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Radiorecurrent Prostate Cancer: An Emerging and Largely Mismanaged Epidemic

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Radiation as primary treatment for organ-confined prostate cancer (PCa) is widely and increasingly utilized throughout much of the world via both external-beam radiation therapy (EBRT) and brachytherapy. Tremendous variations in its utilization exist both within and across countries and are largely unsupported by data to explain such discrepancies.

Controversy remains regarding the efficacy of radiation therapy (RT) for PCa, especially considering that at least 25% of patients will have a positive biopsy following therapy. Nevertheless, local failure as defined by a postradiation biopsy showing histologic evidence of persistent cancer correlates with disease-free survival and metastasis, so the temptation to ignore biopsy findings in otherwise healthy patients appears to be imprudent [1]. Unfortunately, up to one-third of radiation patients will receive secondary treatment for cancer recurrence, indicating that long-term efficacy for RT is far from assured [2]. Compared to radical prostatectomy, RT is associated with a more than two-fold likelihood of cancer-specific mortality in the nonrandomized but well-controlled Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) data [3].

Despite this, the lower immediate morbidity of RT compared to prostatectomy, combined with physician and patient choice, led approximately one-fourth of patients to undergo either EBRT or brachytherapy in that representative American registry. One-fourth of the 217 730 new cases of PCa in the United States predicted by the American Cancer Society in 2010 [4] would translate into 54 433 American patients radiated (with EBRT, brachytherapy, or their combination) annually. Furthermore, a conservative calculation of a 25% failure rate means that there are at least 13 608 new radiorecurrent PCa patients in the United States annually and many times that throughout the world. In other words, radiorecurrent PCa is the fourth most common genitourinary malignancy in men, following primary PCa, bladder cancer, and kidney cancer.

Radiorecurrent PCa represents an emerging epidemic in many developed countries. Nevertheless, the phenomenon remains largely ignored by the urologic community, probably because most patients remain under the care of radiation oncologists who may not be keen to emphasize its prevalence or who may not be aware of available curative options such as salvage cryoablation, prostatectomy, or high-intensity focused ultrasound (HIFU). Its existence is often veiled by antiandrogen therapy, which suppresses prostate-specific antigen (PSA) levels but has absolutely no chance of cure. Disturbingly, >90% of patients undergoing secondary therapy following radiation are treated with androgen deprivation therapy (ADT) in the CaPSURE population, despite a total lack of evidence for efficacy for ADT in this setting as well as the growing understanding of its own morbidity and the complete inability of androgen deprivation to cure patients who often have local recurrences that are amenable to curative local therapy.

A report in this issue of *European Urology* from Williams and colleagues from Canada adds to a growing body of evidence supporting the use of cryoablation for patients with localized disease following RT [5]. Furthermore, their work helps identify which patients are unlikely likely to benefit, and this information can allow us to avoid morbidity for those patients who are unlikely to be cured. Consistent with prior reports [6], Williams et al identified that large numbers of patients can be "salvaged" despite failure of primary RT, but salvage therapy must be administered before cancer advances beyond where local treatment can reach. The best predictor of salvage success identified so far is serum PSA.

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Prior reports suggested treatment was most likely to be effective if administered when PSA levels were <10 ng/dl, and the authors in the present report find even better results if salvage therapy is performed while PSA is still <5 ng/dl. Moreover, the authors appropriately emphasize that cryotherapy is cytocidal without regard to tumor differentiation, so if persistent disease is localized to an area that can be destroyed by cryotherapy, even highly differentiated cancers can still be cured if radiation did not do so.

Nevertheless, high-grade disease is more likely to have already advanced at some point in time, and biopsy after radiation almost always identifies high-grade disease. Radiorecurrent PCa commonly extends locally into the periprostatic tissues. Most reports of salvage prostatectomy indicate a very high likelihood of extraprostatic extension and high incidence of positive surgical margins, finding organ-confined disease in only 20–40% of patients; therefore, despite the aggressive extirpation and well-recognized morbidity of salvage prostatectomy, most men are not cured [1]. However, even the presence of extraprostatic disease should not preclude the use of cryoablation as long as the ice ball can anatomically include all areas of disease. The ability to freeze beyond the prostatic capsule into the periprostatic tissues including the proximal portions of the seminal vesicles is a recognized advantage of cryoablation [7].

As a result of the cytocidal nature of cryoablation that easily can be extended outside the prostate to encompass nearby extraprostatic extension, the authors demonstrate impressive outcomes, including 87% 10-yr overall survival for patients that might have been given up on by physicians ignoring the potential for cure following failed RT. As the authors note, the patients reaching 10-yr surveillance were treated with older cryotherapy technologies, and the authors anticipate that patients treated with newer technologies might have even better results. Metastasis-free survival was achieved in 82% of these patients at 10 yr, although more than one-third of the patients received postsalvage androgen ablation. Perhaps most impressive is the fact that almost all of the patients underwent postsalvage biopsy, and only 17.6% had a positive biopsy, even with the majority undergoing three serial protocol-directed biopsies. Thus local control was exceedingly high, so failures were relegated largely to those patients who had metastatic disease that was almost surely present at the time of salvage treatment.

Patient selection becomes critical to achieving favorable outcomes because morbidity of salvage therapy is clearly higher regardless of whether cryoablation, radical prostatectomy, or HIFU is used. We use an aggressive evaluation process for patients considering salvage cryotherapy so as to identify incurable disease prior to treatment, if at all possible. This involves prostatic magnetic resonance imaging (MRI; unless brachytherapy was performed, which precludes ability to visualize the prostate), to identify areas of malignancy that must be encompassed by the ice ball, as well as pelvic lymphadenopathy, which would preclude local therapy. If these techniques and whole-body bone scan show no incurable disease, we perform transrectal saturation biopsy, including cores from the proximal portion of each seminal vesicle. If the seminal vesicle contains malignancy, we caution patients that cure becomes less likely, although if the MRI suggests that malignancy is only in the proximal portion, then an attempt at ablation may be reasonable in highly motivated patients.

We never perform salvage therapy in the absence of a positive prostate biopsy, and we strongly recommend that treatment never be performed unless biopsy has confirmed that the source of PSA elevation has at least some potential to originate solely from prostatic tumor recurrence. To that end, a biopsy showing only very low-volume cancer is unlikely to explain a rapidly rising or very high PSA, so we do not recommend salvage therapy for such patients based on the likelihood that they have unrecognized metastatic disease. Finally, we strongly encourage men to undergo salvage prior to their PSA level reaching 5.0 ng/dl; otherwise, they must recognize that the potential for cure goes down and becomes difficult to justify when the PSA is >10 ng/dl.

Covering up the existence of radiorecurrent PCa by hormonal PSA suppression is a disservice to this growing number of men who still have potential for cure. If the clinician believes the patient does not justify an attempt at cure, then he or she at least should not subject the patient to the morbidity of androgen ablation purely based on lowering PSA levels. Similarly, salvage therapy by either ablation or extirpation should not be performed unless there is a substantial chance for cure that justifies its morbidity. The report by Williams and colleagues in this edition of *European Urology* adds further support to the use of salvage cryotherapy for carefully selected men whose cancer recurrence is identified while localized to an area that can still be cured.

Conflicts of interest: J. Stephen Jones is a compensated proctor and an uncompensated chairman of Cold Registry for Endocare (Healthtronics).

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