WHEELING™ HOSPITAL

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28 September 2010

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U.S. NRC Region I
Attn: Penny Lanzisera
475 Allendale Road
King of Prussia, PA 19406-1415

Re: License No. 47-05322-02

Dear Ms. Lanzisera:

This is in response to your request for additional information about our low dose rate, permanent seed prostate brachytherapy program.

Attached is my rationale describing and explaining what we do at the Schiffler Cancer Center. As part of that document, I have listed six reasons why it would be a medical and scientific mistake for the NRC to define a medical event as a brachytherapy implant where the D_{90} is outside the range of the prescribed dose by ± 20%.

In defending our own practices, I am also defending a treatment modality that I love — prostate brachytherapy — with as much passion and vigor that I can muster because I am appalled and mortified at the harm ill-conceived NRC regulations may do to this field.

In my attempt to make my position clear and to be thorough and comprehensive, the document has grown in length. Nevertheless, I hope you and your colleagues take the time to read it and call or email me with any questions. For most substantive statements there is a reference cited, and I have bound all the reference documents in the accompanying 3-ring binder.

Permanent seed brachytherapy is the most effective and lowest cost treatment for prostate cancer. Because radioactive seeds are relatively cheap and easy to make, extensive competition has made them a low cost commodity. Although radiation oncologists are reimbursed much more generously when offering competing modalities, they continue to offer brachytherapy because they and their patients recognize the superior outcomes.

Our goal is to cure every patient we treat while minimizing complications. That's not a remarkable statement, but we are as close to achieving that goal as anyone. Looking at the work of our better brachytherapy colleagues, prostate brachytherapy has a greater potential to achieve that goal than any other modality. This is what the NRC is putting in jeopardy and why I have responded in such depth.

Best regards,

Wayne Butler

Wayne M. Butler, Ph.D.

Rationale for Prostate Brachytherapy

Wayne M. Butler Ph.D.
Schiffler Cancer Center
Wheeling Hospital

Our goal in performing permanent seed prostate brachytherapy is to cure every patient we treat while minimizing complications. We weigh both aspects of treatment — cure and complications — with equal gravity. Dr. Gregory Merrick carefully and in considerable detail informs every patient that even though our cure rates are quite high, some patients will fail, and even though our complications rates are very low, some patients will have miserable days and weeks. Of course, no therapy for life-threatening cancer can guarantee cure, and no therapy is without peril. In recognition of the latter, six years ago Dr. Merrick began performing transperineal, template- and ultrasound-guided, 40 – 60 core mapping biopsies to clearly identify low-risk patients who can safely be placed on long-term active surveillance rather than treatment.[1] We now have under surveillance a large cohort of patients, none of whom have dropped out, progressed, or opted for treatment. This is changing the nature of our implant patients from what was primarily a low-risk population in our first years to a population skewed toward intermediate and high-risk men in recent years.

Throughout the years, our implant philosophy has remained remarkably consistent because one brachytherapist, Dr. Merrick, has placed all needles and implanted all the seeds using a plan devised by a one physicist, me. There has been no change in other key personnel for almost ten years,: the same therapist loads all needles and verifies the loading with an autoradiograph, one physicist confirms the seed strength used in the plan and verifies the strength of incoming seeds to be used in the intra-operative plan and post-implant dosimetry, the same certified dosimetrist sets up fluoroscopy in the O.R., sets up and verifies the accuracy and quality of the ultrasound imaging, and performs post-implant dosimetry, and one other physicist has performed all the intraoperative dosimetry since we began doing that 3 years ago. How we arrived at our treatment philosophy is best explained by summarizing what we know about survival and complications in prostate brachytherapy.

Outcomes:

Survival

Dr. Gregory Merrick and I have a profound regret about our brachytherapy program: we wish we had begun years earlier. We waited for the patient outcomes data being reported by John Blasko and colleagues in Seattle to mature. We waited for the characterization of the radioactive seed sources, ^{125}I and ^{103}Pd, to settle on consensus values. When the patient data continued to look good, we finally began implanting patients in 1995. We were amazed at how rapidly post treatment PSA values plummeted compared to external beam radiation therapy. We saw that the low morbidity claimed by users and the seed manufacturers was not just hyperbole but a consistent outcome readily achievable in a community setting.

Our group at the Schiffler Cancer Center has conscientiously, systematically, and prospectively amassed a vast array of clinical, dosimetric, and outcome data on our implant patients. We have since published over 200 peer-reviewed papers on prostate brachytherapy, dozens of them on survival and morbidity. Our most recent paper analyzed the 1,656 patients implanted here from the inception of our program in April 1995 through July 2006.[2] The 12-year biochemical progression free survival (bPFS) was 95.6%, cause-specific survival = 98.2%, and overall survival = 72.6%. The survival outcome most correlated to dosimetric quality is bPFS, and the 12-year bPFS for our population in terms of patient risk groups is: low-risk = 98.6%, intermediate-risk = 96.5%, and high-risk = 90.5%. These are among the best results reported not only for prostate brachytherapy, but also for any prostate treatment modality. The figures below are from our 2010 publication:[2]

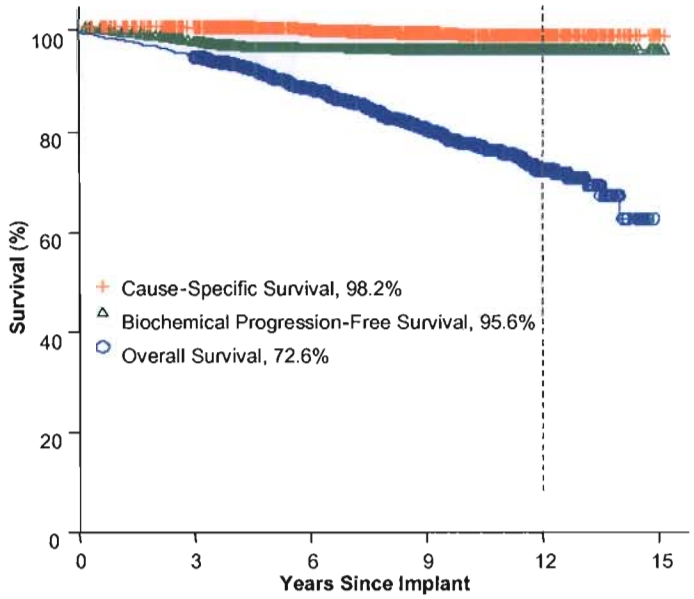


Fig. 1. Kaplan-Meier curves for biochemical progression-free, cause-specific, and overall survival. Each curve represents the same patients.

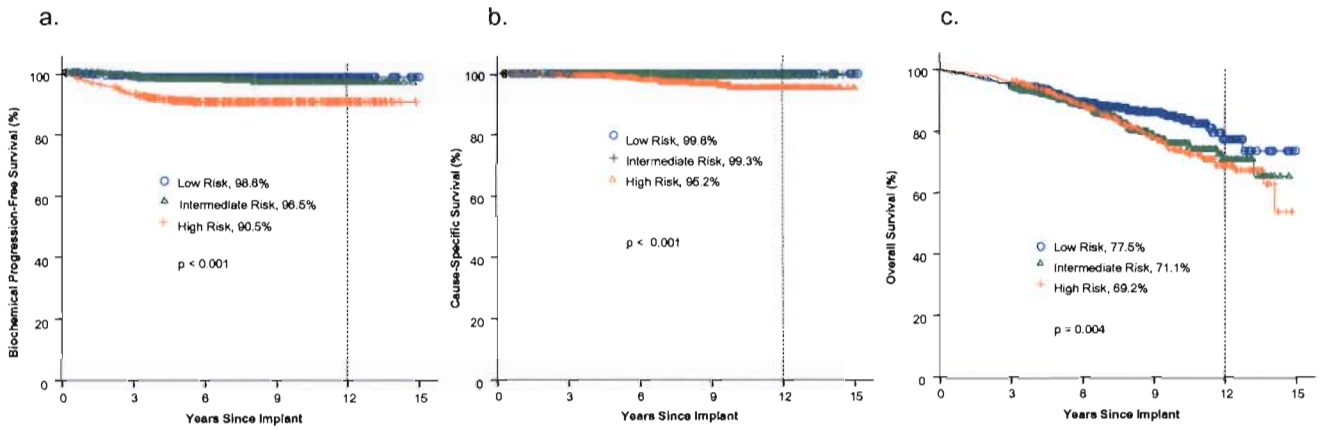


Fig. 2. (a) Kaplan-Meier curves for biochemical progression-free survival, stratified by risk. (b) Kaplan-Meier curves for cause specific survival stratified by risk. (c) Kaplan-Meier curves for overall survival, stratified by risk. (p values represent single tests for linear trends across all factor levels.)

Urinary, sexual, and rectal complications

Because the urethra passes centrally through the prostate, urinary symptomatology is the most likely consequence of excessively high doses. We set up our protocol to document of urinary morbidity beginning with our first prostate implant patient: using the International Prostate Symptom Score (IPSS), we obtain 15 evaluations of urinary function the first year and tapering off gradually to two evaluations per after three years. With such frequent follow-up, we have never lost track of any patient, so our database is unmatched by any other institution in terms of a very large population monitored at such high-frequency intervals. Our most recent paper on urinary morbidity analyzed over 1,000 patients in terms of temporal changes in IPSS plus resolution of the frequency and severity of dysuria.[3] The mean time to return to preimplant baseline was less than 8 weeks, and there was no correlation between any prostate or urethral dosimetry parameters. This rapidity of return to baseline has been unmatched in the published permanent seed prostate brachytherapy literature. We have also shown that our IPSS results are durable beyond 6 years.[4] The figures below are from that publication.

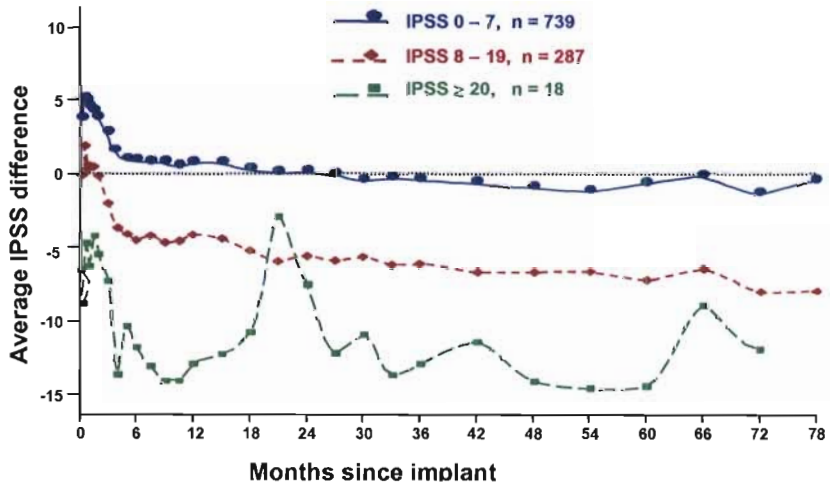


FIG. 3. The mean IPSS difference from the baseline IPSS stratified by pre-implant IPSS group: IPSS 0–7 (739), IPSS 8–19 (287) or IPSS ≥20 (eight).

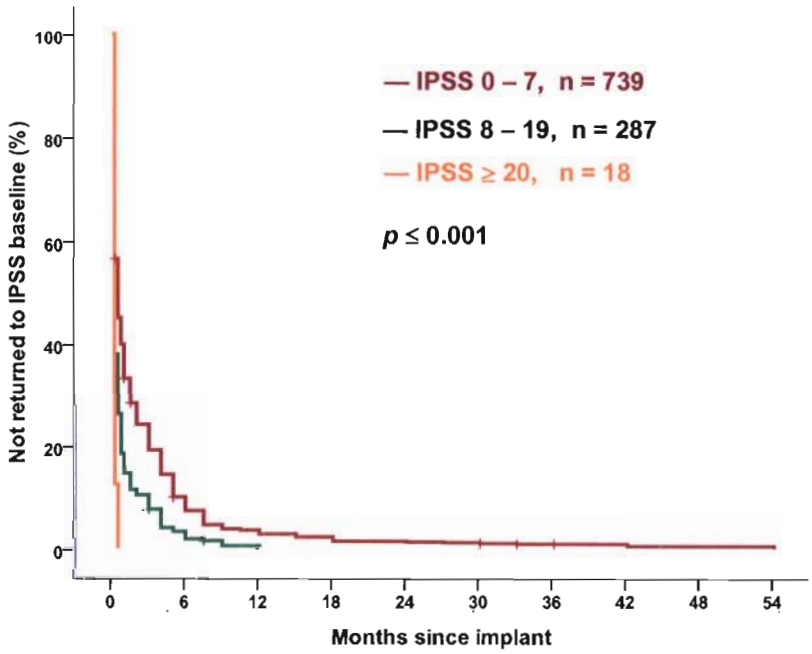


FIG. 4. A Kaplan-Meier curve of the fraction of the population not returned to the baseline IPSS, stratified by pre-implant IPSS group: IPSS 0–7 (739), IPSS 8–19 (287) or IPSS ≥20 (eight).

Because our 5-year potency preservation rate without pharmacologic or mechanical assistance was only 39% — the rate is 92% with assistance — we searched for but could not find a correlation between prostate dosimetry and erectile dysfunction (ED).[5] We determine ED status using a validated patient administered questionnaire: the International Index of Erectile Function (IIEF). We continued looking and eventually found a dose-response between ED and dose to the proximal penis.[6] Dr. Merrick and I concluded that with small changes in seed placement planning and operative execution, the dose to critical erectile structures could be reduced to negligible levels without affecting prostate dosimetry. While in the process of implementing these changes, we published a study on 124 of our patients who were enrolled and implanted in clinical trials during 2001 and 2002. Patients in the study were potent at the time of implant and were still alive in 2008.[7] Factors such as age and preimplant erectile function (as in the figure below) were predictive of potency preservation, but dose to the prostate was not.

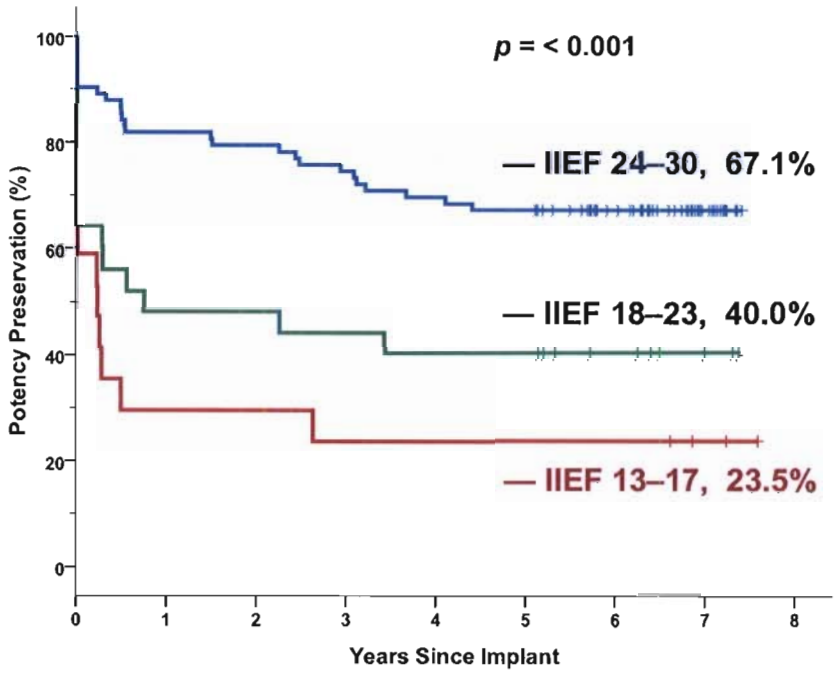


Fig. 5. Kaplan-Meier potency preservation stratified by preimplant index of erectile function (IIEF) scores. For the IIEF 24–30 group, n = 82; the IIEF 18–23 group, n = 25; the IIEF 13–17 group, n = 17.

Although only 55.6% of men retained their potency at 7 years without pharmacologic or mechanical assistance, this was a notable improvement over our earlier studies showing less than 40% retention of potency. Dose to the prostate still did not predict for ED while dose to the penile bulb and crura did, but the statistical significance of dose to these latter structures was less than in our previous work. Our most recent data (unpublished) as well as several published studies from other institutions indicate that dose to the proximal penis is no longer predictive of ED, probably because everyone is conscious of those sensitive structures and avoids placing seeds near them.[8, 9]

Because of the mildness of postimplant bowel symptoms and the coarse gradation of Radiation Therapy Oncology Group scoring, we developed a questionnaire, the Rectal Function Assessment Score (RFAS), specifically to evaluate bowel function. The RFAS has since been utilized by other institutions in outcomes reports. Rectal morbidity is typically a late complication, so we have been especially diligent in

following patients implanted during our early years. In our most recent repeat analysis of that early cohort, we reported that the small increase observed in the mean post-implant RFAS over the preimplant value has continued its long, gradual decline to more favorable scores.[10] Although at no evaluation time was the total score correlated with rectal dosimetry parameters, different individual questions at some time points were correlated with dose. The sequential quality of life assessments based on the RFAS are summarized in the figure below from our most recent paper on that subject.

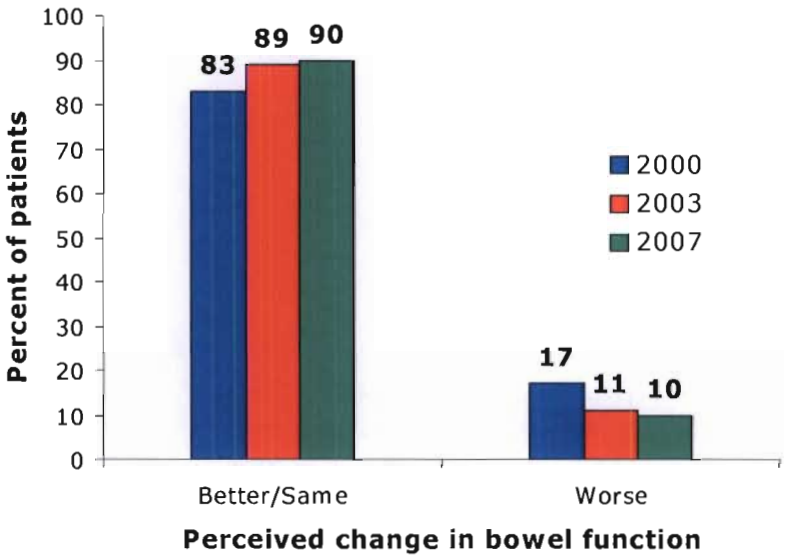


FIGURE 6. Perceived change in bowel function over three survey time points. Only those who completed all three surveys (n = 161) were included.

Prescription and planning criteria

Although our implant program began before there were any consensus guidelines, we have followed the evolving recommendations of the American Brachytherapy Society (ABS), American Association of Physicists in Medicine (AAPM), and American College of Radiology (ACR). Either Dr. Merrick or I or both of us has been involved in writing many of these guidelines. [11-14]

Dosimetric quantifiers in prostate brachytherapy planning

The only professional society that has included any numerical dosimetric criteria is the AAPM in its report of Task Group 137 chaired by Ravi Nath.[14] However, that report makes no suggestions regarding post-implant dosimetry thresholds, and the only recommendation pertinent to disease control is to plan a $V_{100} \geq 95\%$ of the target volume. The only mention of D_{90} is that as a consequence of the V_{100} recommendation, "Therefore, the D_{90} will be larger than the prescription dose (D_{90} > 100% of prescription dose." The report also states:

"Other prostate coverage and quality indices such as the planned *D*90 and *V*150 should be planned to lie in a narrow range, but the value of these parameters is dependent on the radionuclide and seed strength used as well as institutional preference. For beginning users, they should be considered variables adjusted in response to feedback from postoperative dosimetry."

It is physically impossible for $V_{100} = 100\%$ if $D_{90} = 100\%$. This is because, by definition, when $D_{90} = 100\%$, the coolest voxel in the hottest 90% of the volume is equal to the prescription dose and the remaining 10% of the volume is ≤ the prescription dose. When plotting two dosimetric quantifiers with shared indices, there will be a singularity in the graph. This is illustrated in the schematic of the allowed range of data points in a plot of V_d versus D_v shown below. At any Dose *d*, there will be a Volume *v* for which there is only one possible value. If plotting V_{100} versus D_{90}, and $d = 100\%$ of the prescribed dose, the only possible value for *v* when V_{100} is the other axis is 90% of the target volume. Therefore, setting $D_{90} = 100\%$ as a target dose is clinically untenable because you sacrifice coverage of the target.

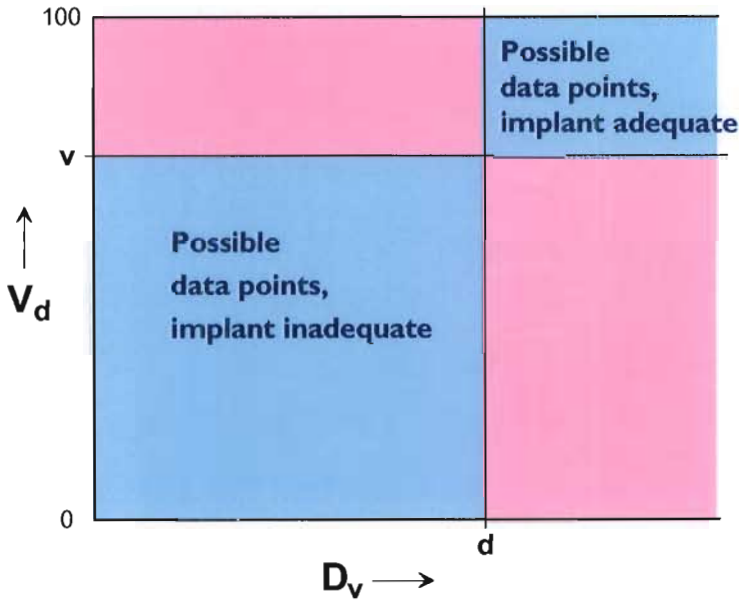


Figure 7. Schematic of a plot of V_d versus D_v. At the point where the D_v dose index percentage equals *d*, coincident with the volume index of V_d, the only possible value of V_d is *v*. When the plot is V_{100} versus D_{90}, the upper right sector of possible data points correspond to implants we consider adequate. Any patient implant with post-implant dosimetry in the lower left sector is considered inadequate.

When Dr. Merrick gives me an ultrasound volume study, he expects me to design an implant that will deliver his prescribed dose the entire target volume — clinical prostate plus 3-dimensional anterior and lateral margins of 5 – 7 mm (depending on patient risk and biopsy factors) and posterior margin not to extend more than 1 mm into the rectal wall. In radiation oncology, complete coverage of the target volume to the prescribed dose has always been the foremost goal. Dosimetrically, this means the volume covered by the prescription dose will be $V_{100} = 100\%$ or the minimum dose covering the target volume will be $D_{100} = 100\%$. The latter necessitates the former. In prostate brachytherapy, there is a term with a long historical provenance — minimum Peripheral Dose (mPD) — that we and many others use to formally label the prescribed dose and emphasize its coverage aspect.

Our first description of our implant philosophy was published over 10 years ago.[15] That paper describes and compares our implant philosophy with others in terms of dose-volume histograms (DVHs). The only summary dosimetric planning parameters we considered important enough to compare between approaches were V_{100} for coverage and V_{150} as a surrogate for complications. In a textbook chapter presented at the AAPM/ABS Summer School on Brachytherapy Physics, Dr. Merrick and I went into greater detail on factors we use to evaluate the quality of an implant plan.[16] Note in the table below reproduced from that book. D_{90} was not among the parameters we considered important for plan evaluation.

Table 1. Prostate implant plan evaluation criteria used at the Schiffler Cancer Center

Evaluated quantity	Parameter	Value
Patient specific needs	PTV, TURP dose, etc.	Primary importance
Planning volume coverage	V_{100}	> 99.8% volume
Urethral volume coverage	Urethral V_{125} Urethral V_{150}	10% – 50% volume < 15% volume
Urethra dose	Mean	110% – 140% mPD
Homogeneity	V_{150}	35% – 45% plan vol., ^{125}I 45% – 55% plan vol., ^{103}Pd
High dose volume	V_{200}	< 15% plan volume, ^{125}I < 25% plan volume, ^{125}I
Number of needles	Minimize	30 ± 4 *, †
Number of seeds	Minimize	130 ± 18 *, †
No. of especially loaded needles	Minimize	5 ± 2 *
Target volume / US volume	Ratio	1.75 ± 0.22 *

V_{100}, V_{150} and V_{200} are the percentage of the planning volume covered by 100, 150 and 200% of the prescribed dose (mPD), respectively.

* There is no statistically significant difference in these parameters between radionuclides, monotherapy, or boost therapy.

† Typically, 3 or 4 extra needles and 7% extra seeds are used at the time of implant beyond those called for in the plan.

Our only mention of D_{90} as a planning parameter is in a chapter of another textbook where we describe it as an index of planning volume coverage secondary to V_{100}, and that as a consequence of achieving $V_{100} > 99.8\%$, D_{90} should lie in the range 125% – 140%.[17]

Defining the target volume

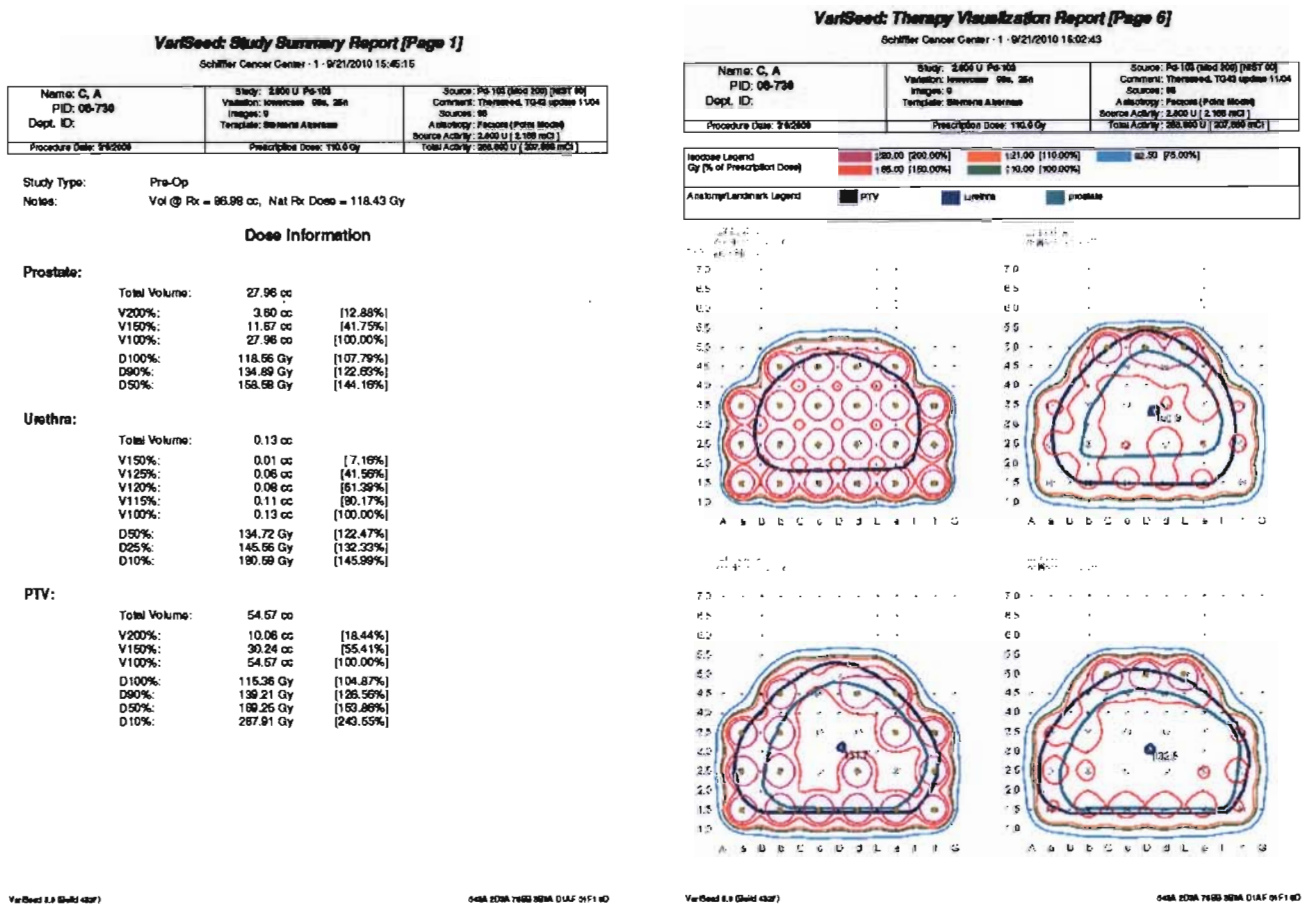
Our decision to expand the target volume beyond the prostate is based on a series of Johns Hopkins Hospital publications referred to as the "Partin Tables".[18] These tables, based on many thousands of radical prostatectomy specimens, present the likelihood of finding disease confined to the prostate, extending beyond the prostatic, involving the seminal vesicles, and involving lymph nodes. The probabilities are stratified in fine detail by clinical stage, pretreatment PSA, and Gleason score. For the typical low-risk patient we treat,

there is about a 25% chance of extraprostatic extension and less than a 6% chance of seminal vesicle or lymph node involvement. For intermediate- and high-risk patients, the likelihood of extraprostatic extension rises to about 50% and 75%, respectively.

How far local disease extends outside the prostate has been reported in four important papers from four institutions, but they all came to a similar conclusion — a 5 mm margin around the prostate would encompass at least 90% of all extraprostatic disease.[19, 20] Some brachytherapists use small or even no margins around the prostate in planning dosimetric coverage of the prostate on the assumption that extraprostatic disease will not require the full prescribed dose for sterilization. That assumption has been shown to be without merit by several papers on external beam radiation of residual disease remaining after radical prostatectomy. A study by King and Spiotto of Stanford compared progression free survival between patients receiving either 60 Gy or 70 Gy of salvage external beam radiation for confirmed local surgical failures.[21] Patients receiving the higher dose had more than double the 5-year progression free survival than the lower dose cohort — 58% versus 25%. Similar results were reported in a non-salvage setting when a large, high-risk, node-negative population was treated with early radiation therapy after radical prostatectomy (before failure) using different external beam dose levels.[22] They found significantly higher progression free survival in patients receiving external beam doses ≥ 70 Gy. This confirmed our conviction, evident from the beginning of our prostate brachytherapy implant program, that the target volume should be the prostate expanded with wide margins and the entire PTV treated to the full prescribed dose.

Written directive documentation

I submit my seed implant plan to Dr. Merrick as a 9-page printout from our treatment planning software, VariSeed™. The first page, illustrated below, contains numerical summaries of clinical and dosimetric data including V_d and D_v data for prostate, urethra, and target volume. I manually highlight any lines of data that are out of the ordinary. This may occur when patient clinical constraints or the desired seed strength result in a V_{200} for the Planning Target Volume (PTV) that exceeds 25% or V_{150} for the PTV is outside the range 55% – 65% or V_{150} for the urethra exceeds 10%. I annotate on that page the calculated volume ratio of PTV to prostate to verify that the enlargement requested by Dr. Merrick has been applied. I also check the ratio of the volume encompassed by the prescribed dose to the prostate volume because that number indicates how robust the implant will be to seed loss or migration. That page also includes the natural prescription dose which is derived from analysis of the differential DVH curve for the entire seed distribution independent of any anatomic volume. This number is very sensitive to seed placement philosophy, and for my modified-uniform/modified peripheral approach should be equal to 1.05 × the prescription dose ± 7%.



VariSeed: Study Summary Report [Page 1]

Schiffler Cancer Center - 1 - 9/21/2010 15:45:15

Name: C, A PID: 06-736 Dept. ID:	Study: 2.606 U Pd-103 Variation: lowercase 99s, 25s Images: 9 Template: Siemens Aisense	Source: Pd-103 (Med 309) [NIST 99] Comment: Theraseed, TG43 update 11/04 Sources: 99 Anisotropy: Fecces (Point Model) Source Activity: 2.600 U [2.166 mCi] Total Activity: 257.660 U [207.660 mCi]
Procedure Date: 9/9/2008	Prescription Dose: 110.0 Gy	

Study Type: Pre-Op

Notes: Vol @ Rx = 86.98 cc, Nat Rx Dose = 118.43 Gy

Dose Information

Prostate:

Total Volume:	27.96 cc	
V200%:	3.60 cc	[12.88%]
V150%:	11.67 cc	[41.75%]
V100%:	27.96 cc	[100.00%]
D100%:	118.56 Gy	[107.79%]
D90%:	134.89 Gy	[122.65%]
D50%:	158.58 Gy	[144.16%]

Urethra:

Total Volume:	0.13 cc	
V150%:	0.01 cc	[7.16%]
V125%:	0.06 cc	[41.56%]
V120%:	0.08 cc	[61.39%]
V115%:	0.11 cc	[80.17%]
V100%:	0.13 cc	[100.00%]
D50%:	134.72 Gy	[122.47%]
D25%:	145.56 Gy	[132.33%]
D10%:	160.59 Gy	[145.99%]

PTV:

Total Volume:	54.57 cc	
V200%:	10.06 cc	[18.44%]
V150%:	30.24 cc	[55.41%]
V100%:	54.57 cc	[100.00%]
D100%:	115.36 Gy	[104.87%]
D90%:	139.21 Gy	[126.56%]
D50%:	169.25 Gy	[153.86%]
D10%:	267.91 Gy	[243.55%]

VariSeed: Therapy Visualization Report [Page 6]

Schiffler Cancer Center - 1 - 9/21/2010 15:02:43

Name: C, A PID: 06-736 Dept. ID:	Study: 2.606 U Pd-103 Variation: lowercase 99s, 25s Images: 9 Template: Siemens Aisense	Source: Pd-103 (Med 309) [NIST 99] Comment: Theraseed, TG43 update 11/04 Sources: 99 Anisotropy: Fecces (Point Model) Source Activity: 2.600 U [2.166 mCi] Total Activity: 257.660 U [207.660 mCi]
Procedure Date: 9/9/2008	Prescription Dose: 110.0 Gy	

Isodose Legend
Gy (% of Prescription Dose)
220.00 [200.00%] 121.00 [110.00%] 82.50 [75.00%]
165.00 [150.00%] 110.00 [100.00%]

Anatomy/Landmark Legend: PTV, Urethra, prostate

310

Figure 8. VariSeed printed output that is reviewed, annotated, and signed by Dr. Merrick. On the left is the Study Summary Report and on the right is the first page of the isodose display where the written directive is placed. The first isodose plane contains only the PTV base, which may partially overlap the bladder wall. The next three slices contain both PTV and prostate. Note that all slices were planned with seeds outside both the prostate and the PTV.

315

Dr. Merrick writes the preimplant directive on the first page of the isodose display, which is page 6 of the printout and illustrated on the right in the figure above. He typically changes the seed loading of 3 or 4 needles to shorten them and reduce the likelihood of seeds being implanted too inferior to the prostate apex. These changes reduce the dose to the membranous urethra and penile bulb and thereby reduce the likelihood of urethral stricture and erectile dysfunction. He also specifies 8 to 10 seeds to be implanted into the proximal 1 cm of the seminal vesicles. The seminal vesicles are not part of the planning target volume (PTV) extending from prostate base to apex on the original ultrasound volume study. However, we and other institutions [23] implant the proximal seminal vesicles, which are readily visualized by ultrasound on an anesthetized patient in the operating room, for two reasons. First, the vesicles are a primary pathway for locally extensive disease as documented in the Partin tables.[18] Second, implantation of the proximal 1 cm of the seminal vesicles helps increase the dose to the prostate base.

320

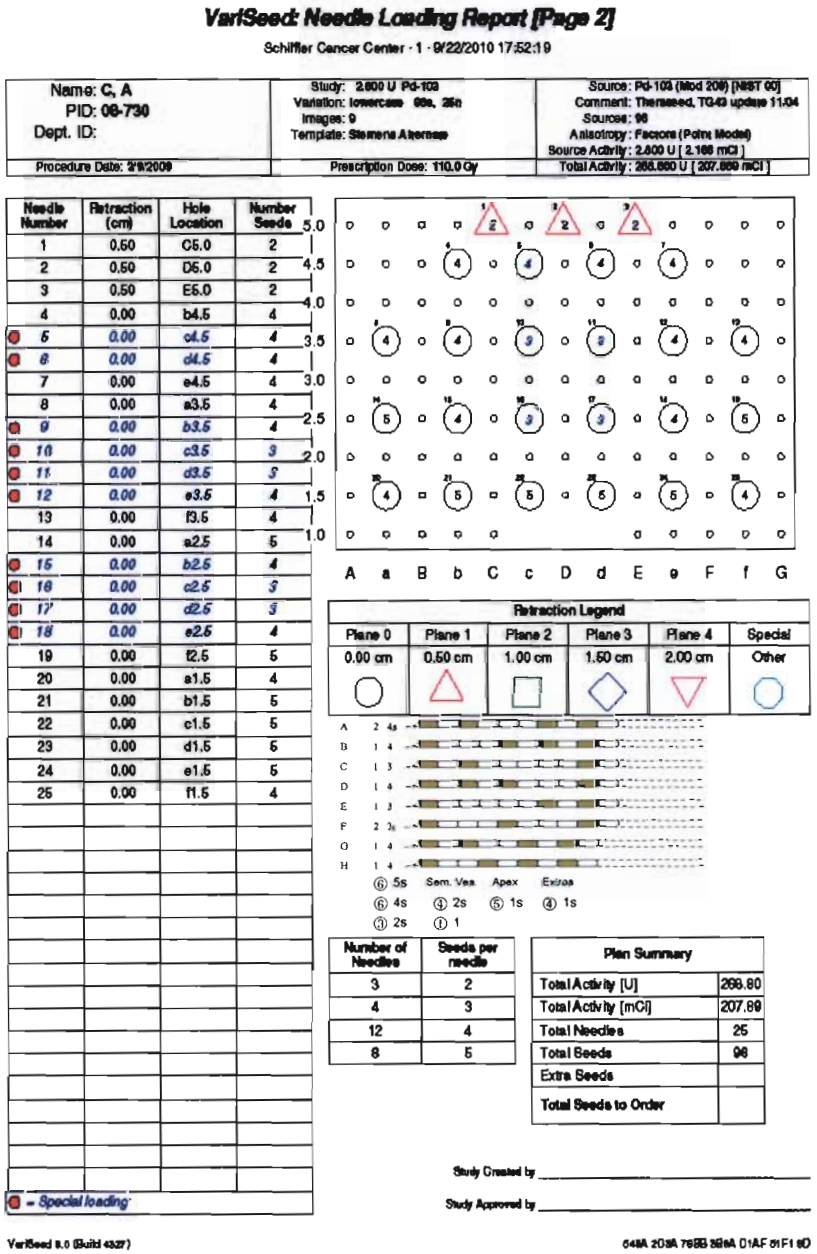
325

Finally, Dr. Merrick will specify additional seeds for areas he wants to dose paint intraoperatively, such as 4 seeds for the prostate apex plus about 4 extra seeds for unforeseen contingencies.

330

Intraoperative procedure and dosimetry

I sign and date the Needle Loading page shown below after I have pasted onto it a schematic of the special needle loads, including those changes requested by Dr. Merrick, plus a count of normal load needles and extra seeds requested on his written directive. (The figure omits how I highlight the special load needles in three locations on the page using various colored markers.) Another physicist writes the calibrated source strength and the total seed strength based on the number of seeds in the written directive. Our dosimetrist records template coordinate data for implanted non-plan seeds under the four left side columns.



VariSeed: Needle Loading Report [Page 2]

Schiffler Cancer Center - 1 - 9/22/2010 17:52:19

Name: C, A
PID: 08-730
Dept. ID:

Study: 2.600 U Pd-103
Variation: lowercase 08s, 25n
Images: 9
Template: Siemens Alternate

Source: Pd-103 (Mod 200) [NIST 00]
Comment: Theraseed, TG43 update 11.04
Sources: 98
Anisotropy: Factors (Point Model)
Source Activity: 2.600 U [2.168 mCi]
Total Activity: 268.880 U [207.680 mCi]

Procedure Date: 2/9/2009
Prescription Dose: 110.0 Gy

Needle Number	Retraction (cm)	Hole Location	Number Seeds
1	0.50	C5.0	2
2	0.50	D5.0	2
3	0.50	E5.0	2
4	0.00	b4.5	4
5	0.00	c4.5	4
6	0.00	d4.5	4
7	0.00	e4.5	4
8	0.00	a3.5	4
9	0.00	b3.5	4
10	0.00	c3.5	3
11	0.00	d3.5	3
12	0.00	e3.5	4
13	0.00	f3.5	4
14	0.00	a2.5	5
15	0.00	b2.5	4
16	0.00	c2.5	3
17	0.00	d2.5	3
18	0.00	e2.5	4
19	0.00	f2.5	5
20	0.00	a1.5	4
21	0.00	b1.5	5
22	0.00	c1.5	5
23	0.00	d1.5	5
24	0.00	e1.5	5
25	0.00	f1.5	4

= Special loading

5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0

A a B b C c D d E e F f G

Retraction Legend

Plane 0	Plane 1	Plane 2	Plane 3	Plane 4	Special
0.00 cm	0.50 cm	1.00 cm	1.50 cm	2.00 cm	Other

A 2 4s
B 1 4
C 1 3
D 1 4
E 1 3
F 2 3s
G 1 4
H 1 4

⑥ 5s Sem. Vea ⑤ 1s Apex ④ 1s Extras
⑥ 4s ④ 2s
③ 2s ① 1

Number of Needles	Seeds per needle
3	2
4	3
12	4
8	5

Plan Summary	
Total Activity [U]	268.80
Total Activity [mCi]	207.69
Total Needles	25
Total Seeds	98
Extra Seeds	
Total Seeds to Order	

Study Created by _____

Study Approved by _____

VariSeed 8.0 (Build 4327)

648A 2D8A 76BB 3B8A D1AF 51F1 8D

Figure 9. The needle loading diagram that serves as the intraoperative prescription.

After Dr. Merrick has achieved satisfactory intraoperative coverage, he declares the procedure complete. The dosimetrist and physicist both report to him the total number of seeds implanted and the number left unused, if any. The difference between the written directive specified number of seeds and the number of seeds actually implanted has never exceeded seven seeds or 10% of the total. If the difference is non-zero, Dr. Merrick will cross out and replace the numbers based on the written directive that I have written in the Extra Seeds box and Total Number of Seeds to Order box before he signs that page as the intraoperative prescription.

Post implant dosimetry and U.S. NRC compliance

When the patient is released from the recovery room — about 1 hour after the last seed deposition — he is brought to our cancer center for a CT scan. For a prostate brachytherapist, the postimplant dosimetry is as portentous as the post-operative pathology report is to a cancer surgeon. Every implant is unique, but there are commonalities that may be applicable to future patients in the difficulties faced and the obstacles overcome. The effectiveness of the lessons to be learned is greatly enhanced if the memory of the procedure is still fresh. For this reason, Dr. Merrick does not leave the office on an implant day until he has reviewed the CT image set and drawn the prostate, PTV, urethra, membranous urethra, rectum, rectal wall, and other organs at risk. Therefore, our dosimetrist is able to complete the postimplant dosimetry within 24 hours.

Patients return the day after the implant for a second CT scan and discussions with Dr. Merrick that may include a review of the day zero dosimetry. We obtain the day one CT scan partly to verify that the patient has not suffered any significant seed loss overnight. As illustrated in the figure below, our publication on seed fixity demonstrated that most seed loss, if any, occurs in the first 24 hours postimplant.[24]

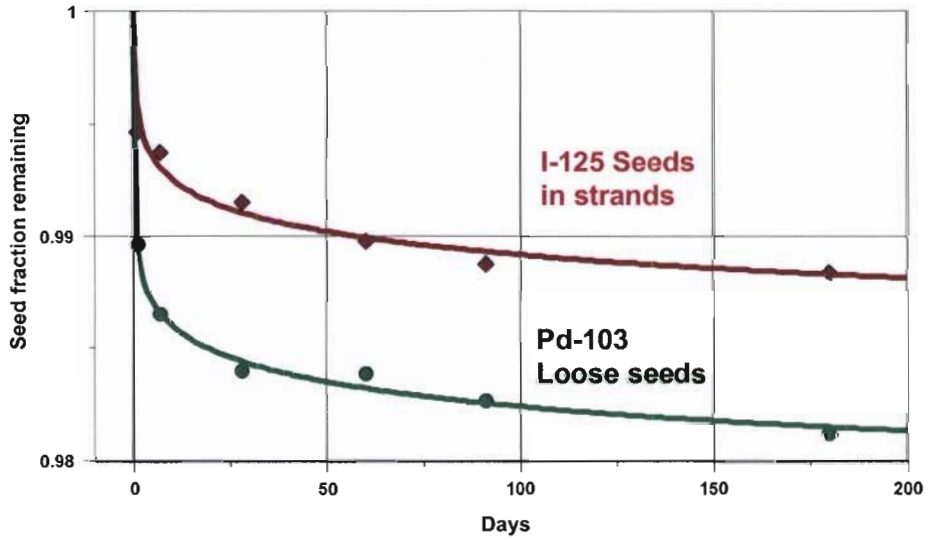


Fig. 10. A summary of the results in (Fig. 1) with patient data interpolated and averaged at six fixed points in time. Diamonds and the upper curve correspond to means for ^{125}I patients and a fitted logarithmic function, while circles and the lower curve correspond to means for ^{103}Pd patients and a logarithmic function fit.

Another reason we obtain a day one CT is to assess the rate of edema resolution and its effect on dosimetry. If the patient day 0 dosimetry is inadequate — $V_{100} < 90\%$ volume or $D_{90} < 100\%$ mPD — the amount of edema resolution by day one may be sufficient to convert the dosimetry to adequate. If the day one

dosimetry remains inadequate, we schedule the patient for a third CT one to two weeks after implant. At that point we are able to factor in the patient's maximum edema, his particular rate of edema resolution, and the decay rate of the radionuclide into our dosimetry evaluation. The last time this step had to be implemented was over six years ago.

Although a patient may have several dosimetric implant evaluations in his chart, the day 0 data is what we include in our research database for reasons of consistency. From the extensive dosimetry report, we enter 35 postimplant dosimetry and volume values. The table below is a summary of some of the values from our last thousand patients implanted from November 2004 to September 2010.

Table 2. Selected pre- and postimplant parameters for the last thousand implants at the Schiffler Cancer Center. Implants span from November 2004 to September 2010 and correspond to sequence numbers 1,273 – 2,273

Parameter	Units	Mean	± SD	Minimum	Maximum
Planning ultrasound volume	cm^3	29.6	± 8.4	11.6	71.9
Preimplant PTV	cm^3	56.7	± 13.1	26.6	113.2
Postimplant CT PTV	cm^3	65.5	± 14.5	22.8	143.6
Postimplant PTV V_{100}	% volume	97.7	± 2.0	86.1	100.0
Postimplant PTV D_{100}	% mPD	75.2	± 8.0	52.5	106.4
Postimplant PTV D_{90}	% mPD	120.9	± 9.4	92.9	153.0
Postimplant rectal wall V_{100}	cm^3	0.054	± 0.108	0.0	0.81
Postimplant rectal wall V_{110}	cm^3	0.023	± 0.066	0.0	0.52
Postimplant urethra D_{50}	% mPD	110.8	± 10.9	34.6	148.0
Postimplant urethra D_{10}	% mPD	125.2	± 15.4	74.1	180.2

We consider all the implants summarized above to be in compliance with U.S. Nuclear Regulatory Commission rules in 10 CFR 35.3045. All seeds were implanted according to the treatment plan and the written directive with the exception that not all extra seeds prescribed were used, but the variance in total number of seeds implanted never differed by more than 7 seeds or 10% of the total. The written directive specifies the minimum peripheral dose (mPD) that will cover the target volume. This means V_{100} = 100% volume and D_{100} = 100% mPD. In terms of V_{100}, the population looks fine with a mean 97.7% ± 2.0%. However, the mean D_{100} is well below 100% at 75.2% ± 8.0%. As an evaluation parameter, D_{100} is defective because the dose measured outward from the 100% isodose surface at the periphery of the implant decreases by about 20 Gy/mm. Therefore, if one honestly draws the target volume to encompass any cold spots, the minimum dose within the PTV will frequently be more than 20% lower than the prescribed dose and thus reportable as a medical event, even though the offending cold spot may be a tiny, inconsequential volume.

For all patients, the volume of rectal wall receiving the prescribed mPD was less than 1.0 cm^3. In our analysis of a prospective randomized trial, there was no incidence of rectal bleeding below that threshold.[25]

The urethral dosimetry in terms of the average dose represented by D_{50} and the maximum dose represented by D_{10} was virtually the same as that reported in our numerous papers on that subject finding no correlation between urinary symptoms and urethral dose, including detailed dosimetry of urethral segments.[26]

Why the U.S. NRC is misguided in its focus on D_{90} ± 20%

The NRC would like to establish regulations based on a dose parameter found to separate a given patient population into groups with greater or lesser probability of long-term biochemical progression free survival (bPFS). Mt. Sinai in New York was the first institution to report such a statistical cut point.[27] It may not be obvious, but to find a statistically valid dosimetric cut point that predicts for bPFS, you need to have a lot of failures due to very poor dosimetry. The Mt. Sinai group reported an overall 4-year bPFS of 79%, and a cut point of 140 Gy stratified those patients into two nearly equal groups with 4-year bPFS rates of 92% and 68%. Because the cut point was close to the usual prescription dose of 145 Gy for ^{125}I implants, the cut point has been widely interpreted as equal to the prescribed dose.

1. ***If a medical event is any implant outside the range of D_{90} equal to the prescribed dose ± 20%, the NRC will be dictating that brachytherapists replicate the poor implant quality and disappointing outcomes of Mt. Sinai in the era 1990 – 1996.***

There are numerous patient-specific factors that prevent exact replication of the treatment plan in its V_{100} and D_{100} values. Although the mean V_{100} may approach 100% volume and have a narrow distribution, the normal distribution of D_{90} values will have a standard deviation of about 10%. Note that two standard deviations, ± 20%, will cover about 95% of a normal population distribution. Therefore, about 5% of implants will have D_{90} < 80% mPD and a corresponding V_{100} of ~ 75% volume simply because of random variation about the mean D_{90} of 100%.

Consider the dosimetric quality of implants performed by brachytherapists using ProQura, a commercial planning and postimplant dosimetry service. We were granted access to the ProQura data base and have written several papers about factors affecting implant dosimetric quality such as our most recent regarding rectal dose brachytherapist experience.[28]

Our latest analysis, submitted for publication, involves the postimplant dosimetry of 6,600 implants performed by 129 brachytherapists. The mean D_{90} was 103%, right where a regulator would want it to be, and the mean V_{100} was at 89%, right where expected due to the mutuality of the parameters. The V_{100} versus D_{90} scatter plot shown below was not part of our scientific journal submission, but its implications are instructive.

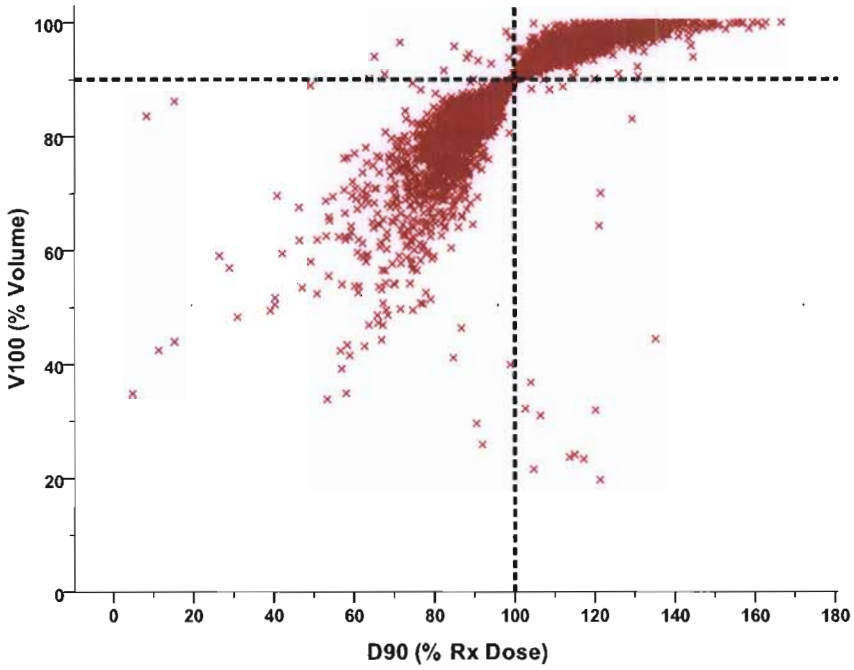


Figure 11. Implant quality in the ProQura database: n = 6,600. (The small number of points in the upper left and lower right "forbidden sectors" are unresolved data entry errors.) The mean V_{100} = 89.2% ± 8.9%, and the mean D_{90} = 103% ± 16%.

In the randomized prostate brachytherapy trials we participate in, the definition of implant adequacy are those in the upper right sector demarked by the dotted lines — $D_{90} \geq 100\%$ mPD and $V_{100} \geq 90\%$. All the others, 2,874 out of 6,600, are out of protocol. The table below details how many implants in this population would be reportable as a medical event if the NRC were to use a regulatory criterion of either 30% or 20%, selecting either high or low or both outliers, and using either D_{90}, V_{100}, or both.

Table 3. Number and percentage of implants out of n = 6,600 submitted by 129 brachytherapists to the ProQura database who would be classified as medical events by the NRC at two dosimetric thresholds.

Variance	Prostate	Low Side		High Side		Two Tail (Hi & Low)	
		n	%	n	%	n	%
30%	D90	121	1.8	249	3.8	370	5.6
	V100	240	3.6				
	Either	273	4.1				
	Both	88	1.3				
20%	D90	383	5.8	796	12.1	1,179	17.9
	V100	723	11.0				
	Either	767	11.6				
	Both	340	5.2				

For a D_{90} variance of ± 20%, over 1/6 of all implants would be labeled a medical event. This regulatory stance would target nearly 800 high-side violations that would be scored as "according to protocol" by our clinical research trials. Many of the implants with a low $D_{90} < 80\%$ mPD may have been a statistically unusual outcome perhaps actually due to *bona fide* seed migration while others may have been performed by brachytherapists in the early stage of the learning curve. Of the 129

brachytherapists contributing post-implant CT study sets to ProQura, 64 had performed ≤ 10 implants, 82 had performed ≤ 10 implants, and only 21 had performed > 100 implants.

The figure below plots our last thousand implants on the same scale as the ProQura implants above. As detailed in Table 2, the mean V_{100} = 97.7% ± 2.0%, and the mean D_{90} = 121% ± 9%. By the research protocol standards where adequate is defined as $V_{100} \geq 90\%$ and $D_{90} \geq 100\%$, there were 7 implants (0.7%) in the inadequate sector out of 1,000. All of the inadequate implants had sufficient edema resolution by the time of the second CT to declare their implants adequate. Using a regulatory criterion of D_{90} ± 20% of the prescribed dose (mPD), none of our last thousand implants were regulatory inadequate on the low side because all implants had D_{90} > 93% mPD. However, there were 521 implants (52.1%) with D_{90} > 120% mPD.

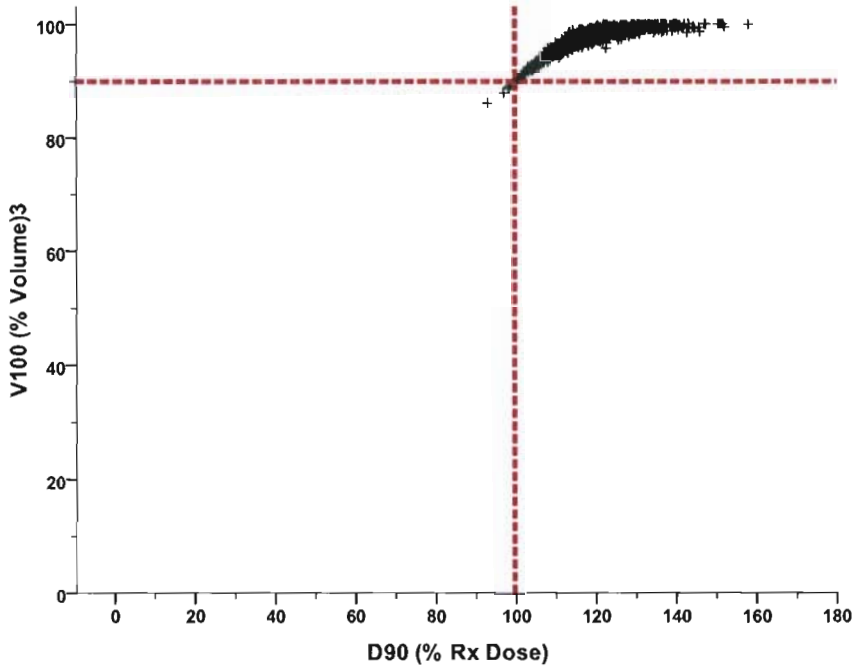


Figure 12. Implant quality of the last thousand implants of the Schiffler Cancer Center at Wheeling Hospital, Nov. 2004 – Sep. 2010. Sequence numbers = 1,273 – 2,273. The mean V_{100} = 97.7% ± 2.0%, and the mean D_{90} = 121% ± 9%.

2. ***None of the major radiological societies — the American Brachytherapy Society, the American Society of Radiation Oncology, the American Association of Physicists in Medicine, and the American College of Radiology — has offered a consensus recommendation of any explicit numerical targets for postimplant dosimetric parameters.***

Some of these organizations have recommended radionuclide dependent prescription doses for brachytherapy as monotherapy and combined modality with external beam therapy. All have recommended the tracking of dosimetric quantifiers, but none has published explicit targets or ranges for postimplant prostate dose parameters. The ACR Practice Guideline for prostate brachytherapy was a collaboration between the ACR, ASTRO, and ABS.[29] The ACR in its most recent Appropriateness

Criteria for prostate brachytherapy considered prostate and organ at risk dose quantifiers, but concluded that the evidence for their inclusion was too weak.[30]

3. ***The NRC specifying a medical event as any implant outside the range of D_{90} equal to the prescribed dose ± 20% unduly infringes on medical decision making.***

Although biochemical progression free survival analysis indicates that patients may be harmed by a D_{90} that is too low, there is no replicated evidence of harm due to high D_{90}. In our effort to correlate high dose volumes with urinary and rectal morbidity, we concluded:[31]

> "Expending substantial effort to monitor and modify higher-dose volumes, at least in the setting of modified peripheral loading patterns, is unlikely to substantially decrease implant-related morbidity."

Virtually every brachytherapist reading a dose response paper pertaining to survival interprets the cut point as a lower threshold and aims to be above that threshold. Of course, a dose response paper reporting a cut point that stratifies morbidity is interpreted in the reverse direction — a cut point that should not be exceeded. Each organ at risk has its own characteristic threshold, but those thresholds are not well-correlated with prostate dosimetric indices. Brachytherapists interpret quality indices the way that the AAPM Task Group 137 report suggested — as adjustable variables responsive to feedback from postimplant dosimetry.[14] As evidence that we are not the only group that consistently implants to a high D_{90}, consider the following:

- The Mt. Sinai group has reported "outstanding local control" and excellent toxicity profiles for ^{125}I monotherapy implants with a minimum $D_{90} \geq 180$ Gy.[32] A more recent paper from that group concludes that for urinary, rectal, and sexual morbidity there is no evidence of a morbidity dose response even for a biologically effective dose (BED) > 220 Gy.[33] The use of BED allows a reasonably unbiased comparison between different radionuclides and brachytherapy combined with external beam therapy. For ^{103}Pd implants, a BED of 220 Gy corresponds to a monotherapy $D_{90} = 180$ Gy.

- The Toronto group headed by Juanita Crook has also reported "excellent biochemical disease-free survival and acceptable toxicity" in men receiving monotherapy ^{125}I implants with $D_{90} \geq 180$ Gy.[34] Their D_{90} was ≥ 124% of the prescribed dose of 145 Gy.

- Based on their experience with over one thousand implants, Morris and colleagues concluded in an editorial in *Brachytherapy*:[35]
  "... postimplant dosimetry should not be misconstrued as an endpoint. Merely meeting published D_{90} guidelines will not guarantee favorable bNED outcomes and, conversely, failing to meet such targets will not always result in an increased risk of recurrence."

As implant quality and biochemical progression-free survival (bPFS) improve, it is inevitable that any cut point stratifying patients by outcome will be higher. In our own radiobiological analysis comparing ^{125}I and ^{103}Pd using a D_{90} based biologically equivalent dose (BED) calculated from AAPM Task Group 137 recommended indices, we reported a BED cut point of 145 Gy stratified the entire population, and we also found that the optimum cut points were risk-group dependent.[36]

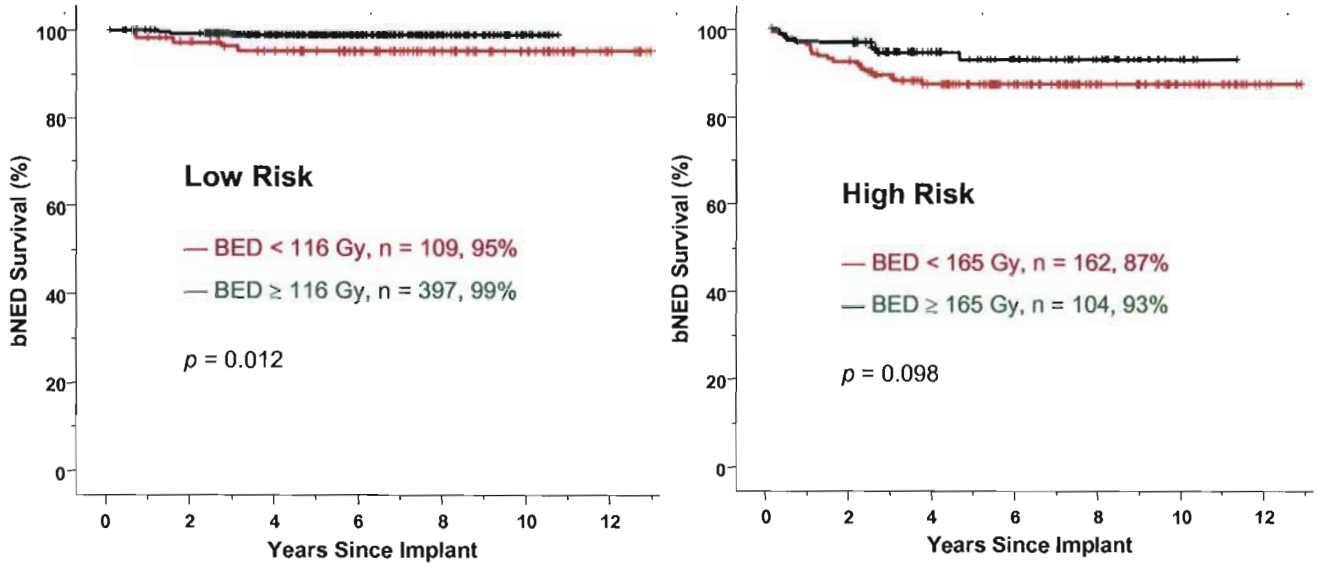


Figure 13. Kaplan-Meier progression-free survival curves for risk groups stratified by biologically equivalent dose (BED) cut points. (a) Low-risk patients. The BED cut point of 116 Gy of prescribed dose was derived from receiver-operating characteristic (ROC) curve analysis (area under curve [AUC] = 0.675) and has a sensitivity of 0.80 and a specificity of 0.56, p = 0.012. (b) High-risk patients. The BED cut point of 165 Gy of prescribed dose was derived from ROC curve analysis (AUC = 0.550) and has a sensitivity of 0.41 and a specificity of 0.77, p = 0.098.

The population cut point of 145 Gy BED in the consensus methodology corresponds to an ^{125}I D_{90} of 180 Gy (1.24 times the 145 Gy mPD for monotherapy) and a ^{103}Pd D_{90} of 155 Gy (1.25 times the 125 Gy mPD for monotherapy). For low-risk patients, the reported cut point of 116 Gy BED is about 1.07 times the monotherapy mPD, but the high-risk cut point of 165 Gy BED corresponds to a D_{90} of 200 Gy for ^{125}I (138% mPD) and a D_{90} of 170 Gy for ^{103}Pd implants (136% mPD).

Applying a regulatory specification of D_{90} not only infringes on medical decision making but will squelch progress and prevent investigating the limits of hotter versus cooler implants within the existing prescribing framework. This is a completely separate issue from dose escalation and dose de-escalation trials that raise or lower the prescription dose while maintaining D_{90} in a consistent, narrow range. Both types of trials are ongoing in prostate brachytherapy. Three years ago we began enrolling patients into NCI Protocol ID #NCT00247312, "Pd-103 Dose De-Escalation for Early Stage Prostate Cancer: A Prospective Randomized Trial." We plan to randomize 600 favorable-risk patients to a monotherapy ^{103}Pd implant of either 125 Gy or 110 Gy mPD. We have implanted 280 patients so far, and the mean $\%D_{90}$ is virtually the same for both arms, and so is the mean number of seeds implanted.

620 However, the individual seed strength and total seed strength implanted in the lower mPD implants are about 12% less than in the higher dose arm.

4. ***Because the D_{90} quantifier is a single point on the DVH curve, it has a different meaning and effect for different brachytherapists.***

625

Different brachytherapists display different characteristic dose volume histogram (DVH) shapes — measured by the slope of the curve at D_{50} — resulting from choices in seed strength, implant philosophy, and coverage decisions. Shown below are DVHs from treatment plans on the same patient designed by eight well-known brachytherapists for an implant using ^{125}I or ^{103}Pd.[23]

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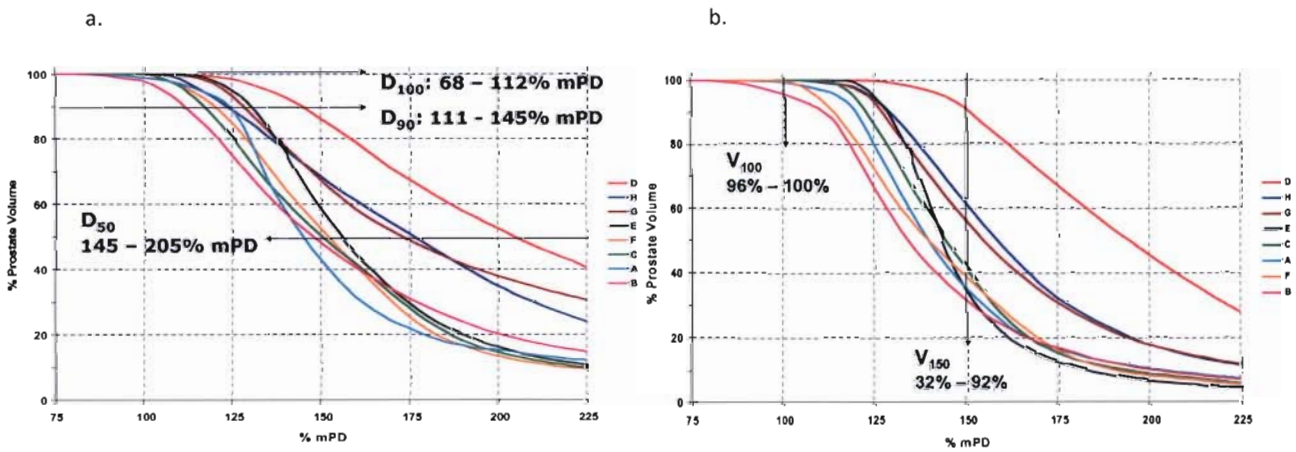

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Figure 14. Prostate monotherapy DVHs for (a) Pd-103 and (b) I-125 stratified by brachytherapist from highest to lowest D60 dose.

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Note the large variations in D_{100}, D_{90}, and D_{50} noted on the left figure and in V_{150} in the right figure. (We are the black curve, institution E, on both graphs.) Depending on the institution selected, the patient would experience considerably different implants. However, the eight brachytherapists have considerable experience in converting their plans into clinical reality, and all have reported good long-term biochemical survival and negligible morbidity (except for brachytherapist D). What they have in common (except for brachytherapist B) is a planned $V_{100} > 99.9\%$.

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5. ***There are other robust ways to judge the quality of an implant than D_{90}.***

655

Almost all of the published data establishing various D_{90} cut points are from retrospective analyses. The cut points arise because there is considerable patient to patient variation in the achieved D_{90}. That normal variance will make any application of a regulatory D_{90} inherently unfair. Conscientious brachytherapists will report themselves while the true outlaws game the system.

660

We published one of the few dosimetry and outcomes studies based on a randomized trial.[37] In that paper, we reported that almost every one of ten DVH-based parameters tested were strongly predictive of biochemical control. Shown below is a graph from that paper illustrating why we consider inadequate an implant with a $V_{100} < 90\%$ volume. There were no failures above that threshold.

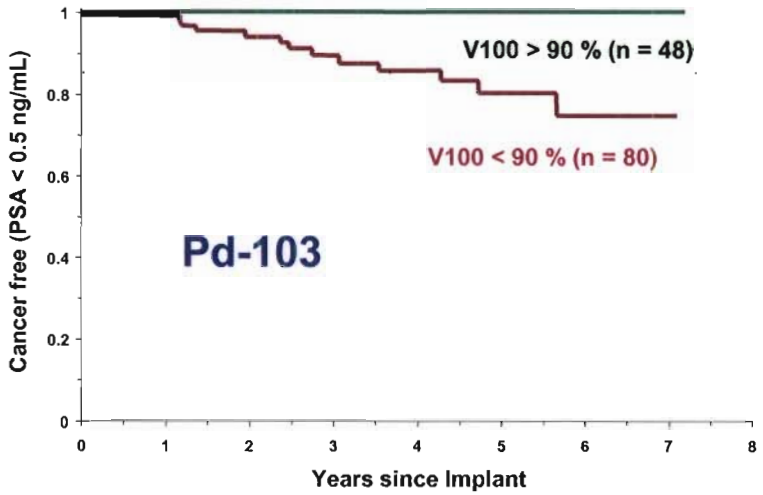

FIGURE 15. Kaplan-Meier survival curves comparing freedom from biochemical failure in patients with a V100 > 90% versus those with a V100 < 90%.

We also found that dosimetric margins predict biochemical control among patients randomized in that trial with the graph for the ^{103}Pd arm shown below.[38] From the wide range of parameters predicting control, why has the NRC focused on one with an inherently wide variation?

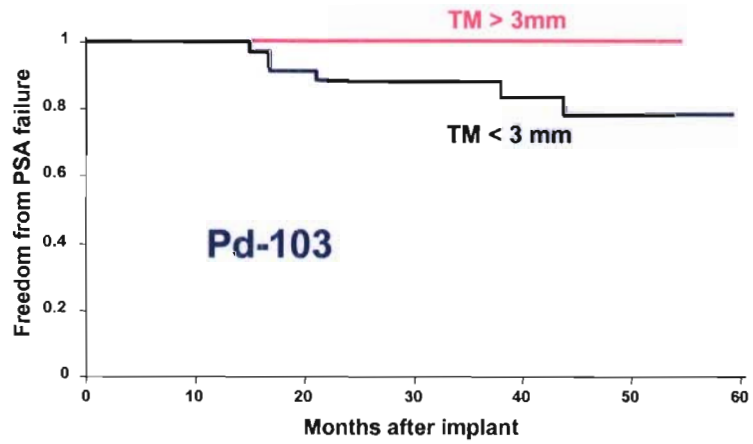

FIGURE 16. Freedom from biochemical failure by average TM <3 mm or >3 mm. The log-rank p-value for ^{103}Pd could not be calculated, because there were no failures in the group with TMs >3 mm.

The means for V_{100}, D_{50}, and dosimetric margins showed much less variation than D_{90}. Likewise, the variation between total planned seed strength and total implanted seed strength is very small.

6. A regulatory specification of D_{90} = 100% mPD makes no radiobiological sense and will have significant negative patient consequences.

Predictions of biochemical control or tumor control probability (TCP) require analysis of the entire DVH for each patient. I undertook that task for all 55 of our biochemical failures matched 2:1 to 110 non-failure control implant patients.[39] All 165 DVHs were divided into 179 dose bins and analyzed using the radiobiological indices recommended by AAPM Task Group 137. The left figure below illustrates an idealized hypothetical situation where two implants of the same prostate have the same D_{90} = 125% mPD (mPD = 145 Gy for the ^{125}I case shown) but differ in terms of seed strength (U) and coverage at other doses and volumes. The right hand figure is a plot of differential tumor control probability (TCP) for both of the DVHs.

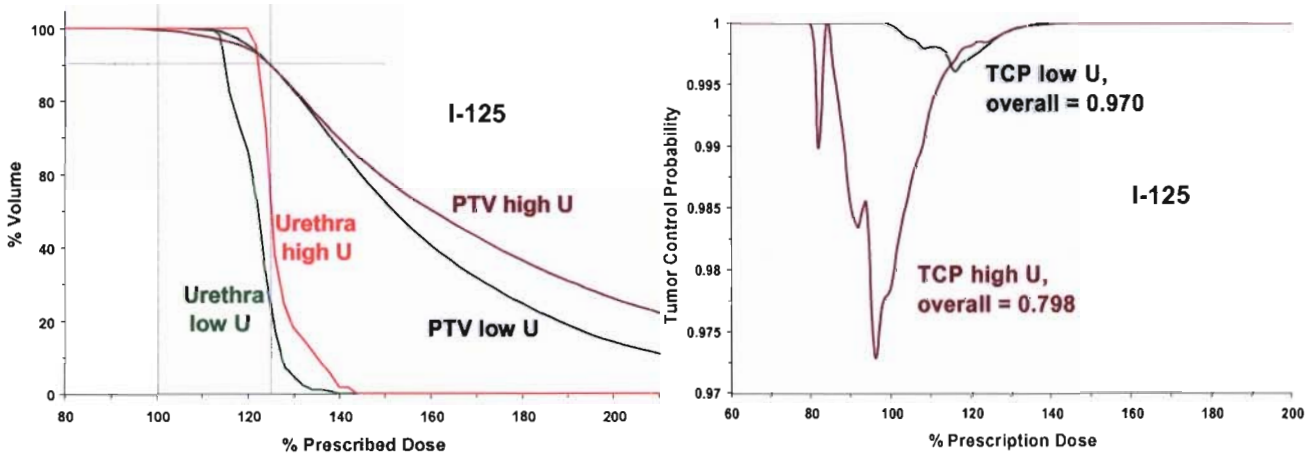

Figure 17. (Left) Dose volume histograms for the prostate planning volume (PTV) and urethra for the same patient using either high or low strength seeds. (Right) Tumor control probability (TCP) for the high and low strength seed situations.

Even though the DVH for the high seed strength implant provides superior coverage at doses > 125% mPD, it has a much lower overall TCP because of less thorough coverage at doses < 125% mPD. Therefore, even a D_{90} = 125% mPD is not sufficient to assure a good biochemical outcome. The low seed strength implant is typical of our clinical postimplant dosimetry, but even there, the overall integrated TCP is not 100%. The overall TCP is the product of the TCP for all the sub-volumes, and the TCP does not exceed 99.99% until the dose in all sub-volumes is > 130% mPD. Likewise for our analysis of ^{103}Pd radiobiology, one does not achieve a near certainty of cancer stem cell until the dose is about 130% mPD.

There is a lot of uncertainty in any radiobiological modeling, whether based on D_{90} or a complete dose volume analysis. Nevertheless, there is a high likelihood that setting a regulatory D_{90} = 100% ± 20% will result in unsatisfactory biochemical control of prostate cancer.

Conclusion

Because we never prescribe to a D_{90} value but to V_{100}, it is ludicrous to retrospectively hold us to a regulatory standard of D_{90} = 100% mPD when there has yet to be a consensus statement from any appropriate medical or scientific society lending authority to that value. All the successful permanent prostate brachytherapy programs have been escalating D_{90} far above that value for years so that the optimum value of D_{90} remains unknown, but published evidence indicates it is clearly above 100%. Enforcing a D_{90} = 100% mPD will mandate that more than half of all implant patients will receive sham brachytherapy, a treatment inadequate to control disease as shown by modern dose-response studies and radiobiological analysis.

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