

Dr. Dattoli on the Choice of Brachytherapy Isotopes

Pd-103 vs. I-125

Palladium-103 and Iodine-125 are the most commonly used radioisotopes for permanent prostate brachytherapy. Neither type of seed needs to be removed from the body after implantation, as they are made from materials that are accepted by the body over time. They are non-ferromagnetic and will not interfere with diagnostic tests such as CT's or MRI's. The choice of Pd-103 versus I-125 is typically based on physician preference, though it is sometimes driven by patients. While the debate continues as to which isotope is superior, Palladium has long been my isotope of choice, even for low-grade prostate malignancies.

My preference dates back to my experience with both Pd-103 and I-125 at New York University Medical Center and Memorial Sloan-Kettering in the mid-1980s. My research and clinical practice in Tampa over the following decade and my experience in Sarasota during the past two decades have confirmed for me the advantages of Pd-103 for my patients.

While there have been no definitive human clinical trials to date comparing tumor-control rates with Pd-103 and I-125, one study reported a lower complication rate for Pd-103 (Peschel RE, et al, Cancer J. 2004 May-Jun;10(3):170-4.) Another study reported a faster recovery rate from radiation-induced prostatitis with Pd-103 (Wallner K, et al, Cancer J. 2002 Jan-Feb;8(1):67-73).

Both Palladium and Iodine are effective implant sources, but I have found the short-lived side effects associated with Pd-103 to be especially advantageous in the context of a large brachytherapy-based practice. The following discussion is not intended to settle the debate, but rather to explain my rationale over the years for encouraging my patient to choose Pd-103.

Radiobiology and the Dose Rate Phenomenon

The physics of Pd-103 versus I-125 has been rigorously studied. A Pd-103 implant is usually planned to deliver a 11,500-12,000 cGy to full decay at an initial dose rate of approximately 20 cGy/hour. I-125 implants deliver radiation at a lower dose rate of approximately 5-10 cGy/hour. The half-life for each isotope is the period of time until its output of radiation is halved. The half-life of Pd-103 is seventeen days compared to sixty days with I-125. With Palladium, most of the radiation dosage is delivered in three months compared to six to eight months with Iodine. While the dose delivery is as stated, side effects with each isotope may be longer in duration due to clinical lag time.

Results favoring Palladium might be expected given radiobiological considerations. Most radiobiologic data is derived from theory or based on in vitro studies. It is known that radiobiological effect (RBE) decreases with decreasing dose rate primarily as a result of

the tumor's ability to repair potentially lethal and sub-lethal damage, but also because of recruitment of a relatively quiescent sub-population of cells and re-population of initial target cell populations; If the dose rate is too low, tumors associated with rapid cell cycles (e.g. 2-5 days) may not be effectively killed. Although no human clinical data with long-term follow-up is available, the higher dose rate of Pd-103 would theoretically be more successful in eradicating aggressive and rapidly proliferating tumors.

In this regard, it should be noted that low energy photons have a higher linear energy transfer (LET), associated with higher RBE. The greater radiobiologic effect is presumably the outcome of greater energy delivered per cell that the photon traverses. The average energy of Pd-103 photons is 21 keV (kiloelectron volts) as compared to 29 keV with I-125. Thus Palladium would be expected to have a slightly higher LET and RBE compared to Iodine.

In Vivo and In Vitro Studies

In vivo animal models (e.g. studies of rat prostate tumors) and also in vitro studies do in fact demonstrate a significant benefit with Pd-103 for higher-grade tumors, but also an advantage in low-grade tumors. An early study by Nag and colleagues demonstrated the tumoricidal effect of Pd-103 was greater than I-125 by at least factor of two (Nag S, et al, *J Brachyther Int.* 1997; 13: 243-251). The RBE of Pd-103 versus I-125 was compared by Ling and colleagues using rat embryo cells transfected with Ha-ras oncogene. While the applicability of results from such in vitro experiments to the clinic is limited, this study reported an RBE of 1.9 for Palladium versus 1.4 for Iodine (Ling CC, *The relative biological effectiveness of I-125 and Pd-103.* *Int J Radiat Oncol Biol Phys.* 1995; 32: 373-378). These favorable Pd-103 results may be based at least in part on the dose rate phenomenon.

Only one early study suggested that I-125 might be more effective for low-grade tumors while Pd-103 would be superior for high-grade carcinomas (Ling CC, *Permanent implants using Au-198, Pd-103 and I-125: Radiobiological considerations based on the linear quadratic model,* *Int J Radiat Oncol Biol Phys.* 1992; 23: 81-87). This was a highly theoretical model based on the biologic effective dose (BED) formula, with questionable alpha/beta ratio assumptions. The study has virtually no clinical applicability, as the central mathematical equation used to calculate the cell survival level relied on variables about which little or nothing is known when applied to human prostate cancer.

It should be noted that a dose of 16,000 cGy with I-125 is considered biologically equivalent to a dose of 11,500 cGy with Pd-103. However, it should be understood that most I-125 dosimetry in past years used an incorrect 'gamma factor' which overestimated the dose. Therefore, when the 11,500 cGy Palladium dose is delivered, it is actually a greater radiobiological dose than was delivered by the older I-125 implants cited in the medical literature.

Because of the lower energy of photons emitted by Pd-103 compared to I-125 (21 keV avg. versus 28 keV avg.) radial dose fall-off is more steep at any distance from Pd-103

seeds, especially since attenuation coefficients (e.g., tissue, scatter, other seeds) increase rapidly with decreasing photon energy and are in fact exponential. Therefore, at greater distance from a Pd-103 implant, the dose is significantly reduced when compared to I-125, e.g., at a distance of 10 cm in tissue, the dose of Pd-103 is approximately 1/10 that for I-125 (Nath R, Int J Radiat Oncol Biol Phys, 1992; 22: 1131-1138). This is not insignificant clinically and shows that tissue penetration is distinctly dissimilar between the two isotopes despite their energies being relatively similar. The same phenomenon, however, may lend itself to cold spots if Palladium seeds are not accurately placed, so an experienced brachytherapist is required to achieve optimal outcomes.

Why I Continue to Choose Pd-103

As mentioned, I have extensive experience using both Iodine and Palladium for prostate cancer (as well as Iridium-192 with High Dose Rate (HDR) temporary brachytherapy as discussed below. Both Pd-103 and I-125 cause their share of temporary urinary symptoms, but I have found the duration to be different with each isotope, while the peak severity of each is essentially the same. The peak with I-125 is slightly greater; 2-3 weeks peak for Pd-103, and 3-5 months peak for I-125.

Over the years I encountered too many patients having long-lasting, lingering symptoms with I-125, and this was somewhat discouraging. In contrast, Pd-103 symptoms are typically short-lived, predictable and I find more easily manageable: With formalized management protocols, we have significantly reduced implant morbidity. The need for catheterization in any patient is less than 2%. The faster clinical response rate associated with Pd-103 generally enables the success of treatment to be assessed more quickly.

Because of the unique concave design of the Palladium seeds, they are very stable within the gland tissue, rarely migrating outside the desired placement. By contrast, the convex (football) shape of Iodine seeds can cause them to migrate from the target. For this reason I-125 is usually inserted as "strands" which secure one seed to the next, although this leaves behind more foreign bodies and makes intra-operative changes which are almost always necessary more difficult. Iodine is a much more penetrating radiation than is Pd-103, potentially adversely affecting the bladder, urethra, rectum and sexual function.

In the unfortunate event of a prolonged catheterization with a Pd-103 implant, a transurethral incision of the prostate (TUIP) or transurethral resection of the prostate (TURP) can be safely performed without concern of interfering with cancericidal dose delivery (if seeds are disturbed or removed) since 95% of the Palladium dose is delivered within 8 weeks. This is certainly not the case with I-125 where consideration of maintaining a catheter for a much longer period must be considered. Also, the steep dose fall-off with Pd-103 allows us to more easily perform implants in patients having previous TURP's and has also enabled us to successfully salvage patients who have previously been treated with radiation and failed.

Many of my patient's treated back in the 1990s at Memorial Sloan-Kettering Cancer Center underwent very contemporary techniques implant with I-125, yet rectal

ulcerations were not uncommon (Wallner K, et al, Short-term freedom from disease progression after I-125 prostate implantation. *Int J Radiat Oncol Biol Phys*, 1994 Sep 30;30(2):405-9). Meanwhile not one of my patient's having Pd-103 implantation has experienced a rectal ulceration.

My data over the years suggests that Palladium is indeed very effective treating low-grade prostate tumors. It is well known that patients may be initially under-graded and many of us believe that up to 40% of patients harbor higher-grade tumors within their glands that were simply missed by initial biopsies, which is another compelling argument for the use of Pd-103.

The disadvantages with Pd-103 are primarily associated with the short half-life, which requires replacement and/or dosimetric corrections if the seeds are not used at the planning date. This rarely allows for re-utilization of the isotope. Also, technical accuracy of seed placement with Pd-103 is more demanding and requires greater skill on the part of the brachytherapist. I always recommend brachytherapy newcomers to use I-125 at first since it is far more forgiving of geographical targeting misses than Pd-103. In that regard, I believe that stricter standards need to be set by the medical community to ensure improved technical acumen; a one to two day teaching course will never suffice.

With regard to our combination protocol with external beam radiation therapy and Pd-103 brachytherapy, I often tell patients that “cancer doesn’t like change,” and virtually all cancers today are treated with combined modalities, including external and internal radiation such as Dynamic Adaptive Radiotherapy (DART) followed by a brachytherapy boost. This change of therapeutic approach is important with virtually every cancer, hence the common utilization of combined modality treatments in contemporary cancer medicine (e.g. chemotherapy and radiotherapy, surgery and radiotherapy, and chemo-surgery-radiation)

This discussion is not intended to end the still ongoing debate over I-125 versus Pd-103, but rather to explain for patients and colleagues my rationale for choosing Pd-103. It is my hope that with improved implant techniques, results with I-125 and Pd-103 will become generalizable. Only a well-conducted, randomized clinical trial will ultimately settle the controversy, but I think the results I have reported in my published studies are telling.

Other Brachytherapy Isotopes

Another isotope, Cesium-131, is currently being investigated as a permanent implant. It has a shorter half-life (9.7 days) and a higher average energy (29 KeV) than both I-125 and Pd-103. This means that Cesium-131 is likely to deliver a higher dose to surrounding healthy tissue over a shorter period of time; and therefore, there is an increased risk of complications over time. Like Gold-198 (Au-198), another isotope that was used some years ago, the shorter half-life of these isotopes with 9.7 days for Cesium-131 and 2.7 days for Au-198 makes them impractical to use in a clinical setting.

A 2018 study by the MD Anderson Cancer Center compared quality of life (QoL) outcomes following brachytherapy with Palladium, Iodine and Cesium isotopes. These researchers reported that “Cs-131 showed a statistically significant decrease in QoL regarding bowel and sexual function at 12 months compared with Pd-103” (Blanchard P, et al, Patient-reported health-related quality of life for men treated with low-dose-rate prostate brachytherapy as monotherapy with 125-iodine, 103-palladium, or 131-cesium, *Brachytherapy*. 2018 Mar - Apr; 17(2):265-276).

Iridium-192 is an isotope used for temporary brachytherapy implants, known as high dose rate (HDR) brachytherapy. Ir-192 brachytherapy is often combined with external beam radiation. HDR is a form of hypofractionated radiation, which involves limited, very high dose rate treatment sessions (fractions). This form of brachytherapy delivers the highest dose of radiation to the entire body due to the penetrating nature of Ir-192. The best-case protocol utilizes 5-6 fractions (treatment sessions over time), but many patients can only tolerate 2 fractions. There are many published studies for HDR, but no long-term data supporting HDR as a sole therapy or a combined therapy compared to permanent implants and/or combination therapy (permanent implants or HDR combined with EBRT).

An Australian study of HDR monotherapy with 10-year follow-up reported that for intermediate and high-risk patients, the biochemical disease free survival rates were 86.9% and 56.1%, respectively. Patients with 3 high-risk factors had a biochemical survival rate of only 39.5%, and that figure was inflated because these researchers did not employ a sufficiently stringent PSA nadir value to measure success. The study also reported that serious urethral strictures affected 13.6% of patients (Yaxley JW, et al, *BJU Int*, 2016 Sep 15).

A more recent study from UCLA reported on intermediate risk patients treated with 6 fractions of HDR as monotherapy (without external radiation or hormonal therapy). The biochemical disease-free survival for these patients after 8 years of follow-up was 90%, which is no doubt an inflated success rate because biochemical failure was defined in this study according to less than stringent criteria (an increase of 2 ng/ml or more above the nadir PSA, that is, the lowest PSA reached following treatment). Only 68% of patients retained erectile function, and long-term genitourinary morbidity was more than 36.3%. (Patel S, et al, *Brachytherapy*, 2017 Mar - Apr;16(2):299-305).

There really is no good argument for Ir-192 HDR, aside from the fact that the procedure reimburses doctors substantially more than Pd-103 or I-125. I performed hundreds of HDR procedures early in my career and I had to use lead shielded goggles to prevent my patients from developing cataracts. Suffice to say in conclusion that to date there are no reported long-term results with HDR that compare to the results that we have achieved over the years with our combined treatment protocol utilizing external radiation therapy and Pd-103 brachytherapy.