Hypofractionated Radiation Therapy: The Dark Side

Hypofractionated IMRT

Conventional IMRT (Intensity Modulated Radiotherapy) is fractionated, typically given to the patient in small daily doses (fractions), usually five days a week over 8 to 10 weeks. At our center, we also utilize the most advanced form of radiation known as known as Dynamic Adaptive Radiotherapy (DART) which takes advantage of multiple forms of 4D imaging, which allows for the most precise radiation delivery possible. It is important to understand that delivering small, incremental doses over time decreases the chance of damaging healthy tissue or tieeues. By contrast, with moderately hypofractionated IMRT, larger doses are administered over a much shorter period of time, often 4 to 6 weeks, compromising normal healthy tissues. And with extreme, ultra-hypofractionated radiotherapy, the dose is even higher, and the duration of treatment is even shorter (5-6 fractions or fewer) with even greater potential for damaging effects to normal tissues.

Proponents of Hypofractionated IMRT suggest this approach has the advantage of convenience by shortening the course of treatments (fewer fractions) resulting in reduced healthcare costs although the individual treatments cost much more. But the majority of studies suggest that acute and late side effects are higher with Hypofractionated IMRT than with conventional IMRT and other methods that use small daily doses. Acute toxicity results in long-term injury to surrounding, healthy tissues (i.e., rectum, bladder, urethra. neurovascular bundles and other critical neighboring structures).

There are only a few long-term published results for hypofractionated IMRT; mostly low and intermediate risk prostate cancer patients with only a maximum of 5-years of follow-up. The published guidelines of the American Society of Clinical Oncology recommend that physicians should counsel patients about the limited follow-up beyond five years as a result of the increased risk of acute and late toxicity associated with Moderately Hypofractionated and Ultra-Hypofractionated IMRT compared to Conventional IMRT. The guidelines suggest Ultra-Hypofractionated Radiotherapy should be limited to clinical trials due to the risk of damaging healthy tissue as is seen with lengthier follow-up, especially with and rectum and bladder injury (Morgan SC, Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO, and AUA Evidence-Based Guideline, Pract Radiat Oncol, 2018 Nov–Dec;8(6):354-360).

The Cyberknife® Robotic System and Other Novel Forms of Hypofractionated Radiotherapy

The Cyberknife® is essentially a linear accelerator mounted on a robotic arm. This modality was developed at Stanford in the 1990s, and the technology is manufactured by Accuray, Inc of Sunnyvale, California. While FDA-approved, the Cyberknife protocol is still considered investigational, with only few published studies to date having more than 5 years of follow-up. At Stanford, Accuray's Cyberknife is now being combined with Varian Medical Systems' IG-IMRT technology. Cyberknife is also called "stereotactic body radiotherapy" (SBRT).

We have reservations about the Cyberknife which is typically delivered in only 3 to 5 treatments.. The bottom line is that whenever you hypofractionated radiation (fewer treatments over a shorter time frame using higher radiation doses per treatment), you are making a compromise for the long haul. That is, you can expect significantly increased side effects over time. With prostate treatment, we're talking about progressive damage over time to the bladder, urethra, rectum, neurovascular

bundles, etc. These symptoms will most likely begin to manifest several years after treatment. The authors of a median 33-month follow-up Stanford study noted that longer term series would be needed to confirm "durable biochemical control rates and low late toxicity profiles" (Rad Onc, March 15, 2009, Volume 73, Issue 4, Pages 1043–1048).

Results of all forms of hypofractionated radiation in terms of cure and toxicity are not nearly as good as the results widely reported with DART and brachytherapy—with long-term data at the Dattoli Center. A large multi-institutional study of 1100 patients treated with stereotactic body therapy reported that after 5-year follow-up, patients with low, intermediate, and high-risk prostate cancer showed biochemical disease-free survival at 95%, 84% and 81%, respectively. But these are relatively short-term results, and the researchers did not use an absolute PSA nadir to determine success, thus inflating their data. The study did not even report on side effects (King CR, et al, Radiother Oncol, 2013 Nov;109(2):217-21).

Similarly inconclusive results were reported with a more recent 8-year follow-up series, with low, intermediate, and high-risk patients at 93.6, 84.3, and 65.0%. This is the longest follow-up of any hypofractionated series. Again, this study did not report on toxicity (Katz A, et al, Fron Oncol, 2016 Jul 8;6:168).

An earlier study by Georgetown University with 2-year follow-up reported serious genitourinary toxicity at 31% (Chen LN, et al, Radiat Oncol, 2013 Mar 13;8:58).

Without mincing words and pitting noted researchers against one another, the biggest obstacle facing Cyberknife (or any other such stereotactic hypofractionated therapy) for prostate cancer treatment is the lack of published, long-term clinical data to prove that it provides any better results than currently proven therapies. So why would anyone choose it? Convenience?

A recent Memorial Sloan-Kettering Cancer Center study of dose escalation with SBRT with low and intermediate risk disease reported that with a dose of 40 Gy delivered in 5 fractions, acute grade 2 rectal toxicities and urinary toxicities affected 11.4 % and 17.1% of patients respectively (Zelefsky MJ et al, "5-Year Outcomes of a Phase I Dose Escalation Study Using Stereotactic Body Radiosurgery for Patients with Low and Intermediate Risk Prostate Cancer," J Rad Oncol Biol Phys, 2019 Jan 3).

Facilities and physicians promoting Cyberknife have large investments to recoup. The marketing machines are grinding out stories and material to hype their products. “Cyber” is a sexy word in advertising buzz today. And, while the therapy has been successfully used with treating intracranial tumors for years (typically for non-curative patients), its application for soft tissue tumors (such as prostate and breast) is touted as “new”—as if once again, everything “new” is “better.” Website material from the manufacturer of the Cyberknife lauds its ability to achieve clinical flexibility, delineation of tumor versus normal tissue for targeting, shorter treatment time and relatively low toxicity of the rectum and bladder. But beware. One physician at a large Cyberknife facility in Oklahoma in an Internet patient support forum admits that “generally speaking, failure (at least in our hands) occurs most often when all our imaging does not make it possible to determine where the tumor stops and the normal tissue starts. We usually err on the side of including more volume, but sometimes we just can’t make the correct decision. We have sometimes been able to go back and re-treat the area we missed.”

A primary goal of combination therapy (DART and seed implants) and full-course DART alone at the Dattoli Cancer Center is to eradicate not only the identified tumors, exactly where they are located in the gland with a focused high dose, but also to treat the entire gland with a lower dose that can stop progression of microscopic tumors which often loom large throughout the gland. We know that whatever biochemical forces were in place to cause the growth of the primary tumor are at work, albeit at a slower pace, throughout the gland. This is known as field cancerization. All the intense focal efforts to treat only the tumor is leaving the rest of the gland untouched—and ripe for future cancer growth. Field cancerization is also a factor with breast cancer and why the entire breast is irradiated or removed (mastectomy) (Field Cancerization, Advances in Cancer Research, 2021).

With DART and subsequent Palladium-103 brachytherapy, we are able to treat the entire gland while spring surrounding tissue and spare the central core housing the urethra, attacking the active tumor cells with higher dose level radiation and rendering the remainder of gland fallow for future tumor growth. It is our goal to have prostate cancer be a one-time event in

the man's life. Meanwhile, larger tumors are focally targeted with DART and brachytherapy with a much higher dose for eradication.

Cyberknife proponents herald their 5-day treatment vs the longer DART program, as "more convenient" for the patient. How "convenient," we ask, will it be for the patient to face a repeat performance (recurrence) 3, 4, 8 or more years down the road? Or how convenient will it be in the long run when the late effects of radiation manifest and patients develop urethral and/or rectal fistulas, bladder damage, rectal ulcerations or perforations requiring colostomies, hip and bone necrosis? These are all well documented complications from hypofractionated radiation in its various forms.

Hyprofractionated forms of radiotherapy such as Cyberknife and Hypofractionated IMRT are characterized as either moderate and extreme (or ultra) depending on the dose and number of treatments. The published guidelines of the American Society of Clinical Oncology recommend that physicians should counsel patients about the limited follow-up beyond five years for most studies evaluating hypofractionation and the increased risk of acute and late toxicity with Moderately Hypofractionated IMRT compared to Conventional IMRT. The guidelines suggest Ultra-Hypofractionated Radiotherapy should be limited to clinical trials due to the risk of late toxicity (Morgan SC, Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO, and AUA Evidence-Based Guideline, Pract Radiat Oncol, 2018 Nov–Dec;8(6):354-360)

A recent study by Netherlands researchers reported, "Moderate hypofractionated (HF) radiotherapy is becoming the new standard in radiotherapy for prostate cancer patients … but it might be associated with increased acute toxicity levels" (*Acute and late toxicity patterns of moderate hypo-fractionated radiotherapy for prostate cancer: A systematic review and meta-analysis*, Sinzabakira F. et al, Clinical and Translational Radiation Oncology Volume 40, May 2023).

Another recent multi-institutional study reported similarly alarming results (Adv Radiat Oncol. 2021 Nov-Dec; 6(6): 100759. Toxicity After Stereotactic Body Radiation Therapy for Prostate Cancer in Patients With Inflammatory Bowel Disease: A Multi-institutional Matched Case-Control Series).

High Dose Rate (HDR) Brachytherapy

Iridium-192 is occasionally used for temporary brachytherapy implants often combined with external radiation. HDR is another form of hypofractionated radiation, with limited very high dose rate treatment sessions (fractions). This form of brachytherapy delivers the highest dose of radiation to the entire body (based on penetrating nature of Ir-192). When used, patients should ideally wear lead-shielded goggles to avoid development of cataracts! The best-case protocol utilizes 5-6 fractions (treatment sessions over time) but most patients can only tolerate 1 session, compromising cancer control.

There are many published studies, but no long-term data supporting HDR as sole therapy, compared to permanent implants and/or combination therapy (permanent implants or HDR combined with external beam radiation). An Australian study of HDR monotherapy with 10-year follow-up reported that for intermediate and high-risk patients, the biochemical disease free survival rates were 86.9% and 56.1%, respectively. Patients with 3 high-risk factors had a biochemical survival rate of only 39.5%, and that figure was inflated because these researchers did not employ a sufficiently stringent PSA nadir value to measure success. The study also reported that serious urethral strictures affected 13.6% of patients (Yaxley JW, et al, BJU Int, 2016 Sep 15).

A more recent UCLA study of intermediate risk patients with 6 treatment fractions and a follow-up of 8 years reported 90% biochemical disease-free survival, but long-term genitourinary morbidity was more than 36.3% (Patel S, et al, "High-dose-rate brachytherapy monotherapy without androgen deprivation therapy for intermediate-risk prostate cancer," Brachytherapy, 2017 Mar-Apr; 16(2):299-305).

TomoTherapy

The TomoTherapy® Highly Integrated Adaptive Radiotherapy (HI-ART®) System is another form of hypofractionated radiation treatment delivered with CT guidance, both of which are continuous in nature and very slow, utilizing a rotational arc. The TomoTherapy system is manufactured by TomoTherapy Incorporated of Madison, Wisconsin. The system achieved

FDA approval and first began treating patients in 2001, without having to undergo clinical trials to assess potential late toxicity or long-term treatment outcomes.

With this system, the patient is often treated for 40 minutes, so the "BEAM-ON TIME" is enormous. This leads to "incident planned radiation," which then has a high integral dose because of the arc and the duration of treatment, with scattered photons and neutrons from the incident planned radiation, and the radiation from a continuously revolving CT scan, which can also impart a sizeable dose to the entire body. As such, with this form of radiation treatment, we believe there is a high risk of developing secondary cancers.

This form of radiation is not recommended for pediatric patients who have cancer (defined as patients in their twenties or less). Once again, with this technology, there is no long-term clinical data. Investigating late toxicity with TomoTherapy, a Canadian study reported that quality of life (QOL) within two years "with respect to bowel and sexual function was significantly affected" (Pervez N, et al, Curr Oncol, 2012 Jun;19(3):e201-10).

Those same researchers reported that at 5 years Grade 2 and Grade 3 late genitourinary toxicity was experienced in 17.0% and 2.44%, respectively (Pervez N, et al, Am J Clin Oncol. 2017 Apr;40(2):200-206). Another short-term Italian study reported late genitourinary toxicity at 6.6% and gastrointestinal toxicity at 5.3% of patients (Cuccia F, Hypofractionated postoperative helical tomotherapy in prostate cancer, Cancer Manag Res. 2018 Oct 29; 0:5053-5060).

In light of the high integral dose associated with arc therapy, we are not convinced that there is no significant risk of late side effects and secondary cancers with this system. Why would a 50-year- old patient or even a 60-year-old want to undergo TomoTherapy for prostate cancer only to risk being afflicted by leukemia or bladder cancer after 5 to 10 years?

Note from Dr. Dattoli

A cornerstone of our practice has been safety providing radiation salvage therapy with patients who had previously been treated with radiation elsewhere. Not so anymore with patients who have been treated with hypofractionated radiation.

These patients have unfortunately burned their bridges for most future salvage treatment options and treatment with our salvage radiation protocols risk disastrous outcomes. That's a huge point and if word spreads, hopefully that will become a deterrent for hypofractionated radiotherapy.