Review paper

# The phylogeny of permanent prostate brachytherapy

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## Abstract

Permanent prostate brachytherapy has been practiced for more than a century. This review examines the influence of earlier procedures on the modern transperineal ultrasound-directed technique. A literature review was conducted to examine the origin of current clinical practice. The dimensions of the modern brachytherapy seed, the prescription dose, and implant/teletherapy sequencing are vestigial features, which may be suboptimal in the current era of low-energy photon-emitting radionuclides and computerized dose calculations. Although the modern transperineal permanent prostate implant procedure has proven to be safe and effective, it should undergo continuous re-evaluation and evolution to ensure that its potential is maximized.

J Contemp Brachytherapy 2013; 5, 2: 89-92
DOI: 10.5114/jcb.2013.35562

**Key words:** brachytherapy, history of medicine, prostate cancer, prostatic neoplasms.

## Purpose

Transrectal ultrasound-guided permanent prostate brachytherapy (PB) was introduced 30 years ago in Denmark, and there are now mature series demonstrating excellent and durable disease control [1–3]. Despite advances in radiobiology and technology, the general procedure has changed little over the intervening years. Prostate brachytherapy is one of several choices in the highly-competitive arena of prostate cancer treatment options, which includes external-beam radiotherapy (EBRT), surgery, cryotherapy, and possibly high-intensity focused ultrasound (HIFU). These treatment modalities have evolved to reduce toxicity, adopting features such as image-guidance (EBRT), nerve-sparing (prostatectomy), robotics (prostatectomy), and urethral warming (cryotherapy). Prostate brachytherapy must also evolve to remain a vital, relevant, and competitive treatment option. The American Brachytherapy Society has recently issued guidelines, based upon current practice, for the 'safe and efficient delivery of PB' [4].

Evolutionary biologists have noted that organisms often retain vestigial traits that reflect their phylogeny (evolutionary history). Such features may be superfluous or even detrimental. Similarly, medical procedures can retain elements of techniques and technology that they have replaced. We have identified several such features in the modern prostate brachytherapy procedure.

## Seed dimensions

Almost all permanent brachytherapy sources ('seeds') have the same dimensions: 4.5 mm in length and 0.8 mm in diameter. How did these dimensions originate, and are they essential to the technique?

Urologists began treating prostate cancer with intra-urethral radium ($^{226}$Ra) tubes more than a century ago [5, 6]. Temporary interstitial prostate brachytherapy was introduced at New York's Memorial Hospital in 1915 [7]. Memorial's large stock of $^{226}$Ra was kept in solution, and the emitted radon ($^{222}$Rn) was utilized for treatment [8]. $^{222}$Rn's greater specific activity (compared to $^{226}$Ra) allowed use of thinner needles, reducing the trauma of implantation [9]. Urologist Benjamin Barringer inserted $^{222}$Rn needles through the perineum and into the prostate, where they remained for hours; in this way, he initiated out-patient temporary interstitial PB. By 1920, he attempted *permanent* implantation using $^{222}$Rn in tiny capsules fashioned from glass capillary tubes [10]. This resulted in painful necrosis, because the emitted β particles easily traversed the glass, depositing a destructive dose into immediately adjacent tissue [11].

Physicist Gioacchino Failla tackled this problem by encapsulating the $^{222}$Rn in gold tubing, rather than glass. In a series of experiments, he determined that a 0.3 mm thickness of gold would filter 99.6% of the harmful β particles, but allow passage of 82% of the therapeutic γ rays [11]. These 'seeds' were 0.8 mm in width and 4-5 mm in length, and could pass through an 18-gauge needle. They became quite popular in the U.S. and were used to implant a wide array of benign (nevi) and malignant (oral, pharyngeal, bladder, prostate) tumors. Seed injectors with magazines (i.e., 'guns') were devised for rapid insertion [12]. The use of $^{222}$Rn seeds persisted for decades, the last U.S. manufacturing facility of $^{222}$Rn seeds closed in 1981 [13].

The modern brachytherapy seed was introduced in 1965. Health physicist Donald Lawrence, in consultation with Memorial radiation oncologist Ulrich Henschke, encased a nylon filament impregnated with $^{125}$I inside titanium tub-

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Received: 30.04.2013
Accepted: 04.05.2013
Published: 25.06.2013

ing [14]. Titanium was preferable to gold, because it transmitted the low-energy γ- and X-rays from $^{125}$I (which does not emit high-energy β particles). While 0.3 mm capsule walls were no longer needed, Lawrence replicated the $^{222}$Rn seed dimensions to ease transition, but also because he fashioned the seeds by hand and could not work with smaller tubing [14]. Multiple manufacturers have since produced iodine ($^{125}$I), as well as palladium ($^{103}$Pd), and cesium ($^{131}$Cs) seeds. While surface variations (such as dimpling, to enhance echogenicity) have been employed, the seed dimensions have essentially been maintained. However, a thinner (0.5 mm diameter) $^{125}$I seed that can pass through a 20-gauge needle has been introduced [15, 16] and is being evaluated to determine if the smaller puncture would reduce urinary and sexual toxicity [17]. The optimal design from the perspective of post-implant dosimetry and localization uncertainties does not appear to have been explored.

## Prescription dosing

The recommended $^{125}$I monotherapy prescription dose for a prostate implant is 144 Gy [18-20]; prescription doses for $^{103}$Pd and $^{131}$Cs implants have been calculated to be radiobiologically equivalent [21, 22]. But how was the 144 Gy dose derived?

It had been determined by Paterson and Parker in Manchester [23] and Quimby in New York [24] that the appropriate dose for treating an epithelial tumor with radium needles was 6,000-8,000 rads delivered over 6-8 days. Quimby generated tables for determining equivalent radiation effect between temporary $^{226}$Ra (mg-h) and permanent $^{222}$Rn (mCi) implants [25]. The most common permanent implant performed at Memorial Hospital in the 1950's was of unresectable lung tumors [26], for which a dose of 8,000 rads optimally balanced efficacy with toxicity [27]. Memorial's physicists had to assist in determining an appropriate prescription dose when $^{125}$I was introduced. With a half-life of almost 60 days, an $^{125}$I implant clearly must deliver a higher dose than a $^{222}$Rn (half-life of 3.8 days) implant. Lung tumor implants with $^{125}$I delivering 16,000 rads were found to be as effective as $^{222}$Rn implants delivering 8,000 rads [27], so a conversion factor of 2 was empirically derived [28, 29]. The same prescription dose (160 Gy) was employed when open $^{125}$I prostate implants were instituted at Memorial in 1970 [30].

Danish urologist Hans Henrik Holm adopted the 160 Gy dose when he introduced ultrasound-guided transperineal PB in the early 1980's [31], as did Haakon Ragde and John Blasko when they brought the procedure to the United States of America [32]. This dose was reduced by 10% (to 144 Gy) in 1999, based upon the exclusion of titanium K-edge characteristic X-rays from low-energy air-kerma strength calibrations [18, 33, 34].

But is a prescription dose derived from the treatment of lung tumors with $^{222}$Rn appropriate for treating prostate cancer with $^{125}$I? Properly distributed, 144 Gy has been demonstrated to be an *effective* PB dose, but is it *optimal*? When Memorial's brachytherapists and physicists empirically adopted a conversion factor of 2 to apply their clinical experience with $^{222}$Rn to dosing with $^{125}$I (without the benefit of radiobiological calculations), they recognized that it was no more than 'an educated guess and is subject to revision on the basis of further experimental studies and clinical experience' [28]. There are indications that 144 Gy may not be optimal for prostate cancer [35], and even the historical dose used for permanent lung brachytherapy required adjustment [36, 37]. Should all prostate cancers, regardless of bulk and grade, be treated to the same dose? Henschke utilized a sliding scale based on implant volume [28], and customized dosing has recently been proposed [38]. Re-evaluation of the dose-response relationship may define optimal dosing prescription, resulting in greater efficacy or reduced toxicity. Perhaps the reason the brachytherapy community has not addressed this issue is that the relationship between dose and response is unclear [39]. This ambiguity reflects the inadequacy of currently accepted dose metrics ($D_{90}$, $V_{100}$) to adequately measure implant quality, only single points on a given DVH. Metrics that are independent of post-implant CT contouring subjectivity are needed to mount meaningful multi-institutional trials.

## Seed/beam sequencing

When Holm introduced the ultrasound-guided transperineal PB in the early 1980's, he prescribed a dose of 160 Gy followed by 47.4 Gy in 20 fractions of EBRT. Rectal toxicity was so high that he was forced to abandon the procedure [40]. Although John Blasko appreciated the potential of the combined-therapy approach, he was daunted by the toxicity that Holm's patients had experienced and prudently altered the prescription [41]. Lower grade/stage tumors were treated with implant monotherapy; more aggressive or advanced tumors received combined therapy, but the implant prescription dose was reduced to 120 Gy. He was also concerned about the dose intensity of concurrent implant and EBRT, so he also altered the sequencing. EBRT (45 Gy over 5 weeks) was delivered first, and the implant was performed one month later.

There are potential advantages to preserving Holm's original sequencing. Although physicists prepare an optimal implant plan, brachytherapists do not always achieve it. There is often underdosing due to an unanticipated degree of tissue elasticity, glandular swelling, and seed migration. By delivering EBRT first, the opportunity is lost to compensate for a suboptimal implant. Reversing the order by implanting before EBRT may be beneficial where dose-painting, achievable with intensity-modulated EBRT, can complement the implant dose distribution. Use of short half-life radionuclides ($^{103}$Pd and $^{131}$Cs at 17 and 9.7 days, respectively) reduces concern regarding concurrent EBRT dosing since > 90% of the brachytherapy dose is delivered after 8 weeks. However, the optimal role of each radionuclide has not been determined, nor has this question been asked in a randomized, multi-institutional, prospective study [42, 43].

## Technique traits

Haakon Ragde's ultrasound unit was monophasic when he and John Blasko performed their first PB implant 1985 (John Blasko, personal communication, 2011). By necessity, they relied on ruler measurements to determine depth of needle insertion; miscalculation could result in inadequate coverage

of the base of the gland, or placement of seeds in the bladder or penile bulb [44]. Although biphasic ultrasound units (with sagittal imaging that allowed direct measurement of insertion depth) were soon introduced, the 'Seattle technique' did not reflect this capability for a decade [45]. Hundreds of brachytherapists travelled to Seattle in the 1990's to learn the procedure; the technique they acquired did not utilize sagittal imaging. It is likely that many prostate brachytherapists still do not fully exploit the capabilities of their equipment.

Other vestigial prostate brachytherapy practices include:

a) source calibrations based on air-kerma strength [34],
b) post-implant assessment based upon CT scanning 30 days after the implant rather than at a time that reflects the temporal resolution of edema and the radionuclide's half-life [46],
c) selection of radionuclide by convention rather than by a methodical multi-institutional study, and
d) treatment planning based on dose calculations to water instead of the tissue of interest [47].

## Conclusions

Evolutionary biologists have demonstrated that organisms retain superfluous behavioral and structural traits that reflect their evolution. These features are not beneficial and may even be detrimental. Similarly, vestigial features persist in medical procedures. Although PB has been demonstrated to be an effective treatment modality, reappraisal of time-honored conventions is warranted. If we rely on dogma rather than intelligent design, PB will struggle for survival in the face of competing technologies.

## Acknowledgements

We acknowledge Carl F. Moxey, PhD of the Department of Biology at Anna Maria College in Paxton, Massachusetts for his contributions on evolutionary biology.

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