How Early Should Early Salvage Radiation Be Performed?

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For patients with prostate cancer with adverse pathological features on the radical prostatectomy specimen there has long been a debate on the relative benefits and harms of adjuvant radiation treatment (RT) for undetectable prostate specific antigen (PSA) vs salvage RT for patients with detectable PSA.

It has been well-established that patients with these adverse pathological features have a high risk of residual disease after prostatectomy.[1] However, some have proposed that early salvage RT may offer oncologic outcomes similar to those of adjuvant therapy while minimizing overtreatment for those cured by surgery alone. The recent report of 3 randomized trials provides high quality data to inform this debate.

RAVES (Radiotherapy – Adjuvant Versus Early Salvage),[2] RADICALS (Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer)[3] and GETUG-AFU 17 compared adjuvant to early salvage RT for patients with adverse pathological features on the radical prostatectomy specimen. RAVES and RADICALS were presented in 2019 at the ASTRO (the American Society for Radiation Oncology) and ESMO (European Society for Medical Oncology) meetings, respectively. At 5 to 8 years of followup there was no difference in biochemical event-free survival between adjuvant and early salvage radiation. In the preplanned ARTISTIC meta-analysis (which also included the GETUG AFU 17 trial) the estimated potential absolute difference in biochemical event-free survival at 5 years between the adjuvant and early salvage radiation approaches was 1%.[4]

It should be noted that these studies have not been published. The process of peer review and providing further details on the study design and results are critically important for clinicians and researchers in fully evaluating whether and how these trials should impact clinical practice.

Nevertheless, if these results hold true and early salvage RT becomes increasingly adopted, "how early should early salvage radiation be performed" is an important and practical clinical question. The AUA defines biochemical recurrence after surgery as PSA 0.2 ng/ml or greater confirmed on a second reading. This cutoff partly reflects the lower sensitivity of historical tests. However, with more sensitive PSA tests now widely available, is there a clinical reason to wait for salvage therapy in a patient known to be at high risk for residual cancer, and with rising PSA (even if less than 0.2 ng/ml)?

The best data to address this question come from a large multi-institutional cohort of 2,460 patients who received salvage RT.[5] Based on variations in clinical practice the patients were referred for and received salvage RT at various PSA levels after radical prostatectomy. Patients who received salvage RT at PSA less than 0.2 ng/ml had the best long-term oncologic outcomes. Five-year freedom from biochemical failure rates were directly correlated with PSA at salvage RT, at 71% (PSA 0.01 to 0.2 ng/ml), 63% (PSA 0.21 to 0.5 ng/ml), 54% (PSA 0.51 to 1.0 ng/ml) and 43% (PSA 1.01 to 2.0 ng/ml). Importantly, 10-year distant metastasis rates were also correlated with PSA at time of treatment, at 9% (PSA 0.01 to 0.2 ng/ml), 15% (PSA 0.21 to 0.50 ng/ml), 19% (PSA 0.51 to 1.0 ng/ml) and 20% (PSA 1.01 to 2.0 ng/ml). The effect of PSA on biochemical control and distant metastasis remained significant when stratified by Gleason score.

For a patient whose prostate cancer was of sufficient clinical significance to warrant radical prostatectomy, these results are not surprising. When residual disease is detectable earlier salvage treatment leads to better outcomes. These data suggest that the historical PSA cutoff of 0.2 ng/ml after radical prostatectomy may no longer represent the optimal guidance regarding salvage therapy for every patient in modern times.

There are 2 important issues to emphasize when interpreting the results of these recent randomized trials. First, they compared adjuvant RT to early salvage RT. In the RADICALS trial the trigger for early salvage radiation was a PSA greater than 0.1 ng/ml and 2 consecutive rises, or 3 consecutive PSA rises without a threshold level, whereas in the RAVES trial the trigger was PSA 0.2 ng/ml or greater. Median PSA at salvage radiation in both trials was 0.2 ng/ml. The safety and efficacy of waiting for PSAs beyond these low levels were not studied, and it would be incorrect for clinicians to inform patients that any salvage timing is equivalent to adjuvant therapy.

Second, patients enrolled in these trials had favorable characteristics. In general, 73% to 91% had Gleason 7 or less disease, median preoperative PSA was 7.4 to 7.9 ng/ml and only 19% to 21% had seminal vesicle invasion. Currently many clinicians may suggest active surveillance rather

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Developing a Registry for Focal Therapy of Prostate Cancer

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Recent improvements in prostate imaging and biopsy technology have stimulated interests and efforts in partial prostate gland ablation (PGA), or focal therapy, for clinically localized prostate cancer. Additionally, patient demand for a treatment paradigm that may minimize biopsies while avoiding the adverse effects of whole gland treatment is well recognized.

Previously, American men had traveled abroad for high intensity focused ultrasound (HIFU) until the U.S. Food and Drug Administration (FDA) approval of this technology for prostate ablation in 2015. Together these factors have fueled increased use of HIFU as well as other ablative technologies such as cryotherapy for PGA.

Accumulation of high quality prospective evidence on the efficacy and safety of PGA has proven difficult for a multitude of reasons. Dozens of clinical trials for prostate cancer have closed prematurely in recent years due to failed recruitment and lack of patient or physician equipoise, among other reasons. Regarding trial design, oncologic end points such as metastasis-free and cancer specific survival in men with low or favorable intermediate risk disease would take years to develop.

Moreover, there is controversy in terms of appropriate patient selection for PGA with respect to tumor grade, volume, location and magnetic resonance imaging characteristics. There is also no consensus regarding treatment or surveillance protocols. Additional hurdles in study design include the challenge of posttreatment prostate specific antigen interpretation and biopsy strategy. This lack of consensus hampers the generalizability of any single study's results.

These challenges beg for evidence collection beyond the context of randomized controlled trials. The FDA has acknowledged a similar need in other areas of medicine and has published guidance on the use of real-world data (eg, data collected as part of a registry) to support regulatory decisions. The concept is not a loosening of evidentiary standards but rather was established by the FDA to outline what constitutes data of suitable quality in a broader context.

The SPARED (Study of Prostate Ablation Related Energy Devices) registry was developed over a series of meetings as part of the Medical

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Focal Therapy of Prostate Cancer Registry

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Device Epidemiology Network with a focus on addressing the need for real-world data on PGA for localized prostate cancer.[1,2] The stakeholders include FDA officers, academic and community urologists, and industry partners, among others.

A necessary first step was to establish consensus regarding enrollment, clinical variables to capture, and whether to incorporate new technologies beyond HIFU and cryotherapy.[3] A Delphi process consisting of several rounds of surveys and conference calls was used to reach consensus on patient and treatment characteristics as well as oncologic, functional and safety outcomes to be included in the registry.

The group agreed to include data for all approved medical devices for prostate ablation as this would allow benchmarking of technologies to each other. Moreover, it was decided to collect data on whole gland ablation and PGA. Finally, consensus was reached on the use of validated quality of life instruments to capture urinary and sexual function outcomes including ejaculate volume, which is an important consideration for some patients.

The multi-institutional SPARED registry launched earlier this year and several sites have already contributed prospectively collected real-world data. Additionally, discussions for partnership with professional societies are underway to encourage more widespread participation in the project. SPARED leadership hope to incorporate data from the United States and abroad into the registry. Data from academic and community centers are welcome.

Furthermore, Dr. Hu leads PC CONCEPT (Prostate Cancer Comparative Outcomes of New Conceptual Paradigms for Treatment), which will capture additional data to inform comparative effectiveness of new treatments such as PGA and stereotactic body radiation as well as traditional options.[4] In parallel to this prospective registry a FDA led multispecialty conference on trial design has given way to a proposed randomized trial for PGA with alternative end points (upgrade on biopsy and repeat or salvage therapy).[5]

Through these incremental advances the accumulation of PGA evidence will define ideal patient selection and outcomes and inform men with prostate cancer, their loved ones, providers, payers and policymakers regarding the effectiveness of PGA. ◆

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The Era of Radiation Survivorship: Victims of Our Own Success

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The introduction of radiotherapy revolutionized the treatment of pelvic malignancies where surgery can be technically difficult and associated with significant morbidity. Increased use of pelvic radiotherapy has cured millions of patients, although sometimes at the cost of devastating urological morbidity due to radiation toxicity. As urologists we are charged with helping these patients, and must understand the pathophysiology of radiation injury, recognize the increasing burden of genitourinary (GU) radiation toxicity and wield techniques to prevent, mitigate and manage these injuries.

How Does Radiation Injure Tissue?

The goal of radiotherapy is selective destruction of cancer cells while minimizing toxicity to normal tissue. Ionizing radiation is so named because the high energy particles overcome the binding energy of electrons, knocking them out of their orbits to create ions. These ions cause cell death in 3 ways.

First, ionizing radiation directly damages cellular DNA, causing strand breaks and/or base damage. This mechanism preferentially kills cancer cells as they are rapidly dividing and less able to repair DNA damage compared to normal cells. Second, radiation interacts with intracellular water to produce reactive oxygen species causing cell death via direct oxidative damage and activation of cell-mediated immunity. This mechanism is less selective and forms the basis for acute radiation toxicity. Lastly, radiotherapy alters gene expression which may provide the basis for development of delayed toxicity.

Radiation toxicity occurs when healthy cells are destroyed or injured. Radiation toxicity is proportional to the dose received, which varies between tissue types. This variability is accounted for in calculation of the absorbed dose which is expressed in units called gray (Gy).[1] Radiation oncologists use 2 important mechanisms to mitigate radiation toxicity, fractionation and targeting.

Fractionation of radiation treatment means that the total dose of radiotherapy is delivered in several smaller treatments. For example, prostate cancer radiotherapy is typically 80 Gy but is delivered in 40 treatments (fractions) of 1.8 to 2.0 Gy each. Fractionation maximizes the killing of cancer cells and minimizes normal cellular death as noncancer cells are better able to repair DNA damage and rebound between fractions.

The goal of improved targeting is delivery of the desired dose to the tumor while minimizing the dose received by adjacent tissues. The details of these techniques are beyond the scope of this discussion but are the rationale for radiation modalities such as stereotactic body radiation therapy, intensity modulated radiation therapy and proton therapy.

The Era of Survivorship

Approximately 15% of all radiotherapy is used in the treatment of pelvic malignancies. Radiation is an effective means of cancer control achieving robust long-term survival. This causes a happy problem. An estimated 4.5 million cancer survivors who received pelvic radiotherapy are at risk for treatment toxicity. Genitourinary radiation toxicity is classified as acute or delayed and graded in severity from 0 to 5 by the Radiation Therapy Oncology Group with grade 3 or higher complications typically requiring surgical intervention.[2]

Acute toxicity is generally proportional to absorbed dose, follows a predictable course and resolves in 2 to 6 weeks after treatment. As urologists we most frequently encounter the delayed toxicity of radiotherapy following prostate cancer treatment (see figure). For patients with prostate cancer the incidence of delayed grade 2 or greater GU toxicity is 15% to 20% and grade 3 or greater is 3% to 6%. This translates into 900,000 survivors with grade 2 or greater toxicity and 270,000 survivors with grade 3 or greater toxicity from prostate cancer treatment alone.[3] The burden of this toxicity is high as patients with grade 3 or greater urinary adverse events typically require surgical intervention.

What are the Solutions?

As urologists we are often faced with the challenge of treating patients who are cancer-free but experience delayed toxicity from radiotherapy. In this setting tissue injury has already occurred and we manage the sequelae of injury using the same techniques as in nonradiated cases, although with generally lower success.

Treatments to reverse or mitigate the effects of radiation injury are lacking. The most commonly used and only U.S. Food and Drug Administration approved example is hyperbaric oxygen for radiation cystitis. Hyperbaric oxygen increases the partial pressure of oxygen in tissue that promotes angiogenesis, progenitor cell mobilization and improved wound healing. Hyperbaric oxygen therapy is effective for the management of radiation cystitis. However, the specialized equipment and required frequency of treatments can create significant barriers to delivery.

Conceptually, the best way to reduce radiation toxicity is to prospectively identify patients at high risk for severe toxicity and direct them toward alternative treatments. The extreme

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