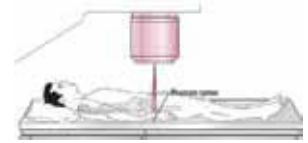


MODERN EXTERNAL BEAM RADIOTHERAPY FOR LOCALIZED PROSTATE CANCER



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MODERN RADIOTHERAPY TECHNIQUES

Background: A Disease of Options

The spectrum of management options for localized prostate cancers spans active surveillance, hormonal therapy, cryotherapy, high-intensity focused ultrasound, surgical removal (with multiple surgical techniques), and radiotherapy (with multiple options). This current review concentrates specifically on external beam radiation therapy (EBRT)(1). It is important to realize that external radiotherapy options are still evolving at the level of definition of treatment volumes, treatment schedules (e.g. fractionation), and treatment techniques (e.g. intensity modulation, image guidance).

In comparing different modalities, the most obvious challenge in evaluating different management options is the long time frame of progression of the majority of prostate cancers, which makes such evaluation often impractical. Given the long natural history of prostate cancer, particularly favorable disease, identifying patients who might not need treatment at all is an imperfect science at this stage, with an ongoing controversy about how to define “insignificant” or “indolent” prostate cancer. Each approach has its champions and advocates amongst researchers, physicians, and patients. In addition, the current cultural, social, and societal pressures of dealing with a disease with such high prevalence make

favorable prostate cancer a model of management confusion. This environment renders direct comparisons of different modalities difficult through randomized controlled studies, which are extremely unlikely to demonstrate clinically significant differences between the currently available treatment options within 10 to 15 years. An important focus, however, should be on insuring the best treatment technique is applied for the treatment of an individual patient. Overall, Table 1 summarizes semi-quantitatively the pros and cons of the main approaches; surgery, brachytherapy, external beam radiotherapy, and the combination of external radiation and brachytherapy

(Continued on page 16)

Table 1. Comparison of options. Legend: “+”=best, “++++”=worst.

Options	Surgery	EBRT	Brachy	EBRT+Brachy
Cure At 5, 10, 15, 20 yrs?	Similar up to 10-15 yrs			
Urinary toxicity	++++	+	++++	++++
Bowel toxicity	+	+++	++	+++
Impotence	++++	++	++	++
Hormonal	+	++	++	++
Overall QOL	Same, similar to general population			
Patient loyalty to Rx	Same			
Inconvenience (time)	++	+++	+	++++
Cost	++	+++	+++	++++

“High radiation doses are only safe when delivered through small radiation fields”

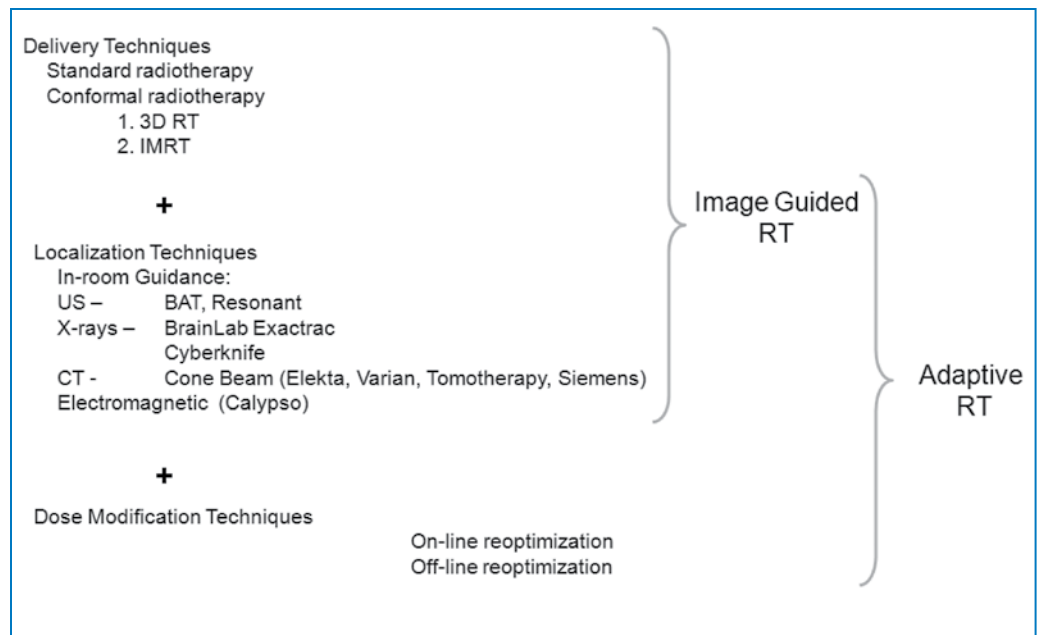
Introduction of EBRT: Dose Shaping (IMRT) and Image Guidance (IGRT) are Complementary

There is general consensus that increasing radiation doses to the prostate and periprostatic tissues does increase the likelihood of tumor control, reflected in improvements in biochemical, local and distant control rates. The need for high radiation doses is also consistent with the excellent control rates associated with brachytherapy techniques, which are alternative methods of radiation dose delivery and dose-escalation. The controversy is mostly about the extent of the improvements with increasing radiation doses, with retrospective studies showing a larger benefit compared to prospective randomized studies.

Typical external beam radiation doses have increased from around 66-70 Gy to 76-86 Gy. Such high doses are only safe with the delivery through small radiation fields. These fields have to be properly designed to conform to the shape of the intended target areas (i.e. the prostate gland +/- seminal vesicles +/- pelvic lymph nodes), and subsequently properly targeted (guided) to adjust for anatomic variations that can occur during a radiotherapy course (e.g. variations in prostate location within the pelvis). The shaping of radiation fields have been done through specialized software that simulates radiation delivery, enabling techniques such as 3D conformal radiotherapy (3DCRT) and intensity modulated radiotherapy (IMRT). The subsequent utilization of imaging technologies within treatment rooms to ensure proper placement of radiotherapy areas have been loosely termed Image Guided Radiotherapy (IGRT). Therefore, IGRT and IMRT are not competing technologies, but complimentary approaches.

External beam radiotherapy techniques have been getting more and more complex over the past 15 years. Figure 1 displays the different steps or components of this evolution. Individual vendors have also developed devices that are utilized in the delivery of radiation therapy. Figure 1 also displays which specific technologies fit within these techniques. This evolution of different technologies in both shaping and aiming radiotherapy has been understandably confusing to both healthcare professionals and patients alike. The following article describes the dominant techniques, devices and approaches currently available in the treatment of localized prostate cancers and presents potential future applications of such technologies.

Figure 1. Overview of Radiotherapy Techniques.



Radiation Shaping: 3D Conformal Radiotherapy (3D-CRT) / Intensity Modulated Radiotherapy (IMRT)

The large majority of radiotherapy is administered with high-energy X-rays (photons). Shaping of radiation fields is performed by the intersection of multiple beams from multiple angles. 3D Conformal Radiotherapy (3D CRT) is a method of shaping radiation fields to conform to individual patient anatomies; this works relatively well for simple geometries, e.g. spherical targets.

Intensity-modulated radiotherapy (IMRT) is a hardware/software solution of further refining this 3D radiation shaping capability to accommodate complicated shapes, e.g. being able to adjust to concavities, convexities and various irregularities. For favorable risk prostate cancers, IMRT makes dose escalation possible by adjusting to the posterior convexity of the prostate gland, allowing further decrease in rectal doses. For more advanced risk prostate cancers, IMRT facilitates dose escalation through better shaping of doses around the seminal vesicles and better avoidance of central pelvic structures such as the bowel and bladder in cases where the pelvic lymph nodes are irradiated. Although not an absolute requirement for dose-escalation, IMRT is now documented to be associated with lower toxicity rates compared to prior techniques such as 3D conformal radiotherapy. This has made IMRT the standard of care technique for the treatment of localized prostate cancers. Currently, all major device manufacturers such as Varian, Siemens, Elekta, TomoTherapy and Accuray (CyberKnife®) provide IMRT solutions. The more advanced IMRT solutions are the rotational “arc” treatments with either TomoTherapy (Helical Therapy) or Varian/Elekta units (Volumetric Arc Therapy, e.g. RapidArc).

Overall, the quality of radiation delivery is generally considered to be relatively equivalent regardless of individual vendors.

Guidance of Radiation Beams

Guidance in radiotherapy means the placement of radiation therapy fields in the intended spot in a patient’s body, typically using images acquired in the treatment room immediately prior to the delivery of radiation. Since external radiation therapy, unlike surgery or brachytherapy, is delivered with repeated sessions, there is variability in the internal anatomy of patients from day to day that can affect the proper targeting of radiation fields. Each session (fraction) attempts to reproduce the same delivery, and an individual session typically lasts 10-15 minutes. Fractions can vary in number anywhere from 5 (defined as Stereotactic Body Radiotherapy) to 45, with the course of treatment ranging from 2 weeks

to 9 weeks. Due to many physiological reasons, the expected position (and to a certain extent the shape) of a target such as the prostate, seminal vesicles and pelvic lymph nodes can change from day to day (inter-fraction changes) or during an individual delivery (intra-fraction changes). These changes can result in motion or deformation of the targeted areas. There are numerous anatomic structures relevant to radiotherapy of prostate cancers, including the prostate gland, possibly with defined areas of bulk of disease within the gland, the seminal vesicles, the pelvic lymph nodes, and various organs at risk such as the rectum, anus, bladder, urethra, small bowel and erectile function apparatus.

Guidance systems are essentially imaging devices installed in the treatment room that allow imaging of targeted areas before and/or during radiation delivery to ensure proper placement of individual radiation fields. Different technologies have been utilized since the mid-1990s. These are described below.

Clinical Applications

High dose external radiotherapy yields cure rates that are similar to either surgery or brachytherapy in patients with localized prostate cancer (Figure 2). Dose escalation through larger fraction sizes has resulted in the recent implementation of novel approaches such as stereotactic body radiotherapy (SBRT). Favorable risk prostate cancer has been an ideal site to investigate the effectiveness of many of these improvements over the past decade. This evolution has still not yet resulted in an agreed upon optimized method of utilizing external beam radiotherapy in the treatment of localized prostate cancers. Therefore, these techniques are very much still a work in progress with significant promise in improving cure and decreasing toxicity.

In-Room Guidance Techniques

Over the past 15 years, with the increasing evidence supporting dose escalation in the management of prostate cancers, planning target volumes have been shrinking to allow for such dose escalation. Current treatment margins for localized prostate cancers are in the 3 to 8 mm range. Given the notable daily positional variations of the prostate gland within the pelvis, daily localization techniques become a necessity. Although there have been attempts to adopt less than daily target localization, the current consensus is that tight treatment fields require daily localization. A multitude of techniques are currently utilized for daily prostate localization such as trans-abdominal ultrasound, intra-prostatic metallic fiducials detected with in-room X-rays or CT scans, and electromagnetic tracking. *(Continued on page 18)*

Radiotherapy Guidance Techniques

This section will provide an overview of the different imaging tools available for prostate IGRT.

1. Transabdominal ultrasound: ([Nomos® BAT Medical](#))

Transabdominal ultrasound has been available for daily prostate localization and does not require implanted metallic fiducials. However, it suffers from notable inter-user variability, with large variations in the rates of usable images and the accuracy of alignments. Compared to positioning with implanted markers, the accuracy of transabdominal ultrasound has also been suboptimal.

2. On-board MV imagers: ([Varian](#), [Elekta](#), [Siemens](#))

Electronic portal imaging (EPI) is the oldest IGRT modality. The images are obtained by using either the treatment beam to get a 2D X-ray images, or an X-ray imager mounted on the gantry of the treatment machine. Typically, metallic fiducial markers are implanted in the prostate and used as surrogates for the position of the prostate. All standard linear accelerators are capable of obtaining EPIs, and most have on-board imagers. However, the process to obtain these images is somewhat slow. The quality of images is sub-optimal when the treatment is used, requiring relatively large size fiducials. With the latest generation machines, on-board imagers are better integrated and provide better quality images. However, they still are relatively inefficient in obtaining frequent images during treatment delivery.

3. Stereoscopic X-rays: ([BrainLab](#), [CyberKnife](#))

These systems consist of 3D X-ray imaging systems that are not dependent on the treatment beam from imaging and are mounted in the room to obtain good resolution X-ray images that can be utilized for efficient and accurate target localization. Metallic fiducials are still required since the prostate gland cannot be visualized with metallic surrogates on the X-rays. However, the set-up allows frequent checks during treatment.

4. In-room CT solutions:

Cone-beam CT ([Varian](#), [Elekta](#), [Siemens](#))

Megavoltage helical CT ([Tomotherapy](#))

Unlike simple X-ray images, a few devices now can generate soft tissue images with computerized TomoTherapy. These are useful to assess the anatomy in greater detail, specifically assessing the normal tissues such as the rectum or the bladder. Metallic fiducials are still typically used since they decrease the inter-user variability of interpreting the position of the prostate on the CT images. These are obtained immediately prior to therapy. Due to the inefficiency and increased radiation dose of repeat imaging, CT images are not used for tracking target areas while the radiation is delivered, but only immediately before the delivery.

5. Electromagnetic Tracking: ([Calypso](#))

This system requires the implantation of implanted beacon transponders. The beacons are then electromagnetically detected. This provides continuous, real-time localization and monitoring information. This is a non-ionizing “IGRT” treatment option where real-time data on prostate motion provides feedback to the treatment machine. Little interpretation is needed of the localization information, unlike the necessity of analyzing images in other techniques. The main advantage of the system is its ability to track positions continuously.

In image guidance for prostate cancer radiotherapy, there are technical questions that are independent from specific devices that are relevant in this context. The following are some of the relevant controversies:

1. *Are there documented differences in outcomes between different radiation delivery systems or vendors?* For better or worse, specific studies comparing clinical outcomes (cure, toxicity) between different radiation delivery systems in a head to head fashion have not been performed. Clinical outcomes have not been specifically documented to be different between these techniques, and they are not necessarily expected to show dramatic differences. Instead, different devices have been adopted and implemented on the basis of their technical merits. Individual vendor claims are mostly driven by marketing efforts rather than adequately documented clinical outcomes.

2. *Are metallic markers needed to assist in image guidance during radiotherapy for prostate cancers?* The use of intraprostatic fiducials was introduced in 1990s and has stood the test of time. Although invasive, transrectal placement of metallic fiducials is a simple procedure with a negligible risk of complications(2). Typically, 3 to 4 markers are implanted. Once within the prostate, migration is very infrequent and the presence of more than one marker mitigates the rare migration event. Therefore, implanted fiducials are a reliable surrogate for the position of the prostate. Although there are some minor concerns about prostate deformation confounding the prostate versus marker position, if the markers are implanted close to the prostate/rectal interface deformation and rotation of the prostate gland become of relative small concerns. Ultimately, the overwhelming advantage of using markers is the ease of detection and absence of any significant inter-user variability. Even when in-room CT scans are obtained, fiducials were demonstrated to significantly decrease inter-user variability. Metallic fiducials are routinely used with devices from Varian, Siemens, Elekta, TomoTherapy and Accuray (CyberKnife).

3. *Is soft-tissue imaging, i.e. using CT imaging in the treatment position, necessary?* With the advent of in-room CT imaging, specifically with Varian, Siemens, Elekta and TomoTherapy devices, documentation of variation of pelvic anatomy during radiation delivery was made possible. Deformation of the prostate, variations in rectal and bladder filling, and their impact on radiation delivery are now better appreciated. In addition, dosimetric evaluation (such as dose recalculations and adaptive radiotherapy) are facilitated with the availability of such soft tissue images throughout a treatment course. Today, in-room CT scans are utilized to align the prostate gland on the basis of implanted fiducials, and only intervene if there is significant deformation due to extreme bladder or rectal anatomic variation. These can be of particular help in patients with locally advanced prostate cancer in whom larger areas in the pelvis need to be treated (seminal vesicles, lymph nodes) and anatomic variability in bladder and bowel position will be consequential compared to when only the prostate gland is treated.

4. *Is adjusting for intra-fraction motion necessary?* Intrafraction motion has mostly been appreciated with the use of repeat in-room KV X-rays, but mostly with MRI based studies and electromagnetic tracking of implanted transponders (Calypso Medical). Intrafraction motion is clearly variable from patient to patient, and from day to day. If intrafraction monitoring is performed, it is typi-

cally done with gating using arbitrary thresholds of 2 to 3 mms. It is still debatable if intrafraction motion correction leads to any clinical benefit. Dosimetric differences are difficult to document when taking into consideration intrafraction motion. These suggest relatively small dosimetric variation due to intrafraction motion when an entire fractionated treatment course is taken into account. However, one study showed decreased acute toxicity with intra-fraction motion management using a 2 mm threshold(3). Such intrafraction motion is now frequently adjusted for by repeat imaging during the actual delivery of radiation, even in the absence of electromagnetic tracking such as with the Calypso system.

5. *Are there other methods that will decrease variability in pelvic anatomy?* Rather than observing and reacting observed intra-fraction motion, strategies to decrease motion have also been suggested. In a randomized study, abdominal compression was shown not be a factor in decreased either interfraction or intrafraction motion. Dietary modifications showed little impact on motion. Finally, placement of intrarectal balloons does reduce intrafraction motion without eliminating it. The main advantage for the use of an intrarectal balloon during radiation delivery has been the sparing of the posterior segment of the rectum, thereby reducing the possibility of rectal damage to that part of the rectum. A more novel approach of (Continued on page 20)

Table 2. Summary of the Currently Available Common Guidance Technologies and Their Technical Benefit

IMAGE GUIDED HARDWARE/SOFTWARE OPTIONS			
TRADE NAME	MANUFACTURER	IMAGE GUIDANCE	STATED BENEFITS
TRUEBEAM	VARIAN	X-Ray Cone-beam CT (kilovoltage)	CT enables soft tissue imaging: better assessment of changing anatomy, including evaluation of the bladder and rectum variations throughout treatment. Marker implantation not required, but strongly encouraged.
SYNERGY	ELEKTA	X-Ray Cone-beam CT (kilovoltage)	CT enables soft tissue imaging: better assessment of changing anatomy, including evaluation of the bladder and rectum variations throughout treatment. Marker implantation not required, but strongly encouraged.
ARTISTE	SIEMENS	X-Ray Cone-beam CT (megavoltage)	CT enables soft tissue imaging: better assessment of changing anatomy, including evaluation of the bladder and rectum variations throughout treatment. Images lower resolution, but dose calculation possible. Marker implantation not required, but strongly encouraged.
HI-ART	TOMOTHERAPY	Helical CT (megavoltage)	Integrated system. CT enables soft tissue imaging: better assessment of changing anatomy, including evaluation of the bladder and rectum variations throughout treatment. Images lower resolution, but dose calculation possible. Marker implantation not required, but strongly encouraged.
CYBERKNIFE	ACCURAY	Stereoscopic X-rays	Efficient, checking position frequently during delivery. Low dose associated with imaging. Marker implantation required.
EXACTRAC	BRAINLAB	Stereoscopic X-rays	Easy to use. System can be added to existing accelerators. Allows frequent imaging, checking position frequently during delivery. Marker implantation required.
RESONANT BAT	ELEKTA NOMOS	Ultrasound Ultrasound	No radiation needed for imaging. Images more difficult to interpret: higher inter-user variability. No markers needed.
CALYPSO MEDICAL	CALYPSO MEDICAL	Electromagnetic tracking	Continuous tracking. Easy interpretation. Special marker implantation required. Can impact MRI imaging after implantation.

proper targeting while sparing normal tissues might be the use of implanted or injected spacers(4). In this case, separation of the prostate and rectum could be achieved by the presence of a physical spacer in the prostate/rectal interface, with the spacer material being absorbed after completion of treatment. Such approaches are not approved for clinical use, they are not available, and are being currently actively investigated.

Dose Escalation (Standard Fractionation)

Conformal radiotherapy techniques, including IMRT, which 3D reconstructions of patient and tumor anatomies to design treatment fields, have been used to deliver higher than standard radiation doses (exceeding 80 Gy) without dramatic increases in toxicity rates. There is a clear radiation dose response with respect to biochemical failures. In a recent publication by Diez et al., a meta-analysis was performed of studies satisfying the following criteria: external beam radiotherapy series reported up to 2008, at least 2 dose groups compared, no brachytherapy, no hypofractionation and including at least 200 patients(5). A total of 5 retrospective and 4 prospective randomized studies were included in the analysis. Looking at specifically the favorable risk group, there was a clear improvement in outcomes with the higher radiation doses. However, the magnitude of the benefit was somewhat smaller in the randomized studies versus the retrospective studies. The dose response curve for favorable risk prostate cancer was demonstrated to be relatively shallow. This indicates that improvements in outcome would only be associated with relatively large increases in dose. In addition, clinically relevant outcomes such as local failure and/or distant failure have been impacted by radiation dose in all risk groups; radiation dose was demonstrated to be associated with less local or distant failure independently from risk groups defined by T stage, pretreatment PSA and biopsy Gleason score.

With respect to toxicity, dose escalation to the 78-80 Gy range has been associated with relatively minimal increases in toxicity rates. A recent report of a large trial comparing different dose groups from 68.4 to 78.0 Gy observed that a mild increase in rectal and urinary morbidity was observed with the higher radiation doses. However, the authors remarked “the rates of late grade 3 toxicity are not significantly large enough to be modeled”. The urinary and gastrointestinal grade 3 and higher toxicity events were observed in 6% and 7% of the patients who were in the highest dose groups. These are overall relatively low toxicity rates. Although complications, in general, have remained relatively minimal, increasing doses to increasing rectal volumes does result in increased rectal bleeding(6).

The typical limits used to minimize rectal toxicity are:

1) limit >70 Gy to <25% of the rectal volume (more stringently <15%), or 2) limit 78 Gy to <10 cc of the entire rectum. However, changing daily anatomy can result in unexpected low or high cumulative doses within normal structures, particularly the rectum.

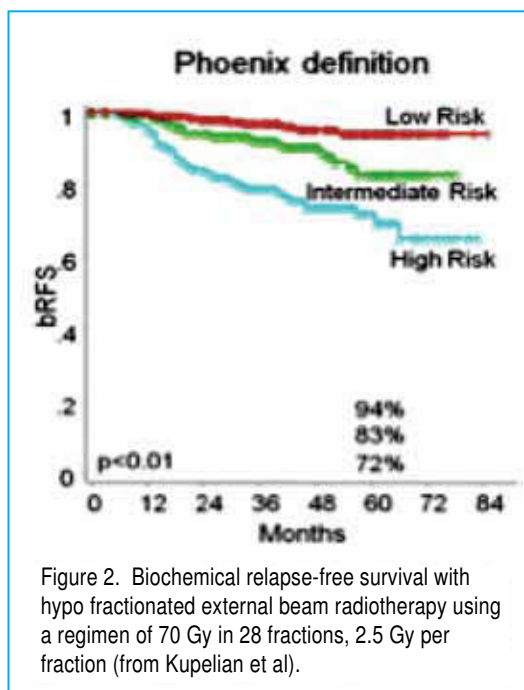
Urinary toxicity is more difficult to correlate with bladder dose/volume parameters. However, a limit of <25% of the bladder to receive >65 Gy has been typically used.

Finally, with respect to potency after radiation therapy, the results are highly variable for a multitude of reasons. A recent review of the literature revealed 44% to 100% of patients being potent prior to radiotherapy(7). At evaluation times ranging from 12 to 78 months, the potency rates after radiotherapy were 27% to 65%. If patients were potent prior to radiotherapy, 46% to 65% were still potent after radiotherapy. These ranges indicate the heterogeneity of patient cohorts and the heterogeneity of methods of evaluating and reporting on potency after treatment in localized prostate cancer patients. With respect to treatment planning, there is data emerging that the doses to the penile bulb / crurae are important in predicting radiation induced impotence. Typically, a limit of <50% of the penile bulb to receive >50 Gy is a reasonable guideline with respect to the evaluation of treatment plans. However, there is still controversy about the correlation between penile bulb doses and post-treatment potency status.

Use Case for IMRT/IGRT In Low/Intermediate Risk Cases: Hypofractionation (Including SBRT)

Conventional fractionation in external beam radiotherapy typically consists of doses around 1.8 to 2 Gy delivered daily, 5 days per week, for total doses in the 75 to 80 Gy range. Treatment courses are typically 8 to 9 weeks long. The rationale behind shortening radiation therapy courses in prostate cancers has been the greater sensitivity to dose fractionation, with an assumed improvement in the therapeutic ratio with the use of large fraction sizes. Large fraction size delivery can only be achieved over small volumes, thereby requiring adequate shaping and targeting. In addition, large fraction size would indicate a shorter treatment course, increasing convenience for patients.

Modern high-dose hypofractionated radiotherapy has been performed with a variety of schedules ranging from 2.1 to 10 Gy per fraction, and total radiation doses ranging from around 33 Gy to 75 Gy. The shortest treatment schedules have consisted of only 5 fractions and the treatment has been termed “Stereotactic Body Radiotherapy” which is defined as 5 fractions or less. SBRT is simply at the extreme of hypofractionation schedules.



The largest hypofractionation experience has been reported with a schedule of 70 Gy delivered at 2.5 Gy per fraction(8). With a median follow-up of 45 months, the biochemical relapse-free survival rates were 94% at 5 years for favorable risk patients (Fig. 2).

For all 770 cases in the series, the grade 3 toxicity rates were relatively infrequent at around 2% for either urinary or rectal complications. Currently, there are multiple reports on hypofractionated radiotherapy regimens, including multiple prospective Phase II and Phase III trials that have used fraction sizes between 2 and 5 Gy, all of which use IMRT and daily image guidance. Most of these trials have been performed in patients with mostly favorable risk and some intermediate risk prostate cancer patients.

The relevant Phase II studies are the following:

1. The University of Wisconsin Phase I/II Trial which has tested 3 dose groups: 2.94 Gy x 22 (total dose 64.68 Gy), 3.63 Gy x 16 (total dose 58.06 Gy), and 4.30 Gy x 12 (total dose 51.60 Gy). The trial has been completed and results are pending. However, the preliminary reports have been encouraging.
2. The Princess Margaret Hospital Phase II Trial testing 3 Gy x 20 (total dose 60 Gy). The treatment was well tolerated as reported by Martin et al. The Grade 3 complication rates have been reported around 1%.

The relevant Phase III studies are the following:

1. M.D. Anderson Cancer Center: testing 77.4 Gy at 1.8 Gy versus 72.0 Gy at 2.4 Gy. A total of 204 patients were accrued. Preliminary results were presented at ASTRO 2010. With a median follow-up of 4.7 years, the 5 year biochemical relapse-free survival rates were 94% versus 97%, the Grade ≥ 3 rectal toxicity rates were 1% and 3%, and the Grade ≥ 3 urinary toxicity rates were 1% and 0%. There were no statistical differences between the 2 groups.
2. Fox Chase: testing 76.0 Gy at 2.0 Gy versus 70.2 Gy at 2.7 Gy. A total of 307 patients were accrued. With a median follow-up of 55 months, there were no differences in gastrointestinal, urinary, and quality-of-life patient reported outcomes between the 2 groups.
3. Ontario Clinical Oncology Group: testing 60.0 Gy at 3.0 Gy versus 78.0 Gy at 2.0 Gy. A total of 1200 patients were accrued to the trial. Results are still pending.
4. RTOG 04-15: testing 70.0 Gy at 2.5 Gy vs 73.8 Gy at 1.8 Gy.

A total of 1067 patients were accrued to the trial. Results are still pending.

Specifically for SBRT experiences, there are many recent reports. However, these patient series suffer from being relatively small with short follow-up. The relevant series are the following:

1. Virginia Mason: testing 6.70 Gy x 5 = 33.5 Gy

A total of 40 favorable risk prostate cancer patients were treated with a stereotactic technique. With a median follow-up of 5 years, the 5 year biochemical relapse-free survival rate was 93%. The Grade ≥ 3 rectal and urinary toxicity rates were 0% and 3%, respectively.

2. Stanford: testing 7.25 Gy x 5 = 36.25 Gy.

This is the most thoroughly analyzed and reported series of patients treated with SBRT(7, 9). This Phase II trial was started in 2003. A total of 67 favorable risk patients were treated, with 57 evaluable at the last report. The eligibility criteria were: stage T1-T2a, PSA ≤ 10 , GS 3+3 or low volume 3+4, No TURP or other treatment, and a low IPSS score (<20). Treatment was delivered either daily or every other day. The planning target volume margins were 3 mm posteriorly and 5 mm elsewhere. Intraprostatic (*Continued on page 22*)

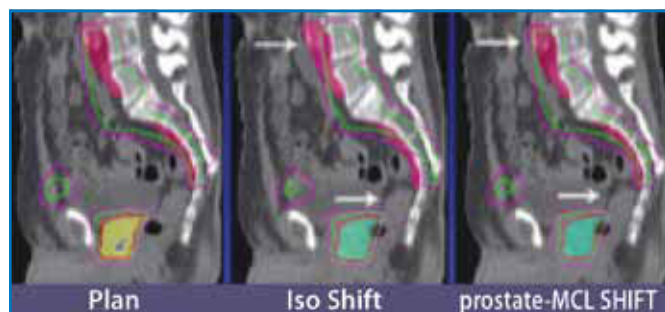
fiducials were used for guidance and no endorectal balloon was used. With a median follow-up of 2.7 years (maximum 5.9 years), the 5 year biochemical relapse-free survival rate was 93%. The Grade ≥ 3 rectal and urinary toxicity rates were 0% and 3%, respectively. An important observation was made that every other day treatment were associated with relatively less toxicity compared to daily treatments.

3. UCLA Prostate SBRT trial: Ongoing. Testing 8.0 Gy x 5 = 40.0 Gy.

This trial is based on the Stanford trial, for patients with low/intermediate risk prostate cancer. The specific emphasis is on documentation of patients' quality of life. Treatments are delivered every other day, with a total of five treatments.

Use Case For Image Guidance In High Risk Prostate Cancer: Pelvic Lymph Node Irradiation

Although there is still some controversy about the impact on cure of irradiation of pelvic lymph nodes in patients with intermediate and high risk prostate cancers, there is no doubt that larger volumes of irradiated tissues will result in higher probability of toxicity. However, with the advent of IMRT and IGRT, pelvic lymph node irradiation is made easier with specific strategies to avoid the bowel and bladder while shaping radiation around the pelvic lymphatic chains. In addition, image guidance provides solution to adjusting to the differential position and motion of the prostate gland versus the pelvic lymph nodes without



J. Pouillot, From Dose to Dose: IGRT to DGRT, Panel On-Board Imaging: Challenges and Future Directions, ASTRO 49th Annual Meeting in Los Angeles, CA, Oct. 29, 2017.

compromising adequate radiation delivery. Such a protocol is being initiated at UCLA for unfavorable risk prostate cancer patients. The approach combines large fraction sizes delivered to the prostate/seminal vesicles, and dose shaping allowing pelvic nodal irradiation without impact on bowel and bladder, all delivered within 10 treatment days.

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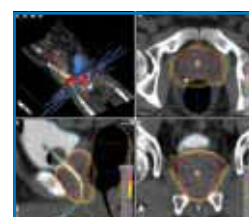


Author of more than 150 research papers, Dr. Kupelian is an internationally known expert in the development and evaluation of cutting edge technologies in Radiation Oncology for a variety of anatomic sites. He has pioneered high-dose hypofractionated radiation therapy for prostate cancers. He has also played a significant role in the introduction and implementation of multiple image guidance techniques in radiotherapy.

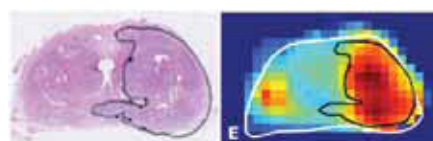
Future Applications

Heterogeneous Dose Delivery:

With the refinement in delivery and guidance, further dose escalation is currently being studied with the design and delivery of radiation dose distributions that are similar to the ones achieved with brachytherapy, specifically HDR brachytherapy. Doses can be now shaped to reach extremely high levels within the prostate gland and limited dramatically outside of targeted areas.



Dose Painting: Targeting intraprostatic areas of disease bulk is an increasingly attractive application of IMRT and



IGRT, with imaging techniques such as diffusion/contrast MRI scanning improving the definition of tumor location. With IMRT, areas of disease bulk within the prostate will be dose escalated,

With IMRT, areas of disease bulk within the prostate will be dose escalated,

whereas other areas with low probability of having disease bulk will potentially be de-escalated.

Adaptive Radiotherapy: Adaptive (or real-time) radiotherapy is the ability to constantly modulate the radiation while the patient is on the treatment table, based on feedback from anatomic changes occurring during the course of therapy. Although currently implemented in other cancer types (such as lung cancers or head/neck cancers, where tumor motion, tumor shrinkage and changes in patient shape due to weight loss can have dramatic impact on delivered doses), such techniques will be gradually tested in the context of advanced prostate cancer.

Conclusion

In conclusion, modern radiotherapy techniques have allowed better cure rates while maintaining low toxicity profiles. Although different devices might have some marginal technical advantages or disadvantages, there is little evidence of difference in clinical outcomes between individual technologies. The combination of high radiation dose, with adequate shaping and aiming, should be the guiding principles and necessary requirements of modern radiotherapy. Further modifications in external beam radiotherapy regimens currently allow potentially more effective but definitely more convenient treatments with the use

of hypofractionation. Results with extreme hypofractionation, i.e. with SBRT which is delivered in only 5 sittings, are encouraging and should be included in the discussion of options with patients with prostate cancer.

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*(Continued from page 2
— From the Editor)*

with more men continuing to relapse over many years.

Precise placement of the radioactive seeds is critically important, both for cancer control and for minimizing side effects. It should be done only by a very experienced doctor with the training and tools to calculate the seed implant dose and to verify the seed implantation actually provides the dose prescribed. The plan is to maximize dose to the cancer, while minimizing dose to the urethra and rectum to reduce side effects.

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CUSTOMIZED DOSE PRESCRIPTION FOR PERMANENT PROSTATE BRACHYTHERAPY: INSIGHTS FROM A MULTICENTER ANALYSIS OF DOSIMETRY OUTCOMES

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* Download the complete paper for free here <http://www.prologics.net/Articles/Customized%20dose.pdf>

PROTON

Proton therapy relies on radiation beams that go a certain distance in tissues and stop. Proton therapy has some physical advantages, but outcomes in prostate cancer patients have not been conclusively demonstrated to be different from outcomes in patients treated with modern techniques delivering radiation with high energy X-rays. It is worth noting that current units delivering proton beams use 3DCRT approaches. Intensity modulation (IMRT) solutions are not currently available for proton therapy units.