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Technological Advances in Radiation Therapy for Prostate Cancer

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Abstract Radiation therapy (RT) for prostate cancer has made huge strides over the past two decades. The addition of image guidance has allowed radiation oncologists to ensure accurate delivery of increasingly precise radiation treatment plans using newer conformal therapy methods such as three-dimensional conformal RT, intensity-modulated RT, and proton beam RT. Regardless of the specific treatment technique, patients can depend on the treatment to target the moving prostate effectively while significantly sparing adjacent tissues, thereby reducing the morbidity of having to undergo prostate cancer therapy. This review summarizes the recent technical advances made in radiation dose delivery, including target volume definition, treatment planning, treatment delivery methods, and positional verification methods during RT.

Keywords Intensity-modulated radiation therapy · IMRT · Image-guided radiation therapy · IGRT · Hypofractionated radiotherapy

Introduction

The 1990s can be thought of as the development and widespread implementation of conformal therapy with intensity-modulated radiation therapy (IMRT). In turn, the technological improvements of the past decade have focused on ensuring accurate delivery of increasingly precise radiation treatment plans. The development of conformal radiotherapy (CRT) and image-guided radiotherapy (IGRT) techniques has substantially increased the accuracy and precision of radiation dose delivery. These techniques are of particular importance in the treatment of prostate cancer, considering the vicinity of organs at risk and the presence of organ motion.

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MRI Treatment Planning

The most focused radiation treatments rely on identifying the target accurately, both for treatment planning and in treatment delivery. In treatment planning, CT scans are essential because of their ability to provide the volumetric tissue density required for calculating the radiation dose delivered. However, CT scans image the prostatic apex poorly. Thus, many centers use MRI fusion with or without an endorectal coil (ERC). ERCs are used for acquiring high-resolution (~0.3 cm^3) imaging of the prostate and surrounding normal organs using a standard clinical 1.5T MRI scanner. Fusion of prostate MRI with planning CT scans can improve target delineation for radiation therapy treatment planning. The information obtained from the MRI can also be used for delineating extracapsular extension and dominant nodules [1, 2]. However, organ deformation introduced by the ERC makes it difficult to register MRIs for planning CTs, which typically are acquired without ERC [3]. One of the ways of overcoming the requirement for an ERC is to utilize 3T MRI. Compared with 1.5T, imaging at high-field strengths such as 3T improves the resolution. As with 1.5T MRIs, ERCs cause significant changes in the prostate dimensions and a significant volume decrease, making image registration with the radiation

treatment planning CT challenging [4]. Some investigators have suggested the resolution provided by 3T MRI without an ERC is as good as the 1.5T MRIs with an ERC [5–8]. Although performing 3T MRI without an ERC would have a number of advantages, including less patient discomfort, lower costs, and better correlation with RT planning, it is not widely available.

One of the more recent areas of interest is recognizing that the biology throughout the prostate is not homogenous. For both the diagnosis of prostate cancer and the ability to dose escalate the dominant malignant sections of the prostate, magnetic resonance spectroscopy is potentially becoming a highly useful tool. Based on evidence that prostate cancer cells lack the ability to produce and accumulate citrate, magnetic resonance spectroscopy imaging (MRSI) reportedly can discriminate between prostate cancer and normal prostatic tissue by differentiating between regions of absent or low citrate concentration in the prostate. As with MRI, the same difficulty exists in translating MRSI information to treatment planning because of the differences in the shape and location of the prostate between MRSI imaging and the planning CT. Some investigators have reported that with proper deformable image registration of the prostate and surrounding regions from the geometry of MRSI imaging to the geometry of treatment, the regions of high tumor burden identified by MRSI may be accurately transferred to the images used for treatment planning [9].

Image Guidance

For effective consistent delivery of highly conformal radiation, not only must the prostate be accurately delineated during treatment planning, but also the treatment must be delivered precisely on a daily basis. The traditional methods of setting up by skin marks or tattoos and basing the location of the radiation by bony landmarks were inadequate. The prostate gland moves independently of the pelvic bones in patients set up for radiotherapy treatment [10, 11]. Prostate motion in supine patients has been related to fluctuating rectal volumes and, to a lesser extent, bladder volumes [12, 13]. Because the prostate gland can differ in its position within the pelvis from one treatment to another, radiation oncologists employ image guidance techniques and implant fiducial markers to verify prostate position so as to minimize and correct for setup uncertainties and interfraction motion of the prostate. The term *image-guided radiation therapy* (IGRT) implies the use of a variety of imaging techniques in the treatment room to determine the location of target areas with the patient in the treatment position. The different imaging techniques include transabdominal ultrasound, in-room X-rays with and without the use of intraprostatic implanted fiducials, and kilovoltage and megavoltage CT techniques.

Fiducial markers are frequently implanted in the prostate to verify its location during image guidance, both to eliminate uncertainties regarding position resulting from prostate motion and to avoid patient setup errors [14, 15]. The implanted fiducial markers predominantly in use today are gold seeds. Typically, three or more metallic gold fiducial markers are inserted into the prostate a few days before the patient undergoes the CT scan used for treatment planning. Investigations on number and positioning of fiducials show that the combination of three fiducials—one at the apex and two at the base—results in the best alignment [16]. The markers typically are detected by in-room stereoscopic X-rays for image guidance. This method also is referred to as *electronic portal imaging*. ExacTrac (BrainLAB AG, Feldkirchen, Germany) is a highly precise automated IGRT system that is a step up from stereoscopic X-rays. ExacTrac uses in-room high-resolution stereo X-ray imaging and an integrated optical infrared tracking system to continuously track patient movement and correct patient positioning with submillimeter accuracy throughout treatment. For prostate cancer, ExacTrac can detect and compensate for random intrafraction patient and internal tumor movement, which potentially can exceed planning target volume (PTV) safety margins [17••, 18].

One of the newest and most innovative types of fiducial marker technologies is an electromagnetic sensor that can track motion while the radiation is being delivered. Calypso Medical Technologies (Seattle, WA) developed an implantable electromagnetic transponder, or "beacon," that is powered by induction, thus requiring no external wires and permitting permanent implantation into the prostate. The system is capable of maintaining millimeter-level accuracy and can correct for intratreatment movement of the prostate, which can exceed 5 mm from the initial position for at least 10 s during a treatment fraction [17••, 19, 20]. The Calypso system is a highly accurate and convenient system for prostate localization. But even with the Calpyso system's real-time motion tracking capability, our current margins for therapy are unlikely to be significantly reduced [21].

A limitation of traditional stereo X-ray imaging used for IGRT is that it does not provide visualization of the prostate or surrounding organs, which can limit the precision and accuracy of treatment delivery. Verification using megavoltage cone beam computed tomography (CBCT) promises advantages over X-ray images because the CT images acquired in the treatment room allow radiation oncologists to evaluate soft-tissue changes such as prostate deformation, rectal distention, bladder filling, and other anatomic daily variations that could have an impact on outcomes [22, 23]. Because the prostate can be visualized on CT

scans, alignment could be performed directly on the prostate gland itself. However, because interpretation of prostate location on CT images is associated with interuser variability, even with CBCT, intraprostatic fiducial markers are still often used. CT-on-rails is an alternate method from CBCT for acquiring a CT for image guidance. Instead of the couch moving into the CT gantry as it does for CBCT, CT-on-rails keeps the treatment couch fixed while the CT is accomplished by a movable gantry mounted on rails. Investigations have shown the overall system to be accurate within 0.5 mm [24, 25]. However, it is more cumbersome than CBCT because the couch must be rotated 180° between CT acquisition and radiation delivery, and the delay between image acquisition and treatment delivery allows more time for the patient or prostate to shift between imaging and treatment [26]. On the other hand, the CT images from CT-on-rails are diagnostic quality kilovoltage CTs rather than the lower quality megavoltage CTs from CBCT.

Because IGRT (particularly daily targeting) has been performed starting only recently, long-term outcomes are not available. Randomized studies are not available and are unlikely to be performed in the future. However, the detrimental impact of missing the target has been shown in a number of studies before the image guidance era [27, 28]. For prostate cancer, high radiation doses are needed for adequate tumor control and require smaller treatment margins that might be inadequate for moving targets such as the prostate and variable organs at risk such as the bladder and rectum. Utilizing the knowledge we have attained from daily IGRT, we have been able to calculate what the implementation of IGRT would translate to in terms of the dose delivered. Dosimetric studies have shown significant benefits to target dose coverage with image guidance. IGRT makes it feasible to maintain adequate prostate target dose coverage with reduced PTV margins when intraprostatic fiducials are used in daily imaging guidance [29, 30]. Treating to smaller PTV margins can result in the reduction of overall dose to organs at risk and could potentially reduce rectal and bladder morbidity and/or facilitate prostate dose escalation [31]. With daily imaging of the prostate, IGRT has improved the accuracy of treatment delivery and allows radiation oncologists to decrease the expansion of the target volume and deliver high-dose radiation without compromising normal tissue sparing.

IMRT, Arc Therapy, SBRT

Along with the development of image guidance, continued refinement has been made to the technology of treatment delivery with IMRT. Since its introduction into clinical use in the mid-1990s, IMRT has emerged as the most effective and widely used form of external beam radiotherapy (EBRT) for localized prostate cancer. By using an inverse planning algorithm to derive beams with nonuniform intensities, IMRT can produce more conformal dose distributions than 3D conformal radiation therapy (3D-CRT), allowing the high-dose region to match the shape of the target volume [32, 33]. The dosimetric superiority of IMRT over conventional techniques has facilitated the safe delivery of higher dose levels in prostate radiotherapy while reducing the dose to the bladder and rectum, resulting in improved tumor control and reduced treatment toxicity [34, 35]. In the initial implementation of IMRT, there were two techniques for achieving intensity modulation. Multileaf collimators (MLCs) are devices made up of individual "leaves" of high atomic numbered material. MLCs are used on linear accelerators (linacs) to provide conformal shaping of radiation therapy treatment beams. Linac-based IMRT delivery can be accomplished by using either sequential delivery of multiple static apertures from an MLC ("step-and-shoot") or dynamic multileaf movement ("sliding window" or dynamic multileaf collimation) [36]. Traditionally IMRT has been delivered with the "step-and-shoot" method, but more recently, new machines are available that can deliver dynamic multileaf IMRT efficiently and with less scatter dose to the patient. Tomotherapy was introduced before the era of linac-based CBCTs and was the first radiation delivery machine that could provide a megavoltage CT scan prior to each treatment to ensure patient alignment before delivering continuous arcs of intensity-modulated radiation with a tomotherapy machine. A tomotherapy machine is essentially a scaled-down linear accelerator made to fit into a CT housing, which can then rotate at a high velocity. Intensity-modulated arc therapy using RapidArc (Varian Medical Systems, Palo Alto, CA) is a new form of IMRT that uses a linac to deliver intensity-modulated radiation with different monitor units at varying dose rates with MLC leafs in continuous arcs [37]. In general, one full rotation arc field of RapidArc delivers the intensity-modulated radiation more efficiently than the conventional static-gantry multifield IMRT. Comparison studies have demonstrated that the RapidArc technique can reduce doses to organs at risk compared with the static gantry IMRT technique with significantly reduced treatment times [38–40].

Hypofractionation

The newfound means to shape radiation in unprecedented ways opened up the opportunity to explore whether the standard fractionation schedule of treating at 1.8 to 2.0 Gy per day is the ideal program. The clinical outcome of a radiotherapy treatment plan depends on biological param-

eters such as the α/β ratio (a measure of radiation sensitivity). The fractionation of the radiotherapy regimen at a given site is determined based on the assumed α/β ratio of the tumor cells. In prostate cancer, the α/β ratio is a subject of ongoing debate, with recent studies suggesting values between 0.8 and 3 Gy rather than the higher value of 8 to 10 Gy associated with most cancers [41–44]. If these estimates are accurate, hypofractionated radiation (>2 Gy/fraction) should increase tumor control by increasing the biologically equivalent dose to the prostate without increasing normal tissue toxicity. Several studies have been undertaken to determine whether a radiobiological advantage can be attained with larger doses per day. The Cleveland Clinic began delivering hypofractionated IMRT for localized prostate cancer in 1998. The schedule decreased the overall treatment time, delivering 70 Gy at 2.5 Gy/fraction in 5.5 weeks [45••]. Compared with a contemporary patient cohort treated with 3D-CRT at 2 Gy/fraction to 78 Gy, the hypofractionated IMRT group had a comparable biochemical relapse profile and late rectal toxicity rates. University of Miami and Fox Chase Cancer Center investigators performed a randomized trial involving 303 men with intermediate- and high-risk prostate cancer. Patients were randomly assigned to receive 26 fractions of hypofractionated IMRT or 38 fractions of standard IMRT with or without concurrent androgen deprivation therapy. At a median of 39 months after treatment, the investigators observed no significant difference in biochemical failure or adverse GI or GU effects [46]. To address the concern that hypofractionated radiation schedules potentially can increase toxicity to normal organs situated close to the prostate, multiple studies have looked at toxicity profiles of hypofractionated regimens using both 3D-CRT and IMRT to doses of 50 to 70 Gy and have reported that toxicities are comparable to conventional radiation schedules [45••, 47–49]. Studies looking at standard fractionation IMRT with hypofractionated sequential or simultaneous integrated boost for localized prostate cancer also have reported preliminary results that hypofractionated boost is well tolerated [50, 51].

The natural extrapolation of hypofractionation regimens is to push the technological limits of conformality and shorten the regimen to as few treatments as necessary. Stereotactic body radiation therapy (SBRT) is a technique modeled after intracranial stereotactic radiosurgery (SRS) that takes advantage of technological advances in image guidance and radiation dose delivery to direct potent ablative doses to tumors with acceptable toxicity that is not achievable with conventional techniques. Using the assumption of a low α/β ratio of 2 Gy for prostate cancer (discussed in the previous section), it has been estimated that a 5 fraction SBRT regimen of 7.46 Gy per fraction would provide an actuarial 5-year biochemical-free survival of more than 95% compared with roughly 80% with a conventionally fractionated course of 78 Gy in 39 fractions, while maintaining an equivalent risk of late effects [42]. Because SBRT delivers ablative doses to the tumor, it is important to limit the volume of normal tissue that is irradiated to spare severe toxicities. Unlike conventionally fractionated radiation, in which margins are given around the target volume to account for uncertainty in tumor motion and setup error, it is unacceptable with the high doses used in SBRT. A commonly used approach to account for these uncertainties is via real-time imaging for tracking. The CyberKnife (Accuray, Sunnyvale, CA) provides this functionality through two orthogonal, diagnostic X-ray cameras mounted on the ceiling that provide real-time imaging for tracking, while a frameless image-guided process directs a lightweight linac mounted on a robotic arm along six spatial axes. Implanted fiducials are used to localize the prostate and deliver treatment in real-time. Early results of SBRT regimens have demonstrated that the prostate cancer treatments can be safely administered in as few as five treatments. Phase I/II trials using SBRT regimens of 6.7 to 7.25 Gy per fraction in 5 fractions have shown that the treatment is feasible with minimal acute or late toxicity [52–54]. A multi-institutional phase I trial using a 5-fraction scheme with a starting dose of 9 Gy per fraction is currently accruing at the University of Texas Southwestern Medical Center, Dallas, Texas. Other groups are investigating the use of SBRT as both the sole intervention and as a boost following conventionally fractionated radiation therapy. Careful long-term follow-up will be necessary to establish the efficacy and safety of this approach given the long natural history of prostate cancer and the high expected survival.

Proton Therapy

One of the most exciting new technologies that has garnered a lot of attention is proton therapy. Protons are positively charged subatomic particles with a biological effect similar to that of conventional radiation but a physical advantage in terms of their unique depth-dose distribution compared with photons. The physical properties of protons result in the majority of energy being deposited at the end of a linear track, a sharp maximum called the *Bragg peak*. Beyond the Bragg peak, the radiation dose falls off rapidly with essentially no exit and a much-reduced dose proximal to the target volume. Photons, on the other hand, lack mass and charge, and the X-ray beams deposit dose in a continuous fashion such that there is some dose deposited in the beam's path beyond the target. The benefit of proton therapy in prostate cancer is unclear. The sharp distal dose falloff of protons, on the one

hand, allows delivery of dose to tumor while sparing distal tissues but, on the other hand, any misestimation of the path length can lead to a complete miss of a distal portion of the tumor or a high dose being delivered to adjacent normal tissue. There also can be some uncertainty about the particle range in tissue and exact location of the steep fall off because of sensitivity to tissue heterogeneity. Such concerns are especially pertinent for a deep-seated mobile target such as the prostate that is dependent on variation in bladder and rectal filling as well as bony-hip anatomy. Protons also have a significant penumbra (gradual dose falloff at the lateral edge of the beam) at depth, compromising their ability to spare adjacent tissues.

Higher radiation doses delivered to the prostate have been associated with improved tumor eradication and biochemical disease-free survival in randomized clinical trials [55–57]. Proton beam therapy offers the potential of achieving dose escalation and decreasing toxicity by taking advantage of the unique dose deposition characteristics of the Bragg peak to avoid normal tissue. Although proton therapy for prostate cancer has been used for decades, it has recently increased in popularity with the opening of new proton facilities. Proton therapy was first delivered to prostate cancer patients in 1976 at the Harvard Cyclotron in Boston in conjunction with the Massachusetts General Hospital (MGH). The first publication of this experience in 1979 was based on 17 patients and demonstrated feasibility [58]. Clinical experience has since grown at centers in the United States, including MGH and Loma Linda University Medical Center in California, and in Europe and Japan. Specifically, studies in prostate cancer have focused on escalating the dose with protons.

As implemented in the United States, proton therapy uses different techniques than with IMRT. Rectal toxicity is one of the most important dose-limiting factors for the treatment of prostate cancer and depends on the volume of the rectum and rectal wall irradiated. As previously mentioned, dosimetric studies suggest that because proton beam ranges are very sensitive to the material crossed such as gas versus solid matter in a distended or undistended rectum, the Bragg peak of protons can be shifted or distorted. To decrease rectal toxicity, proton therapy to the prostate is often performed with a rectal balloon filled with water, which has the theoretical advantage of distending the rectal wall and moving it away from the high dose anteriorly, and better controlling the proton dose distribution and decreasing inhomogeneities due to the air-tissue interface [59]. The rectal balloon is used because conventional gold fiducial markers used for prostate localization in photon therapy have been shown to cause radiation dose distortion [60]. The degree of radiation distortion is greater in proton therapy, with recent studies showing that conventional gold fiducials can cause an 85% dose reduction in proton therapy [61]. Conventional gold fiducial markers also create artifacts in CT images resulting in inaccurate treatment planning. Thus, researchers have begun to investigate the influence of alternative fiducial markers, such as microscopic gold particles, for proton therapy for prostate cancer, reasoning that a lower number of gold atoms in a fiducial would reduce multiple proton scattering and dose perturbation [21].

Because of the technical differences between protons and IMRT, a lot of effort has been made to identify which therapy is intrinsically advantageous. Although the unique dose distribution of protons suggests a potential dosimetric advantage, studies comparing 3D conformal proton beam therapy and photon IMRT have shown mixed results [62–64]. Whether these differences between proton beam radiation and IMRT plans actually translate into clinically relevant results remains unknown. The controversy between standard proton therapy and IMRT with photons will likely persist indefinitely. Intensity-modulated proton therapy (IMPT) is an emerging technique for delivering proton therapy that uses inverse planning optimization and intensity-modulated beams from multiple different directions to yield potentially a more conformal dose distribution with sharper dose gradients, and less scatter from secondary particles compared with 3D conformal proton beam therapy. Dosimetric studies comparing IMPT with IMRT have shown that the techniques deliver results that are comparable, in general, with respect to target coverage and the most dose-limiting normal tissues, although there is some concern that IMPT is potentially more sensitive to setup uncertainties than 3D conformal proton therapy [65]. A considerable amount of research and development is still required to improve IMPT and further exploit its potential, and head-to-head trials are needed to test clinically relevant outcomes of interest [66].

Early results with proton therapy have duplicated studies made with 3D conformal photons. MGH and Loma Linda reported a randomized phase III dose-escalation trial (Proton Radiation Oncology Group/American College of Radiology 95-09) using mixed conformal photons with proton boost in 392 patients with early-stage prostate cancer. The study found that 79.2 CGE is superior to 70.2 GE in terms of 5-year PSA (prostate-specific antigen) failure-free survival without worse severe toxicity [67]. However, the contribution of the proton beam component is unclear because the study did not compare the efficacy of protons versus photons, and results are similar to those reported in a similar trial comparing 70 Gy versus 78 Gy using photon EBRT. To investigate whether protons can be used to escalate radiation dose even further in the treatment of prostate cancer, MGH/Loma Linda recently closed a prospective pilot study using protons alone to 82 CGE. It seems that this may represent the ceiling on dose achievable using current proton beam therapy [68].

Conclusions

The past two decades have seen huge strides made in the use and utilization of radiation for the treatment of prostate cancer. Starting with IMRT, the addition of image guidance allowed the radiation to be accurately and reliably delivered despite the radiation being increasingly conformal and precisely targeted. The addition of proton therapy to the armamentarium for the treatment of prostate cancer only further benefits patients with prostate cancer. Regardless of the specific treatment technique, patients can depend on modern treatments to target the prostate effectively while significantly sparing the adjacent tissues, thereby reducing the morbidity of having to undergo prostate cancer therapy.

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References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Zhang J, Hricak H, Shukla-Dave A, et al.: Clinical stage T1c prostate cancer: evaluation with endorectal MR imaging and MR spectroscopic imaging. Radiology 2009, 253:425–434.
2. Bloch BN, Furman-Haran E, Helbich TH, et al.: Prostate cancer: accurate determination of extracapsular extension with high-spatial-resolution dynamic contrast-enhanced and T2-weighted MR imaging–initial results. Radiology 2007, 245:176–185.
3. Kim Y, Hsu IC, Pouliot J, et al.: Expandable and rigid endorectal coils for prostate MRI: impact on prostate distortion and rigid image registration. Med Phys 2005, 32:3569–3578.
4. Heijmink SW, Scheenen TW, van Lin EN, et al.: Changes in prostate shape and volume and their implications for radiotherapy after introduction of endorectal balloon as determined by MRI at 3T. Int J Radiat Oncol Biol Phys 2009, 73:1446–1453.
5. Augustin H, Fritz GA, Ehammer T, et al.: Accuracy of 3-Tesla magnetic resonance imaging for the staging of prostate cancer in comparison to the Partin tables. Acta Radiol 2009, 50:562–569.
6. Bloch BN, Lenkinski RE, Rofsky NM: The role of magnetic resonance imaging (MRI) in prostate cancer imaging and staging at 1.5 and 3 Tesla: the Beth Israel Deaconess Medical Center (BIDMC) approach. Cancer Biomark 2008, 4:251–262.
7. Bloch BN, Rofsky NM, Baroni RH, et al.: 3 Tesla magnetic resonance imaging of the prostate with combined pelvic phased-array and endorectal coils; Initial experience (1). Acad Radiol 2004, 11:863–867.
8. Sosna J, Pedrosa I, Dewolf WC, et al.: MR imaging of the prostate at 3 Tesla: comparison of an external phased-array coil to imaging with an endorectal coil at 1.5 Tesla. Acad Radiol 2004, 11:857–862.
9. Wu X, Dibiase SJ, Gullapalli R, Yu CX: Deformable image registration for the use of magnetic resonance spectroscopy in prostate treatment planning. Int J Radiat Oncol Biol Phys 2004, 58:1577–1583.
10. Schallenkamp JM, Herman MG, Kruse JJ, Pisansky TM: Prostate position relative to pelvic bony anatomy based on intraprostatic gold markers and electronic portal imaging. Int J Radiat Oncol Biol Phys 2005, 63:800–811.
11. Nederveen AJ, Dehnad H, van der Heide UA, et al.: Comparison of megavoltage position verification for prostate irradiation based on bony anatomy and implanted fiducials. Radiother Oncol 2003, 68:81–88.
12. Boda-Heggemann J, Kohler F, Wertz H, et al.: Fiducial-based quantification of prostate tilt using cone beam computer tomography (CBCT). Radiother Oncol 2007, 85:247–250.
13. van Herk M, Bruce A, Kroes AP, et al.: Quantification of organ motion during conformal radiotherapy of the prostate by three dimensional image registration. Int J Radiat Oncol Biol Phys 1995, 33:1311–1320.
14. Chung PW, Haycocks T, Brown T, et al.: On-line aSi portal imaging of implanted fiducial markers for the reduction of interfraction error during conformal radiotherapy of prostate carcinoma. Int J Radiat Oncol Biol Phys 2004, 60:329–334.
15. van der Heide UA, Kotte AN, Dehnad H, et al.: Analysis of fiducial marker-based position verification in the external beam radiotherapy of patients with prostate cancer. Radiother Oncol 2007, 82:38–45.
16. Kudchadker RJ, Lee AK, Yu ZH, et al.: Effectiveness of using fewer implanted fiducial markers for prostate target alignment. Int J Radiat Oncol Biol Phys 2009, 74:1283–1289.
17. •• Kupelian P, Willoughby T, Mahadevan A, et al.: Multi-institutional clinical experience with the Calypso System in localization and continuous, real-time monitoring of the prostate gland during external radiotherapy. Int J Radiat Oncol Biol Phys 2007, 67:1088–1098. *This initial report of a multi-institutional trial demonstrates that the Calypso System is a clinically efficient and accurate localization method for positioning patients for prostate EBRT. The article offers the first data demonstrating that intrafraction motion occurs and can be corrected for with the Calypso System.*
18. Langen KM, Willoughby TR, Meeks SL, et al.: Observations on real-time prostate gland motion using electromagnetic tracking. Int J Radiat Oncol Biol Phys 2008, 71:1084–1090.
19. Balter JM, Wright JN, Newell LJ, et al.: Accuracy of a wireless localization system for radiotherapy. Int J Radiat Oncol Biol Phys 2005, 61:933–937.
20. Li JS, Pollack A, Horwitz E: Clinical experience on localization and real-time tracking of the prostate during external radiotherapy using Calypso 4D localization system. Int J Radiat Oncol Biol Phys 2007, 69:S189.
21. Li JS, Jin L, Pollack A, et al.: Gains from real-time tracking of prostate motion during external beam radiation therapy. Int J Radiat Oncol Biol Phys 2009, 75:1613–1620.
22. Kupelian PA, Langen KM, Zeidan OA, et al.: Daily variations in delivered doses in patients treated with radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2006, 66:876–882.
23. Moseley DJ, White EA, Wiltshire KL, et al.: Comparison of localization performance with implanted fiducial markers and cone-beam computed tomography for on-line image-guided radiotherapy of the prostate. Int J Radiat Oncol Biol Phys 2007, 67:942–953.
24. Court LE, Dong L: Automatic registration of the prostate for computed-tomography-guided radiotherapy. Med Phys 2003, 30:2750–2757.
25. Kuriyama K, Onishi H, Sano N, et al.: A new irradiation unit constructed of self-moving gantry-CT and linac. Int J Radiat Oncol Biol Phys 2003, 55:428–435.
26. Owen R, Kron T, Foroudi F, et al.: Comparison of CT on rails with electronic portal imaging for positioning of prostate cancer patients with implanted fiducial markers. Int J Radiat Oncol Biol Phys 2009, 74:906–912.
27. de Crevoisier R, Tucker SL, Dong L, et al.: Increased risk of biochemical and local failure in patients with distended rectum on

the planning CT for prostate cancer radiotherapy. Int J Radiat Oncol Biol Phys 2005, 62:965–973.
28. Heemsbergen WD, Hoogeman MS, Witte MG, et al.: Increased risk of biochemical and clinical failure for prostate patients with a large rectum at radiotherapy planning: results from the Dutch trial of 68 GY versus 78 Gy. Int J Radiat Oncol Biol Phys 2007, 67:1418–1424.
29. Pawlowski JM, Yang ES, Malcolm AW, et al.: Reduction of dose delivered to organs at risk in prostate cancer patients via image-guided radiation therapy. Int J Radiat Oncol Biol Phys 2010, 76:924–934.
30. Hammoud R, Patel SH, Pradhan D, et al.: Examining margin reduction and its impact on dose distribution for prostate cancer patients undergoing daily cone-beam computed tomography. Int J Radiat Oncol Biol Phys 2008, 71:265–273.
31. Chung HT, Xia P, Chan LW, et al.: Does image-guided radiotherapy improve toxicity profile in whole pelvic-treated high-risk prostate cancer? Comparison between IG-IMRT and IMRT. Int J Radiat Oncol Biol Phys 2009, 73:53–60.
32. Ling CC, Burman C, Chui CS, et al.: Conformal radiation treatment of prostate cancer using inversely-planned intensity-modulated photon beams produced with dynamic multileaf collimation. Int J Radiat Oncol Biol Phys 1996, 35:721–730.
33. De Meerleer GO, Vakaet LA, De Gersem WR, et al.: Radiotherapy of prostate cancer with or without intensity modulated beams: a planning comparison. Int J Radiat Oncol Biol Phys 2000, 47:639–648.
34. Zelefsky MJ, Fuks Z, Happersett L, et al.: Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. Radiother Oncol 2000, 55:241–249.
35. Zelefsky MJ, Fuks Z, Hunt M, et al.: High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002, 53:1111–1116.
36. Spirou SV, Chui CS: Generation of arbitrary intensity profiles by dynamic jaws or multileaf collimators. Med Phys 1994, 21:1031–1041.
37. Otto K: Volumetric modulated arc therapy: IMRT in a single gantry arc. Med Phys 2008, 35:310–317.
38. Palma D, Vollans E, James K, et al.: Volumetric modulated arc therapy for delivery of prostate radiotherapy: comparison with intensity-modulated radiotherapy and three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 2008, 72:996–1001.
39. Kjaer-Kristoffersen F, Ohlhues L, Medin J, Korreman S: RapidArc volumetric modulated therapy planning for prostate cancer patients. Acta Oncol 2009, 48:227–232.
40. Yoo S, Wu QJ, Lee WR, Yin FF: Radiotherapy treatment plans with RapidArc for prostate cancer involving seminal vesicles and lymph nodes. Int J Radiat Oncol Biol Phys 2010, 76:935–942.
41. Wang JZ, Guerrero M, Li XA: How low is the alpha/beta ratio for prostate cancer? Int J Radiat Oncol Biol Phys 2003, 55:194–203.
42. Fowler J, Chappell R, Ritter M: Is alpha/beta for prostate tumors really low? Int J Radiat Oncol Biol Phys 2001, 50:1021–1031.
43. Liao Y, Joiner M, Huang Y, Burmeister J: Hypofractionation: what does it mean for prostate cancer treatment? Int J Radiat Oncol Biol Phys 2009, 76:260–268.
44. Leborgne F, Fowler J: Late outcomes following hypofractionated conformal radiotherapy vs. standard fractionation for localized prostate cancer: a nonrandomized contemporary comparison. Int J Radiat Oncol Biol Phys 2009, 74:1441–1446.
45. •• Kupelian PA, Willoughby TR, Reddy CA, et al.: Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. Int J Radiat Oncol Biol Phys 2007, 68:1424–1430. *This is one of the largest studies demonstrating clinical outcomes after high-dose hypofractionated radiation therapy for localized prostate cancer that are comparable to outcomes achieved with standard radiation therapy regimens taking 2 weeks longer.*
46. Pollack A, Li T, Buyyounouski M, et al.: Hypofractionation for prostate cancer: interim results of a randomized trial. Int J Radiat Oncol Biol Phys 2009, 75:S81–S82.
47. Livsey JE, Routledge J, Burns M, et al.: Scoring of treatment-related late effects in prostate cancer. Radiother Oncol 2002, 65:109–121.
48. Pollack A, Hanlon AL, Horwitz EM, et al.: Dosimetry and preliminary acute toxicity in the first 100 men treated for prostate cancer on a randomized hypofractionation dose escalation trial. Int J Radiat Oncol Biol Phys 2006, 64:518–526.
49. Coote JH, Wylie JP, Cowan RA, et al.: Hypofractionated intensity-modulated radiotherapy for carcinoma of the prostate: analysis of toxicity. Int J Radiat Oncol Biol Phys 2009, 74:1121–1127.
50. McCammon R, Rusthoven KE, Kavanagh B, et al.: Toxicity assessment of pelvic intensity-modulated radiotherapy with hypofractionated simultaneous integrated boost to prostate for intermediate- and high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2009, 75:413–420.
51. Miralbell R, Molla M, Rouzaud M, et al.: Hypofractionated boost to the dominant tumor region with intensity modulated stereotactic radiotherapy for prostate cancer: a sequential dose escalation pilot study. Int J Radiat Oncol Biol Phys 2009 Nov 10 (Epub ahead of print).
52. King CR, Brooks JD, Gill H, et al.: Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. Int J Radiat Oncol Biol Phys 2009, 73:1043–1048.
53. Madsen BL, Hsi RA, Pham HT, et al.: Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. Int J Radiat Oncol Biol Phys 2007, 67:1099–1105.
54. Katz AJ, Santoro M, Ashley R, et al.: Stereotactic body radiotherapy for organ-confined prostate cancer. BMC Urol 2010, 10:1.
55. Zietman AL, DeSilvio ML, Slater JD, et al.: Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. JAMA 2005, 294:1233–1239.
56. Kuban DA, Tucker SL, Dong L, et al.: Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008, 70:67–74.
57. Dearnaley DP, Sydes MR, Graham JD, et al.: Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. Lancet Oncol 2007, 8:475–487.
58. Shipley WU, Tepper JE, Prout GR Jr, et al.: Proton radiation as boost therapy for localized prostatic carcinoma. JAMA 1979, 241:1912–1915.
59. Slater JD, Yonemoto LT, Rossi CJ Jr, et al.: Conformal proton therapy for prostate carcinoma. Int J Radiat Oncol Biol Phys 1998, 42:299–304.
60. Chow JC, Grigorov GN: Monte Carlo simulations of dose near a nonradioactive gold seed. Med Phys Dec 2006, 33:4614–4621.
61. Newhauser W, Fontenot J, Koch N, et al.: Monte Carlo simulations of the dosimetric impact of radiopaque fiducial markers for proton radiotherapy of the prostate. Phys Med Biol 2007, 52:2937–2952.
62. Mendenhall NP, Li Z, Morris CG, et al.: Early GI and GU toxicity in three prospective trials of proton therapy for prostate cancer. Int J Radiat Oncol Biol Phys 2009, 75:S11–S12.
63. Chera BS, Vargas C, Morris CG, et al.: Dosimetric study of pelvic proton radiotherapy for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 2009, 75:994–1002.
64. Trofimov A, Nguyen PL, Coen JJ, et al.: Radiotherapy treatment of early-stage prostate cancer with IMRT and protons: a treatment planning comparison. Int J Radiat Oncol Biol Phys 2007, 69:444–453.

65. Soukup M, Sohn M, Yan D, et al.: Study of robustness of IMPT and IMRT for prostate cancer against organ movement. Int J Radiat Oncol Biol Phys 2009, 75:941–949.
66. Unkelbach J, Chan TC, Bortfeld T: Accounting for range uncertainties in the optimization of intensity modulated proton therapy. Phys Med Biol 2007, 52:2755–2773.
67. Zietman AL, Bae K, Rossi C, et al.: A phase III trial employing conformal photons with proton boost in early-stage prostate cancer: conventional dose (70.2 GyE) compared to high-dose irradiation (79.2 GyE): long-term updated analysis of Proton Radiation Oncology Group (PROG)/American College of Radiology (ACR) 95–09. Int J Radiat Oncol Biol Phys 2009, 75:S11.
68. ZIetman AL, DeSilvio ML, Slater JD: A prospective phase I/II study using proton beam radiation to deliver 82 GyE to men with localized prostate cancer: preliminary results of ACR 0312. Int J Radiat Oncol Biol Phys 2008, 72:S77.