, there is no firm consensus on the post-implant time that provides the most representative patient anatomy for which to determine dose for LDR implants. Yue and colleagues have studied this problem with various biomechanical assumptions of prostate edema.180 Tanaka and colleagues performed a 74 patient prospective study correlating need for post-edema imaging with implant quality,181 and AAPM recommendations currently under review have proposed to widen the current reporting criteria towards adding statistical analysis to retrospective studies to address this dilemma.182

On almost all fronts, the field of prostate brachytherapy has made significant advances in the past decade. Only the future will reveal which of these technological advances and methodological improvements will become the standard of care for the next generation of medical physicists.

III.C. Breast brachytherapy

One of the fastest growing medical procedures is breast brachytherapy. While in the 1970s and 1980s LDR iridium interstitial implants of the breast were sometimes used to boost the dose to the site of the tumor following whole breast irradiation, this most recent wave of applications uses brachytherapy to implement 1 week long accelerated partial irradiation, which shots an electron beam down a long tube to a target centered in an applicator, and the Axxent® system (Xoft Inc., Fremont, CA), a miniature x-ray tube that moves through a catheter in a manner similar to a conventional, radionuclide high dose-rate unit. These units generate 50 kVp x rays, with considerably less penetration than a 192Ir source. Thus, the dose at the surface...
of the balloon and the effects of heterogeneities will be higher with EB than with conventional HDR sources. Currently, the EB units cannot treat interstitial type implants. Should they evolve to acquire this ability, these disadvantages would be of less concern.

Given the rapid proliferation of partial breast irradiation techniques and devices over the last decade, rapid development of techniques and procedures is likely to continue until a smaller set of alternatives surface as the preferred method. A national trial comparing whole breast irradiation to partial breast irradiation (National Surgical Adjuvant Breast and Bowel Project B-39/Radiation Therapy Oncology Group 0413), delivered either as interstitial, intracavitary, or intensity-modulated external-beam irradiation, is unlikely to provide evidence of the superiority of one technique over another. This is in part due to the inclusiveness of the study, allowing centers to enter patients even though they could not randomize the patient to any of the arms, but also because that is not the question the study intends to answer: Does partial breast irradiation, however implemented, yield clinical outcomes as good as or better than that of whole breast irradiation?

III.D. Lung brachytherapy

Lung cancer is one of the leading causes of cancer death for both men and women in the United States. Photodynamic therapy (PDT), brachytherapy, electrocautery, cryotherapy, and Nd-YAG laser therapy are therapeutic options available for management of endobronchial malignancies. In cases of the tumor being in the lung tissue, rather than the bronchi, external beam radiation therapy is the appropriate therapy. All of these treatment modalities have been used even for both palliation of late obstructing cancers and primary treatment of early radiographically occult cancers.

The significance of brachytherapy treatment for endobronchial cancer has been demonstrated by many investigators. Intraluminal bronchial irradiation is used to give an added radiation dose to lung cancers that are located in the major bronchi (the breathing passages). While increasing the dose to the tumor, brachytherapy, due to its short treatment distance, minimizes the radiation dose given to sensitive nearby tissues such as adjacent normal lung, heart, esophagus and the spinal cord. Brachytherapy is also used to treat recurrent endobronchial tumors where additional surgery and external beam radiation therapy are no longer options.

Conventionally, LDR brachytherapy uses 192Ir ribbons. For these treatments, the brachytherapy sources were placed in catheters introduced in the patient’s bronchus through the nostril and located near the tumor site. Placement of the catheters is normally performed using a bronchoscope, allowing visualization of the exact location of the tumor. In addition, the procedures are performed under fluoroscopy to identify a landmark for determination of the treatment length. Often, two images are taken during the procedure, one with the tip of the bronchoscope at the distal margin of the tumor and one at the proximal margin. The treatment length is determined by adding at least 1 cm to each end of the marked tumor length. These catheters must be carefully secured to the patient’s nose to prevent dislodgement during the treatment. In this treatment technique, the patient normally receives a dose of 30 to 40 Gy, prescribed at a 1 cm distance from catheter, in a single implant over 1 to 3 days. However, due to the risk of displacement of the catheter during the treatment and also the possibility of irradiation of surrounding people, these patients require hospitalization and surveillance. The source activities and arrangement must be custom designed for each patient. Ordering, receiving and handling the brachytherapy sources and their inventory and disposal after the treatment for each patient are among the medical physicist’s tasks. For these reasons, LDR brachytherapy for the lung has mostly been replaced by HDR techniques.

Introduction of HDR brachytherapy eliminated some of the above-noted problems. In HDR treatment technique, catheters will be placed in the patient’s endobronchial tube, as with the LDR approach. However, unlike the LDR treatment, the HDR treatment is performed in fractionated fashion. The number of fractions and dose per fraction are dependent on the disease stage and also any combination with chemotherapy or external beam therapy. Typically, three to five fractions of 5 to 7.5 Gy per fraction at 1 cm from the catheter at 1 week time intervals between the fractions, or four twice-daily fractions of 8 Gy would be used.

One of the main advantages of the HDR system relative to LDR brachytherapy is the optimization of the dwell times for minimization of dose to normal tissue while the dose to the treatment volume is maximized. While some facilities perform the same optimization using the LDR approach, the HDR treatment planning systems simplify this procedure.

In summary, the results of various investigators indicate that the combination of new technology with a better understanding of the biological, clinical, and dosimetric aspects of the radiation holds promise for advancement of this treatment modality.

Interstitial implants of the surgical bed during lung surgery have been used off and on since the early days of the 20th century. Recently a clinical trail opened using permanent sources in either a single or double line along the resection. The sources are sewn into a mesh and the mesh sewn on the lung. Because the length of the incision is not known before the surgery, treatment planning can only be approximate. Even with the best planning and careful laying of the mesh, upon closing the patient the tissues carrying the sources tend to bunch and the resultant dose may have little relationship to that planned. Since there is evidence of benefit from these treatments notwithstanding the dosimetric uncertainty, the problem may be more regulatory than clinical.

III.E. Novel clinical applications and delivery schemes

Brachytherapy has expanded, over the last decade, not only in terms of number of procedures, but in terms of di-
versity of clinical applications and techniques as well. This growing clinical diversity is due in part to the advent of $^{192}$Ir and $^{125}$I sources in the 1970s and 1980s. These new sources allowed implantation of sites, sizes, and geometries that the previous rigid needles would not, while computer- and image-based dose evaluation supported greater dose distribution individualization. High dose-rate units in the 1980s changed the patterns of practice, mainly by adapting older techniques to fractionated, outpatient settings.

A much greater change came with IVBT, which differed significantly from conventional brachytherapy: treatment distances were in millimeters, typically shorter than available dosimetric information; source placement was by physicians other than radiation oncologists (interventional cardiologists); the target was not cancer; effective and safe doses were poorly understood, as were the target tissues. In addition, biological goal of IVB was unconventional: its goal was not to depopulate a population of malignant tumor cells, but to interrupt a benign proliferative process that compromised efficacy of invasive cardiac catheterization procedures. While some treatments used conventional LDR $^{192}$Ir sources within a catheter in the vessel, beta sources were also used. A variety of source configurations proliferated, including radioactive-liquid or -gas filled balloon catheters, catheters with the source material impregnating the wall, and stents incorporating radioactive materials. Dosimetric characteristics and other properties of IVBT sources were carefully examined in the AAPM Task Group No. 60 and No. 149 reports. The practice of IVBT increased incredibly quickly, passing with great rapidity from research institutions to small hospitals. IVBT work on refining IVBT stopped abruptly, along with the clinical practice, with the availability of drug-eluting stents.

The diversity of approaches in IVB foreshadowed even more novel delivery schemes and additional applications of brachytherapy, including to other benign clinical conditions. Some of the newer applications appear dissimilar to conventional brachytherapy.

- **Macular degeneration.** Brachytherapy for macular degeneration began with $^{103}$Pd episcleral plaques similar to the episcleral plaques used for ocular melanoma treatment. While this therapy provided benefit, a new intraocular approach using $^{90}$Sr in a device with a long needle-like tip is now in clinical trials (Epi-Rad90 Ophthalmic System, NeoVista, Fremont, CA). The invasive nature of this treatment differs markedly from most previous eye applications, and the treatment using a single small beta source presents extreme dosimetric challenges.

- **Radiochelated microspheres.** Although first developed in the 1960s, the wide-spread use of radio-labeled microspheres followed the commercial availability of the products and approval by the Food and Drug Administration in the early 2000s. The approved use currently is for liver cancer, where the microspheres are injected intra-arterially into the hepatic artery branch that feeds the tumor. The microspheres, being 20 to 40 μm in diameter, become lodged in the capillary mouths, irradiating the tumor from the periphery. The radiochel in the commercial product, $^{90}$Y (an almost pure beta emitter), penetrates only a few millimeters from the resting place of a sphere. For this treatment, investigators are just beginning to map the distribution of microspheres and establish the dose distribution with any accuracy.

- **Radiolabeled macromolecules.** Bordering on systemic therapy, many of the macromolecules are only slightly smaller than microspheres. The mechanism of targeting also differs from conventional systemic therapies, which either were metabolized and absorbed or were located in a compartment. Most often, these molecules attach to a target, frequently based on antibody interactions. As with the microspheres, the localization and dose distribution remain investigational as of this writing.

The last two applications fall into the category of microbrachytherapy, i.e., brachytherapy using microscopic carriers. Sometimes a fine, and often arbitrary, line divides microbrachytherapy from unsealed radionuclide therapy. In microbrachytherapy the radionuclide is tagged to carriers that are relatively large on the microscopic scale, and the physical size of the carrier influences strongly the localization of the dose distribution. In unsealed radionuclide therapy, the source carrier tends toward smaller molecules that often localize through metabolic processes, although, as noted above, these differentiations are only general. Very likely, the use and development of microbrachytherapy will increase in the near future, and the issues surrounding the dose distribution will be resolved.

**IV. CONCLUSION**

There has not been a period since its beginning that brachytherapy has not been a dynamic and changing discipline. The current era presents a face of brachytherapy that is changing faster than ever, with a future that portends an even greater diversity of sources and applications. The AAPM has been at the forefront of brachytherapy development, particularly with the work of task groups under the Brachytherapy Subcommittee.

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