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Progress in Low Dose Rate Brachytherapy for Prostate Cancer

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Low dose rate (LDR) brachytherapy has a proven critical role in achieving the modern standard of successful prostate cancer treatment, cure with quality of life (QoL) preservation. In the past decade, cure has been demonstrated in the most lethal form of prostate cancer treated with combined external beam and LDR brachytherapy. Additionally, QoL has moved from toxicity avoidance to preservation of function, with unprecedented sexual function preservation proven with intensive combination therapy. The technical advances that have made such outcomes possible have defined the full, dynamic complexity of the permanent prostate implant procedure, as well as effective solutions. Progress in LDR brachytherapy as it relates to prostate cancer biology, local control, toxicity reduction with function preservation, external beam integration, medical event prevention, patient selection, and comparative brachytherapy is reviewed. As in all brachytherapy procedures, the final clinical outcomes of cure, and QoL depend entirely on a foundation of verifiable technical excellence.

Introduction

In the last decade several pivotal events in low dose rate (LDR) brachytherapy for prostate cancer forced a serious review of its viability and role in the current therapeutic landscape. The Philadelphia Veterans Affair hospital medical events, the decrease in brachytherapy training in academic centers, and the financial disincentive of brachytherapy relative to more lucrative approaches, all threatened to limit a technique that requires adequate procedure numbers to sustain surgical expertise.[1,2] The shift from treatment to surveillance of low-risk cancers drastically decreased the need for primary LDR permanent implantation.

Bolstering use were 2 major studies that proved that the best outcomes in potentially lethal prostate cancers required brachytherapy.[3,4] Additionally, a cost analysis proved the value of prostate LDR over competing options by a significant margin.[5] In the last 2 decades, as the definition of treatment success has moved from toxicity avoidance to cure with function preservation, the most aggressive treatments given by combining LDR and external beam have proven excellent sexual function preservation.[6] Detailed studies on postimplant dosimetry have disclosed that underlying dynamic mechanisms of the prostate and adjoining normal tissue influences the quality of the implant and thereby patient outcomes.[7-10] In this review, we will highlight the progress made in cancer biology, tumor control, function preservation, LDR brachytherapy and external beam integration, gradient dose optimization, individualized therapy, and comparative brachytherapy. These advances bring the field closer to fulfilling the modern definition of success; cure with QoL and full function preservation.

The dominant challenge facing the brachytherapy practice community is developing a mechanism to efficiently transmit brachytherapy expertise. Historical learning models requiring years of experience to reach a level of mastery are fast being replaced by competency achieved through realistic simulation. A dedicated corps of experts has risen to fill the gap in residency training through intense simulation-based workshops, emphasizing the proven value of committing the extra time per patient to provide quality brachytherapy.

Progress in Prostate Cancer Biology: The Challenge of Local Control and Lethal Prostate Cancer

The most consequential discovery confirmed in the past 2 decades is that local control in prostate cancer affects

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https://doi.org/10.1016/j.semradonc.2019.08.002

metastasis free survival and prostate cancer specific mortality. The first indication of the importance of local control to overall mortality outcomes came from the I-125 prostate brachytherapy experience with over a thousand patients at Memorial Sloan Kettering.[11] The Memorial Sloan Kettering retropubic methodology was abandoned due to a wide variation in the quality of the permanent implants. Nonetheless, the long-term follow-up established a critical link between local control and distant metastasis control. Of the patients who achieved local control, 77% were metastasis free at 15 years, while those with locally recurrent disease had only a 22% metastasis free rate, emphasizing that local control was pivotal to the metastasis free rate.[11] The importance of local control for postprostatectomy patients with high-risk factors was demonstrated by Thompson et al, who showed a reduced risk of metastasis and a survival benefit with adjuvant radiotherapy.[12] In addition, studies have confirmed the need for early salvage radiotherapy to improve relapse free survival.[13] Remarkably, recent studies suggest a benefit for local control even after metastases have occurred. Perhaps limiting the continuous stream of cancer cells from local disease, or other mechanisms may improve prostate cancer specific outcomes.[14]

In a sentinel biology comparison by Welch et al, prostate cancer was shown to follow a sequential biology as opposed to the simultaneous local and distant progression typical of aggressive breast cancer.[15] In contrast to breast cancer where despite intensive screening metastasis at initial diagnosis still occurs commonly, in prostate cancer, metastasis at initial diagnosis dropped precipitously with screening, from 20% to less than 5%. This provides the most compelling case to screen for potentially lethal prostate cancer, especially cancers with Gleason Grade 5.[16,17] Such high-risk, lethal prostate cancer necessitates an early diagnosis and ablative treatment approach. LDR brachytherapy has consistently enabled high local control due to extreme, targeted dose delivered within the tumor, impossible to match with external beam treatment.

Progress in Tumor Control: Superior Results in Potentially Lethal Prostate Cancer

The state of the art in high-risk prostate cancer is depicted schematically in Figure 1. The clinical failure of the competing options is graphed. The androgen deprivation therapy (ADT) plus external beam approach has been proven superior by Level 1 evidence to external beam alone in all consequential end points including overall survival.[18,19] Combination therapy has been proven superior by Level 1 evidence to external beam and superior by a large retrospective study in the most lethal prostate cancers, with a 30 point difference in metastasis free survival at 10 years.[3,4] Unlike external beam plus ADT, there is no Level 1 evidence for improved outcomes by adding ADT to combination, although retrospective studies suggest a benefit.[20,21] In ADT plus external beam trials, there is a continuous failure rate with long-term follow-up without evidence of plateau, while combination trials such as ASCENDE demonstrate a plateau.[4] This results in divergence of failure with increased follow-up. In high risk patients such failure will require ADT in a greater percent of external beam than combination patients, termed the late ADT gap. There is an initial ADT gap in combination versus external beam trials as well. On average combination patient receive a year or less of ADT while external beam patients receive 18 months to 24 months.

In a prospective randomized trial of external beam versus combination therapy, there was a 20% difference in biochemical control at 9 years with a clear plateau in the biochemical no evidence of disease (bNED) curve from combination, with continued decline in the external beam only cohort.[4] At present follow-up, the advantage is in biochemical control only, and further follow-up will be necessary to establish metastasis free and prostate cancer specific mortality differences. In a large cohort of Gleason Grade 5 patients, a significant difference in metastatic rate was noted at 10 years.[3] Combination patients had a metastasis free rate of 87%, while external beam and surgery were in the range of 60%. A significant prostate cancer specific mortality difference was established.[3] This was a retrospective trial and has all the limitations of such trials.

In a large cohort of likely localized high-risk patients (Prostate Specific Antigen <15, Gleason 8 or less) Merrick saw no benefit to ADT and reported a bNED of over 90% at 10 years with or without ADT.[22] Even in his Gleason 9,10 series only 50% of patients received greater than 6 months ADT, 25% none, and bNED of 90% at 10 years was accomplished.[23] Analysis of outcomes by prognostic stratification within high-risk prostate cancer patients confirmed significant differences in outcomes favoring combined LDR with external beam plus ADT.[24] On multivariate analysis of large retrospective studies there is a benefit to ADT addition, but how much of the benefit is due to rescue of less than ideal implant dosimetry is uncertain.[25] In the current era of accurate, MRI based postimplant dosimetry, will ADT prove to be critical? Randomized trials will ultimately be necessary to define which patients treated with combination benefit from ADT.

The 1 recently defined, incontrovertible evidence of ADT benefit in brachytherapy patients is tumor downsizing.[25,26] Multiparametric MRI (mpMRI) has allowed detailed tumor definition, including extra-capsular extension and seminal vesicle involvement. A 4-month injection may dramatically downsize the tumor and bring it within the range of implant approaches. This may be the group with the greatest benefit from ADT when combined with LDR.

It has been contended that the toxicity from combined LDR and external beam exceeds external beam plus ADT, in a decisive way.[27] However, with a metastasis free survival nearly 30% above external beam alone, many would accept a 5% difference in toxicity. The same toxicity accounting challenge holds for ADT as well. If the toxicity of 24 months ADT typical of external beam is compared with 4-12 months ADT typical of most combination regimens, few would doubt where the greater toxicity would reside.[28] There is a cumulative toll of long-term ADT therapy.

The impact of ADT on QoL is clarified by a recent study from England.[29] In this study, the average QoL measured for a curative prostate cancer patient was not statistically different from the QoL of an end stage palliative prostate cancer

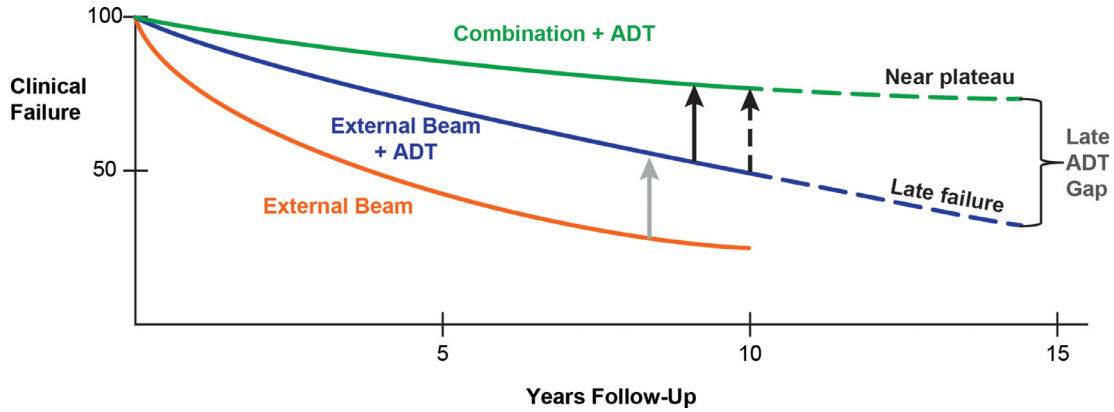

Figure 1 Schematic view of the current state of the art in high-risk cancer therapies. The grey arrow represents the Level 1 proven advantage of adding Androgen Deprivation Therapy (ADT) to external beam. The solid black arrow signifies the level 1 proven advantage of LDR based combination therapy relative to external beam. The dashed black line represents the mass retrospective proven advantage of combination over external beam in the most lethal prostate cancers. The late ADT gap shows the potential increased failure risk without combination therapy for high-risk cancers.

patient. Curative treatment was associated with significant incontinence, impotence, and global effects of ADT. Physician advocating for global cure and QoL outcomes cannot dismiss the QoL impact of ADT. Limiting ADT while achieving superior results in local control are major advantages of brachytherapy approaches. The advantages, disadvantages, and complications of ADT therapy are summarized in Table 1. For a complete list see the review by Keyes et al.[28]

While the difference in adjuvant ADT, whether delivered over 4-12 versus 24 months, may seem a small advantage, it is critical to consider the lifetime effect of a therapeutic choice. In the external beam plus ADT series with sufficient follow-up there is continued failure, and that failure in high-risk patients will require more ADT and more costly medications, currently up to $500K per patient.[30,31] In Figure 1, this is called the late ADT gap. The benefit of aggressive combined external beam and brachytherapy treatment is avoidance of late ADT complications and the QoL limitations such therapy brings, not to mention metastasis prevention and financial toxicity. Quality of life is a major and pivotal concern in prostate cancer patients, and the full accounting of external beam (more ADT early, and much more ADT late) versus combined external beam and LDR (less ADT early, and none or much less late) is the metric that should be considered for lifetime QoL impact. In this view, there may be a major advantage in favor of combined LDR and external beam therapy.

Progress in Clinical Outcomes: Beyond Toxicity Reduction

Clinical studies traditionally sought out proof of increased cure rates while reducing toxicity. As the functional anatomy era progressed, the notion of function preservation as a positive outcome emerged in contrast to toxicity prevention. The full mapping of the sexual, urinary, and recto-anal function, streaming through and adjacent to the prostate make this a major cure and QoL challenge in radiation oncology. Defining the critical erectile tissues resulted in a remarkable preservation of function by patient reported outcomes.[6] Nearly 90% of men who received combined external beam and LDR brachytherapy were able to be sexually active at 5 years, and greater than 70% had minimal erectile dysfunction. While this therapeutic approach did not result in 100% preservation of sexual function (all men experienced some decrement), it does shift the emphasis from toxicity avoidance to preservation. In bladder function sparing efforts, a greater emphasis on limiting the dose to the bladder neck is also practiced during brachytherapy treatment planning and source placement, to limit urinary toxicity. Rectal symptoms both acute and chronic may be reduced through the use of hydrogel placed between the prostate and rectum, proven beneficial in clinical trials.[32]

The next step in sexual function preservation beyond vessel sparing is ejaculation sparing. For some men, loss of ejaculate is tantamount to impotence. To accomplish ejaculate

Table 1 Observed Advantages, Disadvantages, and Complications of Androgen Deprivation Therapy (ADT)

Advantages
Overall survival advantage with external beam
Prostate downsizing
Tumor downsizing
Disadvantages
Hot flashes
Weight gain
Loss of libido, erectile dysfunction
Cognitive dysfunction
Mental illness
Loss of muscle mass
Loss of motivation
Complications
Severe depression, suicide
Personality change
Personality annihilation
Cardiovascular death (early)
Cardiovascular death (late)
Dementia

sparing, numerous strategies must be integrated. For patients where mpMRI confirms a disease-free bladder neck, the implant dose may be limited. A lower dose to the bladder neck will limit the long-term use of alpha blockers which are known to cause loss of ejaculate through retrograde ejaculation.[33] For patients where mpMRI suggests a lack of involvement of the seminal vesicle, a portion of the seminal vesicles may be spared from receiving a therapeutic dose, thereby improving ejaculate production. Finally, the likely proximal cause of erectile dysfunction is extremely high dose to the nerves adjacent to the prostate, especially at their point of termination at the apex and immediate sub-apex. Peripheral source loading often places radioactive sources on or in the immediate vicinity of the neurovascular bundle, leading to extremely high dose to the nerves. Moving the source positions within the gland and away from the neurovascular bundle limits this extreme dose. This multi-faceted approach to ejaculation sparing can be carried out without compromise of tumor dose escalation.

Progress in Brachytherapy and External Beam Integration

A common approach to combining external beam and LDR brachytherapy is sequential pelvis or prostate and seminal vesicle external beam therapy followed by a brachytherapy boost. The brachytherapy boost post external beam treatments leaves little recourse for dose correction, should the LDR dose be lower or higher than planned. An alternative approach is to perform the brachytherapy first and integrate the LDR delivered dose as background for external beam planning.[34] The brachytherapy dose and external beam dose can be integrated and adjusted instead of accepting the sum dose resulting from the sequential approach. Aggressive tumors visible on MRI can be preferentially boosted during the brachytherapy and external beam treatments. This also allows control of brachytherapy and external beam dose summation in critical adjacent functional anatomy visible on MRI, including the external sphincter, sexual structures, and bladder neck.[35,36]

The advantage of this approach is demonstrated in the composite dose summary presented in Figure 2. The brachytherapy dose, which is based on peripheral source placement with the exception of the needles adjacent to the nerve bundle in ejaculation sparing, delivers a high dose to the peripheral zone of the prostate (Fig. 2B) where most tumors originate but provides less reliable dose coverage to the CTV margin because of rapid dose fall off. With the addition of the external beam (Fig. 2C), doses are smoothed and preferentially delivered to areas that are not dosed by the implant. The external beam dose can be modulated along the CTV margin to address microscopic extension. Figure 2D shows the composite external beam and brachytherapy dose.

Brachytherapy provides highly conformal dose delivery with steep gradients. A question asked in the past decade is whether modern external beam treatments can match such gradients. Comparing high dose rate (HDR) brachytherapy to Cyberknife, Fuller et al contended that external beam therapy could approximate the steep brachytherapy gradients with dose decline from full dose to moderate dose (50 Gy) in less than 1 cm.[37] The rectum is the critical adjacent organ at risk limiting dose escalation. Typical volumetric rectal optimization

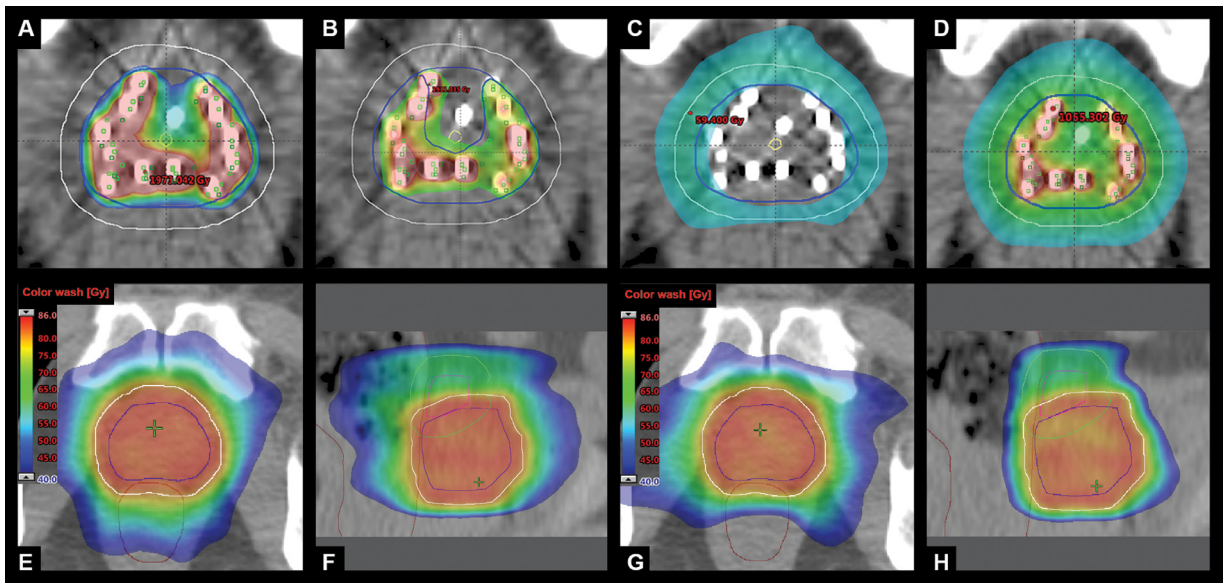

Figure 2 Progress in treatment planning. Upper panels show LDR and intensity modulated radiation therapy (IMRT) integration and lower panels show gradient optimization. (A) Prescribed 90 Gy LDR dose coverage to the prostate in blue. (B) The 135 Gy dose coverage on postimplant dosimetry encompassing most of the peripheral zone. (C) IMRT corrected for LDR dose with central dose de-escalation over the LDR dose. (D) Combined LDR and IMRT dose encompassing the planning target volume. (E&F) Axial and sagittal view of the prostate PTV in white, seminal vesicle in purple, seminal vesicle PTV in green, and rectum in brown, planned with standard optimization. The 40 Gy isodose cloud is shown. (G&H) Axial and sagittal view of the prostate planned with gradient optimization.

will deliver a safe dose to the rectum, but dose gradients are not as steep as achieved with gradient optimization.[38] Typical inverse plans using the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) rectal dose constraints, that require the volume of the rectum receiving less than 70 Gy, 60 Gy, and 45 Gy to be less than 15%, 35%, and 50%, respectively, and a normal tissue objective generically applied by commercial software, has the potential to create a low dose cloud of 40 Gy over most of the rectum as shown in Figure 2E and F.[39] With gradient optimization (Fig. 2G and H), the 40 Gy dose cloud is well-controlled and does not extend as far into the rectum. This confirms the capacity of inverse planning using gradient optimization to produce brachytherapy-like and proton-like dose gradients when such gradients are necessary. The combination of LDR brachytherapy with gradient optimized external beam and hydrogel can further minimize any consequential dose to rectum.

Progress in Medical Events: Beyond Penalty to Cause

Perhaps the greatest challenge in medical oversight is the movement away from penalties to defining the cause of procedure based errors. In the past decade dynamics during and after a prostate brachytherapy procedure contributing to poor technical quality implants have been defined. The first is the continuous shift of the base cephalad during the implant procedure. Failure to adjust needle depth to the final base position results in errors similar to that reported at the Philadelphia Veterans Affair, termed base depth error.[1] Base depth errors occur when the entire implant is placed caudal to the planned position, bringing very high doses to functional tissues below the apex, with failure to fully treat the base. The second is the shift that occurs after probe removal resulting in sources being positioned much closer to the rectum than observed in the OR with the probe in place. The rectum is held apart from the prostate by the probe, but immediately recoils after the procedure.

The base depth error can be traced to the initial methodology taught based on a single plane ultrasound. Needles were placed to the base plan and it was assumed this was a stable plane. Needle depth was measured from the grid and subsequent needles were referenced to the grid. Sagittal ultrasound views revolutionized base definition but also disclosed dynamic challenges related to base depth and needle penetration. As the case proceeds, the position of the prostate base depth relative to the grid changes due to bleeding in the genitourinary diaphragm and prostate (Fig. 3). In addition, in a subset of patients, the needle can bind with the prostate, pushing the prostate along with the needle instead of piercing the prostate tissue to reach the base. Sufficient needle speed is necessary to enhance tissue cutting and overcome binding. Furthermore, a region of the prostate with extensive tumor may have a different pattern of needle binding and penetration compared to an uninvolved region of the prostate.

When biplane ultrasound probes became available, the depth of the prostate base was confirmed by the sagittal view. However, needles may appear to be at depth on a sagittal view due to the compression of the prostate rather than penetration and, as sources are released, the compressed tissue relaxes, and the sources may be dropped caudally compared to the needle position. Initial solutions to address the penetration failure included rapid thrust of the needle into the bladder with withdrawal. This strategy worked for single sources but resulted in a potential pathway for stranded sources to pass into the bladder.[40]

Evaluating the implant for prostate base coverage using CT images is ambiguous due to edema, distortion, and merging of the prostate and bladder tissue at the base. MRI based

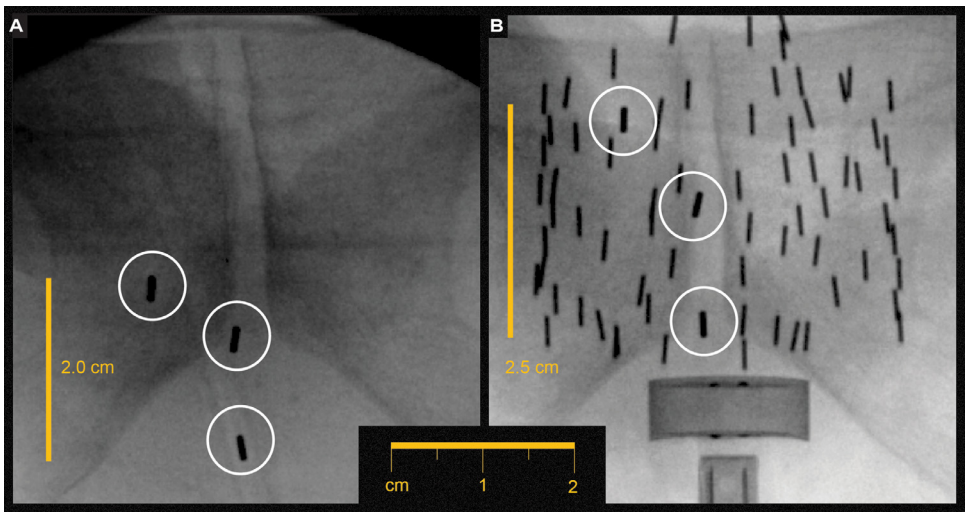

Figure 3 Fluoroscopic image acquired before and after a prostate LDR brachytherapy procedure. (A) In the preimplant image, fiducial markers are placed near the prostate base, middle, and apex. (B) At completion of the LDR implant, the fiducials are cephalad relative to their preimplant positions by a minimum of 1 cm or 2 ultrasound cuts relative to bony anatomy. Note the source shift relative to bony anatomy (fluoroscopic position unchanged between pre and post-implant images). Additionally, the fiducials have spread out due to acute edema. The gold line denotes the distance from the top of the upper source to the bottom of the lower source.

dosimetry has proved that the entire executed implant is commonly caudal to the planned implant, with 2 consequences; the base is often under-dosed and the sub-apex receives full prescription dose with severe consequences.[41] The knowledge of base depth error is invaluable and was only discovered with MRI based dosimetry. There is a large variation in the base shift phenomenon and therefore, no rigid empiric correction to compensate is possible. Dynamic adjustment of needle depth to the final base position on sagittal view is necessary.

The second systematic error due to source proximity relative to the rectum on postimplant assessment is not anticipated by the spacing of sources on an ultrasound view in the operating room. This mechanism has been recently elucidated and is a complex 3-part dynamic response termed the Bermuda Triangle (Fig. 4A). One side of the triangle involves the recto-anal flexure, a natural bend in the rectum below the apex. The second side of the triangle is the prostate and the third side of the triangle is the genitourinary diaphragm and the sub-apex tissues. When the ultrasound probe is placed in the rectum, the flexure is straightened, and the implantation position creates the illusion of a free space below the prostate (Fig. 4B). Some early planning strategies placed sources below the apex to ensure dose coverage. Unfortunately, when the probe is removed, the rectum recoils to its natural position, and even sources within the prostate on the posterior prostate surface are now closer to the rectum, risking rectal complications (Fig. 4C). In addition, acute edema of the prostate during implantation may change the relationship of the most posterior row of needles to the rectum and to the urethra.

In Figure 4D, the sources are in perfect position by grid coordinates but reside in edematous tissue. When the edema resolves the sources will be closer than anticipated to the rectum (Fig. 4E). Finally, the entire prostate may be shifted anterior and cephalad due to bleeding in the genitourinary diaphragm. This bleeding temporarily prevents rectum recoil, holding the sources at a greater distance from the rectum on the first day (Fig. 4F). When final dosimetric evaluation is performed, the bleeding has resolved and the sources are closer to the rectum (Fig. 4G).

Restricting dose to the rectum on ultrasound planning and implantation will not solve the dynamic effects of rectal recoil and edema resolution. Several strategies effectively deal with both tendencies but involve compensatory shifting of needles away from the ideal plan to reduce the effects of source proximity to the rectum. The simplest compensation is to place rectal adjacent sources anterior to the ideal position and never posterior. A second strategy is placement of the needle 1 grid position anterior while angling posterior to reach the ideal position at the base. The third strategy is to split the single needle in 2, placing the base sources in the planned grid position and the apex sources 1 row anterior to the planned grid position.

Avoiding the 2 major dynamic pitfalls by recognizing them during implantation can eliminate the vast majority of consequential brachytherapy medical events.

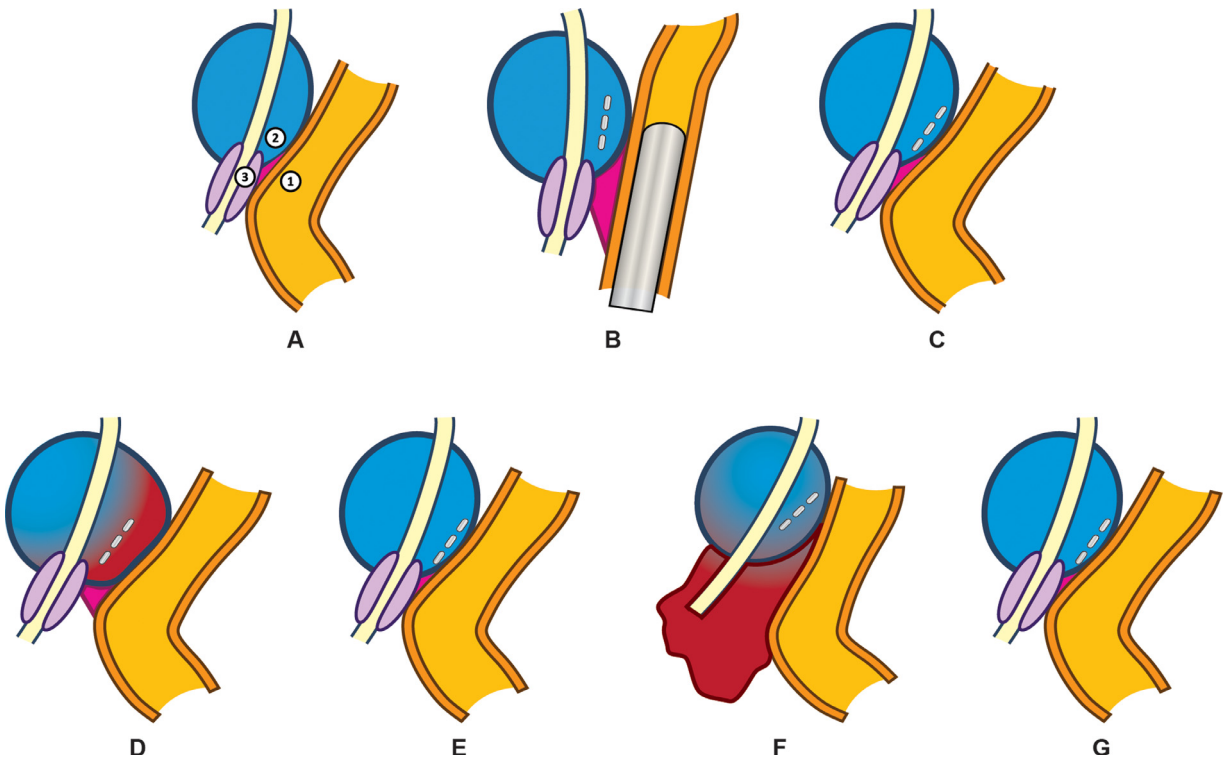

Figure 4 Mechanism of higher than anticipated rectal dose postimplant. (A) A complex dynamic interplay of 3 adjacent structures termed the Bermuda Triangle includes rectum (brown), prostate (blue), and GU diaphragm (purple), resulting in source position closer to the planned position. (B) The ultrasound probe straightens the recto-anal flexure and creates a space below the prostate. (C) After probe removal the rectum recoils into its natural position bringing sources closer to the rectum. (D) Sources placed in edematous prostate tissue will be farther from the rectum immediately following the implant procedures. (E) The final source position after edema resolves. (F) Bleeding in the GUD lifts the prostate away from its normal position. (G) Prostate returns to its normal position after bleeding resolves.

Progress in Individualized Therapy: Beyond National Comprehensive Cancer Network (NCCN) Risk Stratification

The current treatment options and NCCN guidelines employ risk stratification to guide treatment options. The limitation of current risk categories is apparent when mpMRI is obtained, assisting in the definition of tumor and tumor extension.[42] Figure 5 A-D illustrates an axial mpMRI of a prostate for a 54-year-old man with favorable intermediate risk who was found to have an anterior T3 lesion. If the patient had been treated as favorable intermediate risk, it is doubtful that sufficient treatment intensity would have been applied, and even the benefit of hormone therapy in downsizing the tumor would not have been indicated.

Figure 5 E-H shows a coronal and sagittal, diffusion weighted MRI of a patient with unfavorable intermediate risk prostate cancer that was noted to have an extensive, aggressive lesion at the base of the prostate in the transition zone, a region typically uninvolved by cancer. His dominant lesion would not have been detected if the patient was imaged and planned with CT alone. Such information is an invaluable refinement over decision by NCCN risk.

Obtaining mpMRI requires a waiting period of 6-8 weeks after biopsy. In addition to defining patients beyond their apparent NCCN risk, it is valuable in predicting outcomes from treatment. Sphincter length is easily measured and predicts postoperative incontinence risk.[43] Nerve configuration (bundle vs plexus) can define the necessary operation (standard nerve sparing or Veil of Aphrodite technique) to preserve sexual function.[44] If extracapsular extension is apparent, the patient should be counseled that adjuvant radiotherapy may be needed if surgery is selected. Median lobe enlargement prompts formal bladder emptying studies to determine if limited excision is necessary prior to LDR.

This approach prevents immediate, impulsive anxiety-based treatment decisions and allows a neutral advocacy stance for patient counseling. If the functional anatomy profile favors a good surgical outcome (long sphincter, clear nerve bundles, prostate confined tumor) a patient's decision for surgery can be fully supported. Conversely discovery of more advanced tumor may shift a patient away from insufficient treatment.

Progress in Comparative Brachytherapy: Beyond Simplistic Theories and Medical Marketing

Several key controversies in comparative brachytherapy approaches have been clarified in the past decade. Perhaps the most important clarification is the limitation of simplistic theories used to rationalize one approach over another. Early in comparative LDR approaches, as a new isotope was introduced, a theoretical advantage would be purported and

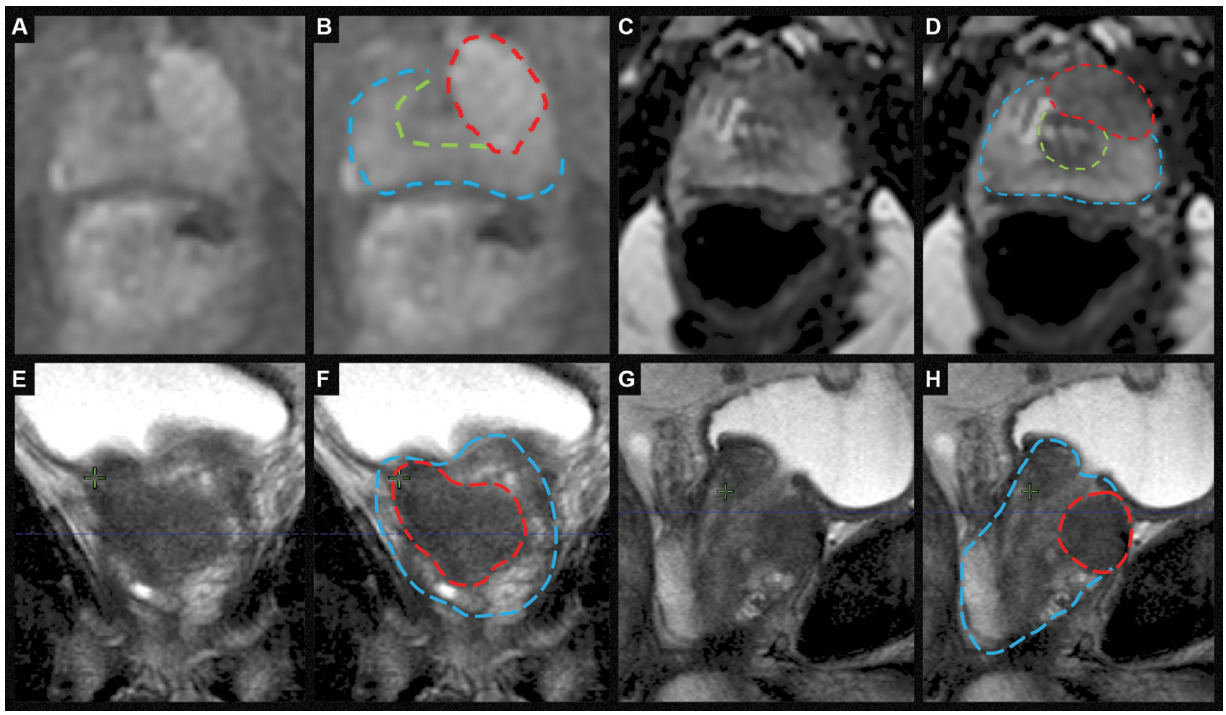

Figure 5 Tumor definition by multiparametric MRI. (A) Dynamic contrast enhanced axial MR image demonstrating an anterior T3 lesion in a young favorable risk patient. (B) Prostate in blue, transition zone in green, and tumor in red contoured. (C) An axial image of the prostate using a diffusion sequence demonstrating the same lesion. (D) Contours shown for panel C. (E) Coronal T2 sequence demonstrating an extensive unsuspected transition zone tumor (charcoal smudge sign). (F) Contours shown for panel E. (G) Sagittal view of the T2 showing the proximity to the bladder neck. (H) Contours shown for panel G.

adopted as fact. For example, Pd-103 was promoted to have an advantage over I-125 in aggressive cancers because such cancers were assumed to require more rapid, intensive treatment. In a large single institution trial for aggressive cancers with mature follow-up, there was no difference in outcomes between Pd-103 and I-125.[45]

Almost a direct extension of this rationale is the radiobiological assertion that prostate cancers have a lower alpha-beta ratio than many other cancers and therefore, large fractions are necessary to achieve cure. This theory was used to assert the potential superiority of HDR versus LDR brachytherapy, and hypofractionation beam versus standard fractionation.[46,47] The original prediction based on the low alpha-beta model was equal or superior tumor control with no difference in late effects and a decrease in acute effects. In recent reviews and analyses, the authors conclude equal, not superior tumor control and near-equal late effects, but no advantage in acute effects. What was advanced as a useful hypothesis in the study was interpreted by many as established fact. To their credit the originators have remained objective and measured, and in recent analyses they remain cautious about the potential danger of large fractions, even within the moderate hypofractionation protocols.[48] Although some extreme hypofractionation studies have proven tolerable and more convenient, selective reporting of toxicity raises questions about the global efficacy (cure with QoL) emphasized in this review. In a widely hailed proof of the large fraction Stereotactic body radiation therapy (SBRT) approach with long-term follow-up, excellent biochemical control outcomes were achieved in a favorable population.[49] Gastrointestinal and genitourinary toxicity was scored by physicians, not patient reported outcomes and were superior to toxicity outcomes-based Medicare claims.[50] Considering that the study involved low-risk and favorable intermediate-risk patients, sexual toxicity outcomes should have been included because sexual outcomes are a dominant concern at consultation in such patients. Desai has initiated a functional anatomy SBRT approach, Poten-C, to directly address the poor sexual function outcomes with SBRT with dose restriction to nerves, a promising and necessary measure to determine whether competitive sexual preservation can be accomplished with extreme hypofractionation.[51] In a direct comparison of LDR, HDR, and IMRT with patient reported outcomes, sexual dysfunction was significantly greater in the HDR cohort.[52]

The low alpha-beta theory is questionable because of genetic variation and the variance in biology coded in the Gleason Score. Is it plausible that a Gleason 10, completely undifferentiated cancer has the same radiobiology as a low-risk cancer? A more comprehensive theory for prostate cancer management would first require recognition of functional anatomy. The low alpha-beta theory was advanced before the complex functional anatomy was recognized.[6] Even if a large dose per fraction for prostate cancer was advantageous, it would be necessary to assert that the normal tissues in the region are uniquely resistant to large fractions relative to prostate cancer. In fact, normal tissue alpha-beta values have been assigned without recognizing that the treated normal tissue are functions, integrated neuro - muscular- vascular circuits and organelles, not simple tissues. It is telling that in a major randomized trial, baseline bladder function predicted much greater late toxicity in the hypofractionation group.[53] Dysfunction of complex physiology (urination) at baseline was significantly more vulnerable to permanent worsening with large fractions, contradicting the equal late toxicity prediction. Furthermore, radiobiologic parameters to map vulnerability of complex physiological functions are not currently available. At least in this instance, the vulnerability of physiological function varied with fractions size. While a tumor located in a field of redundant, expendable normal tissue (i.e., a tumor within liver or lung) lends itself perfectly to large fraction ablative approaches, the adjacent function context of prostate cancers makes large fraction approaches questionable.

Additionally, a comprehensive theory must recognize the role of variable sensitivity within the tumor, not just cellular sensitivity. Cells within the tumors cycle through variable points of sensitivity over time and a fractionated approach takes advantage of this vulnerability, while a time constricted approach places extreme pressure on the radiation to treat resistant or hypoxic cells. HDR approaches mean that dose delivered over minutes must eradicate all cells in the target despite variable sensitivity. The failure of single fraction HDR proves the impossibility of overcoming this.[54] The proposed answer to this failure is even larger single fraction treatments or multiple fractions. Neither solution is ideal. Single high-dose treatments will risk greater complications, while multiple fractions result in 2 or more procedures rather than 1, doubling the cost and risk of the brachytherapy component. The principle advantage of the LDR approaches is continuous dose delivery for weeks or months from a single procedure, addressing tumor level resistance based in hypoxic, noncycling cells, or cells on the margin not encompassed by high dose initially but falling into the high-dose envelope as the tumor responds.

Another purported advantage of HDR is the assertion that dose delivered versus planned dose is superior with HDR, which was called into question by a meta-analysis of greater than 3000 patients.[55] Based on the presumed dose delivery, the failure rate was greater than predicted, and most consistent with either marginal miss or tumor level resistance. Cause of failure after HDR is admittedly difficult to assign. Unlike LDR where source position provides a trace of what was actually delivered, there is no delivered dose confirmation following HDR. A recent study asserted a dosimetric advantage for HDR compared to LDR in sparing organs at risk adjacent to the MRI defined tumor but required 2 fractions of HDR to realize an advantage.[56] Again, this doubles the cost, procedure time, and medical risk of the brachytherapy component for a small gain. There is no trial to date with actual superior global outcomes (cure with QoL including sexual outcomes) with HDR relative to LDR.

While this review is critical of practice based on conversion of theory to dogma, the technical advances in HDR therapy in the last 10 years are impressive and hold great promise. HDR cure rates performed at equivalent levels to LDR in extreme high-risk cancers.[3] The combination of a single fraction HDR combined with hypofractionated external

beam is a proven efficacious and low toxicity approach.[57] This is an ideal combination of intense dose escalation in an economical time frame. The capacity of modern HDR optimizations to take advantage of tumor definition by mpMRI will allow dose shift strategy of preferential dose escalation to tumors with dose de-escalation to uninvolved regions. HDR delivered in a suite with the probe in place allows probe displacement of the rectum centimeters away from the prostate, especially advantageous in postexternal beam salvage treatment relative to LDR. Clinical trials are in progress and integrating the highest quality HDR with the highest quality external beam may ultimately have a proven advantage over other approaches, but that proof must be based in hard clinical outcomes. Until 100% of men are cured with 100% function preservation there is significant work remaining in both LDR and HDR approaches.

Conclusion

Thirty years ago, Willet Whitmore, the father of academic urology, posed a question that went unanswered until recently. Is cure possible when cure is necessary? In his era, Whitmore was convinced that until a cure was available for highly lethal prostate cancers, screening to find such cancers made no sense. In the last year an affirmative answer to Whitmore finally came; in the most lethal form of prostate cancer intensive combination therapy with LDR and external beam or HDR plus external beam accomplished cure in the vast majority of patients, and 87% were metastasis free at 10 years.[3] Although cure at all cost would have been acceptable in the face of such lethality 30 years ago, the modern standard of success requires not only cure but preservation of critical function.[6] Remarkably that too has been demonstrated in recent studies.

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