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EDITORIAL

Evidence-based Risk Stratification to Guide Hormone Therapy Use With Salvage Radiation Therapy for Prostate Cancer

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Analogous to the overtreatment of men with intact prostate cancer, there is an increase in the use of hormone therapy for men receiving salvage radiation therapy (SRT) for biochemical recurrence. We are fortunate to now have 2 published randomized trials, Radiation Therapy Oncology Group (RTOG) 9601 and GETUG-AFU-16, to help inform us of the potential benefits and harms of hormone therapy in this patient population (1, 2). However, an oversimplification of the results from these trials appears to have led to the notion that all men undergoing SRT should receive hormone therapy. In parallel, the use of "early" SRT is increasingly being recommended (3), and the data for "clinically meaningful" benefits of hormone therapy when added to early SRT are nonexistent. Many potentially missed the key significant interaction test in the RTOG 9601 manuscript between pre-SRT prostate-specific antigen (PSA) and benefit from hormone therapy. Fortunately, multiple guidelines and frameworks have appropriately recommended against the use of androgen deprivation therapy (ADT) for men receiving early SRT (PSA $\leq$0.5 or $<$0.7 ng/mL) based on the randomized and retrospective data generated to date (4-6). Herein, I will provide an evidence synthesis on the use of hormone therapy for men receiving SRT.

Question: Are all men receiving SRT created equal?

Answer: No. We must risk stratify these men just as we do for localized prostate cancer.

It is very common for radiation oncologists to risk stratify patients with intermediate-risk localized prostate cancer into favorable and unfavorable intermediate risk, which is now endorsed by National Comprehensive Cancer Network guidelines. Most clinical trials that include favorable intermediate-risk patients do not recommend the use of hormone therapy (eg, RTOG 0126, RTOG 0232, NRG GU-005), but for those with unfavorable intermediate- or high-risk disease they mandate the use of hormone therapy (RTOG 9413). Why do we not risk stratify for patients receiving SRT? What many people may not realize is that despite RTOG 9601 including such an unfavorable risk population, the outcomes are nearly identical to those of patients treated on RTOG 9408, a trial predominately of intermediate-risk disease (7). With long-term follow-up, the prostate cancer–specific mortality curves are nearly superimposable between these 2 trials (Fig. 1), which further supports the point that if we risk stratify in localized disease to guide hormone therapy use (favorable vs unfavorable), we should in the salvage setting as well (early vs late).

Numerous studies, perhaps most notably the recently updated Stephenson nomogram, have demonstrated that one of the strongest prognostic factors, if not the strongest, to predict metastatic outcome in patients receiving SRT is a patient's pre-SRT PSA (8, 9). Patients with low PSA receiving early SRT (PSA $<$0.5 ng/mL) had $\sim$10% risk of developing distant metastasis 10 years posttreatment. This increases beyond 40% as the pre-SRT PSA rises to $>$2.0 ng/mL. Similar findings have been validated in other

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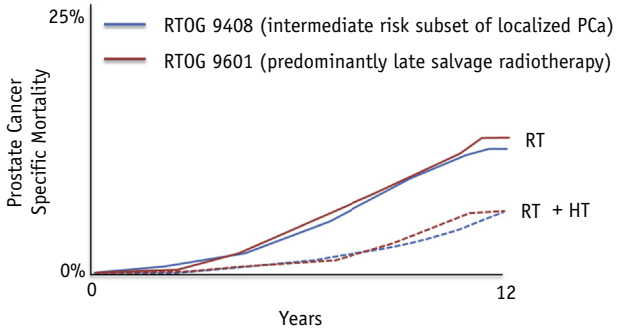

Fig. 1. Overlay of the prostate cancer–specific mortality cumulative incidence curves from the intermediate-risk subgroup from the RTOG 9408 trial (blue, RT ± 4 months of hormone therapy) and the entire cohort from the RTOG 9601 trial (red, salvage RT ± 24 months of hormone therapy). Solid lines are the RT arms for both trials, and the dashed lines are the RT plus hormone therapy arms for both trials. Time zero of each curve is trial defined before the initiation of RT. *Abbreviations:* RT = radiation therapy; RTOG = Radiation Therapy Oncology Group. (A color version of this figure is available at https://dx.doi.org.10.1016/j.ijrobp.2018.06.037.)

multicenter studies and even confirmed in RTOG 9601 and GETUG-AFU-16 on multivariable analysis (1, 2).

Question: Why is pre-SRT PSA so important?

Answer: Because there is no longer any prostate (these are postoperative patients), a rising PSA is more reflective of metastatic spread. Elegant studies done by the Mayo Clinic have shown that as the postoperative PSA rises, the pattern of spread migrates to increasing probability of pelvic nodal metastasis and then distant metastasis (10). Thus, treatment of patients with early SRT is most likely to be targeting disease that is confined to the prostate bed and/or pelvis, and microscopic disease is effectively treated with 64 to 72 Gy. With PSA >0.7 ng/mL, the disease is increasingly likely to have developed micrometastatic disease, or even visible metastatic disease by molecular imaging, and thus systemic therapy is needed.

Question: Did the randomized trials not show that the addition of hormone therapy improved outcomes for men receiving SRT?

Answer: Yes and no. Remember, not all men receiving SRT are created equal. RTOG 9601 excluded men with PSA <0.5 ng/mL for a significant proportion of the trial enrollment, and only ~10% of patients had PSA ≤0.3 ng/mL (Table 1) (1, 5). Thus, RTOG 9601 was a trial predominately of late SRT in men with very high-risk adverse features. The trial demonstrated that men who received early SRT had no improvement in distant metastasis–free survival or overall survival (Table 2).

One of the most notable findings from RTOG 9601 was that pre-SRT PSA was not only *prognostic,* it was *predictive* of benefit from hormone therapy. The interaction test was significant, which means that patients with lower pre-SRT PSA are less likely to intrinsically benefit from hormone therapy, in both a lower absolute benefit (decreased overall survival by 4.1% from adding bicalutamide for pre-SRT PSA of <0.7 vs 24.6% overall survival improvement from adding bicalutamide when PSA >1.5 ng/mL) and in a relative sense as well (hazard ratio of 1.13 vs 0.45 for PSA <0.7 vs >1.5 ng/mL, respectively). This is in contrast to other adverse features, such as higher Gleason score, which did not predict which men will benefit most from the addition of hormone therapy.

Similarly, GETUG-AFU-16, a trial predominately of patients receiving early SRT, failed to show an improvement in development of metastasis or overall survival and has thus not shown clinically meaningful benefit for these patients from the addition of 6 months of a gonadotropin-releasing hormone (GnRH) agonist (2, 5). The GETUG trial did demonstrate that short-term hormone therapy provides a biochemical control benefit. However, neither biochemical control nor disease-free survival are a surrogate endpoint for survival, as recently shown by the intermediate clinical endpoints in cancer of the prostate (ICECaP) initiative, and more importantly biochemical control is noninterpretable when giving a testosterone-lowering agent such as a GnRH agonist (11). GnRH agonists suppress testosterone, which decreases activation of the androgen receptor and thus decreases PSA production. Importantly, testosterone remains suppressed to subnormal levels for an additional 6 to 12 months. Thus, if measuring time to biochemical recurrence, GnRH therapy should always improve time to biochemical recurrence as you are suppressing the endpoint you are measuring for a prolonged period of time. This was nicely demonstrated in RTOG 9408, which showed that the addition of 4 months of hormonal therapy improved biochemical recurrence, even for low-risk patients, by 10%, almost identical to the GETUG trial for men with PSAs <0.5 ng/mL (Fig. 2) (7). Furthermore, the group that primarily benefited in the GETUG-AFU-16 trial was men with PSA >0.5 ng/mL, consistent with the data from RTOG 9601 in that men with higher PSA had both a greater absolute and relative benefit from hormone therapy (1, 2). In the GETUG trial, the men with PSA <0.5 ng/mL had a crude biochemical control benefit of only 12% from the addition of ADT, compared with 36% in men with PSA >0.5 ng/mL. In summary, the GETUG trial has definitely not shown clinical benefit from the addition of ADT for men receiving early SRT.

Question: What do you mean by clinically meaningful endpoints?

Answer: The reason we treat patients is to improve their quantity and/or quality of life. Things that affect these endpoints are clinically meaningful. Things that simply alter a laboratory result, such as the PSA, are not clinical benefits. This has been statistically demonstrated through the intermediate clinical endpoints in cancer of the prostate (ICECaP) initiative that pooled over 28,000 men enrolled on randomized clinical trials and

Table 1 Details of randomized trials of salvage RT with or without hormone therapy

Study	GETUG-AFU-16	RTOG 9601
Years	2006-2010 (n = 743)	1998-2003 (n = 760)
Treatment arms	Salvage RT ± GnRH Agonist	Salvage RT ± Antiandrogen
Hormone therapy duration, mo	6	24
Pre−salvage RT PSA	0.2-2.0 ng/mL	Pre-SRT PSA 0.5-4.0 ng/mL*
	Undetectable PSA postoperatively	Allowed detectable PSA postoperatively
Pre-RT PSA	Range, 0.2-2.0	Range, 0.2-4.0*
	Median, 0.3	Median, 0.6
	0.2-0.3: 50%	0.2-0.3: 10%
	0.2-0.5: 75%	0.2-0.4: 25%
Type of salvage RT	Mostly early salvage RT	Mostly late salvage RT

Abbreviations: PSA = prostate specific antigen, RT = radiation therapy.
* RTOG 9601 initially only included patients with pre-SRT PSA ≥0.5 ng/mL and later changed to 0.2 ng/mL.

demonstrated that biochemical recurrence fails to be a surrogate endpoint for survival endpoints (unpublished) (11). In contrast, development of distant metastasis was a strong surrogate endpoint with a correlation coefficient over 0.9. Thus, to recommend additional treatment, especially a treatment that is expensive and has side effects, a clinically meaningful benefit in at least distant metastasis is warranted. This rationale is what the Food and Drug Administration used for the recent approval of apalutamide for the treatment of M0 castration-resistant prostate cancer given its large improvement in distant metastasis, despite a lack of survival benefit.

Question: What are the downsides of giving hormone therapy to men who will not derive a clinically meaningful benefit?

Answer: As previously stated, our goals as physicians are to improve quality or quantity of life and not to merely suppress laboratory values. As physicians we swear to do no harm, and it is always easier to overtreat patients. Hormone therapy has not significantly reduced the development of metastatic disease or death in men receiving early SRT in nearly all of the randomized and retrospective data (level 1-3 evidence), and, thus, any added toxicity should be scrutinized. The side effects of hormone therapy are well established and include the increased risk of hypertension, metabolic syndrome, hyperglycemia, gynecomastia, muscle loss, body fat increase, potential cognitive and cardiac morbidity, bone density loss, and decreased libido, penile length, and sexual function in a population that often already has significant baseline erectile dysfunction from surgery and SRT. This does not include the subsequent complications and further therapies delivered for the aforementioned side effects. Financial toxicity and the burden to society is very relevant because an estimated >30,000 men experience recurrence after surgery each year, and the costs of short-term hormone therapy can exceed $7000 (total of $0.2 billion/year if short-term hormone therapy given for all men with recurrent prostate cancer).

Question: How do I select who will benefit from hormone therapy?

Answer: I use the large multicenter consensus framework that was developed, consisting of radiation oncologists, urologists, and medical oncologists, to guide who I treat with no, short-term, and long-term hormone therapy until results from ongoing and maturing clinical trials are reported (simplified in Table 3) (5). This reference provides detailed recommendations that are largely driven by a

Table 2 Oncologic benefit for the addition of hormone therapy to early versus late salvage RT

	Outcome	GETUG-AFU-16	RTOG 9601
Early	Biochemical control*	12% absolute improvement†	Not stated
Salvage RT	Distant metastasis	No significant improvement	No significant improvement
	Overall survival	No significant improvement	No significant improvement
Late	Biochemical control*	36% absolute improvement†	Not stated
Salvage RT	Distant metastasis	Not stated	*0.7-1.5 ng/mL:* 11% absolute improvement‡ *>1.5-4 ng/mL:* 18% absolute improvement
	Overall survival	No significant improvement	*0.7-1.5 ng/mL:* 9.5% absolute improvement *>1.5-4 ng/mL:* 24.6% absolute improvement

Abbreviation: RT = radiation therapy.
Early and late salvage RT were defined differently for each trial. A cutoff of 0.7 ng/mL was used in RTOG 9601, and a cutoff of 0.5 ng/mL was used for the GETUG-AFU-16 trial.
* GETUG-AFU-16 reported progression-free survival, but most events at 5 years are presumed to be from biochemical recurrence.
† Crude rates.
‡ Trend toward significance, $P = .13$.

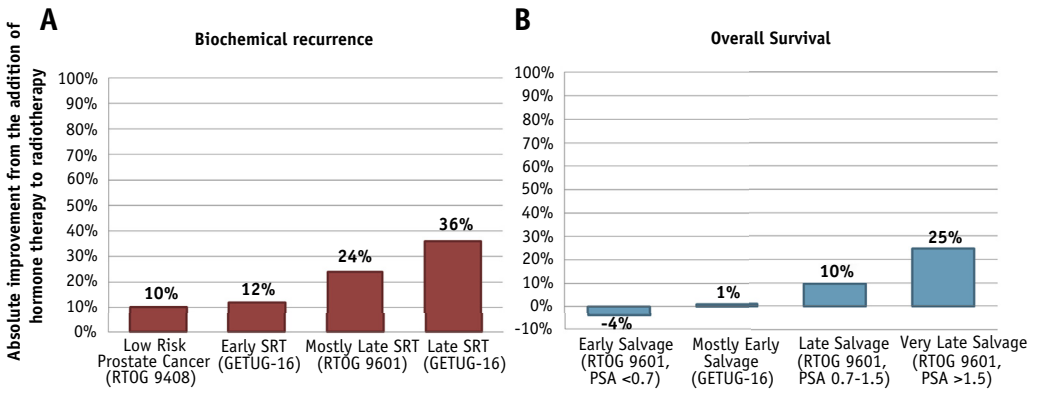

Fig. 2. Absolute improvements in (A) biochemical recurrence and (B) overall survival from the addition of hormone therapy to varying disease states. No clear clinically meaningful biochemical control benefit or overall survival benefit is seen for patients treated with early SRT. "Mostly Late SRT" refers to RTOG 9601 being a trial predominately, but not exclusively, of late SRT. "Mostly Early SRT" refers to GETUG-AFU-16 being a trial predominately, but not exclusively, of early SRT. *Abbreviation:* SRT = salvage radiation therapy.

patient's pre-SRT PSA. One important limitation of these types of guidelines and frameworks (6) is that they ignore the intrinsic biology of the patient's tumor. Fortunately, the first ever biomarker stratified trial in prostate cancer has now opened, NRG GU-006 (NCT03371719), which aims to determine whether patients who primarily receive early SRT benefit from even newer, more potent hormone therapy (apalutamide) and whether we can molecularly determine which patients benefit most from the addition of hormone therapy.

I encourage patients who have PSA <0.7 ng/mL to enroll on NRG GU-006, a trial of SRT ± apalutamide. In fact, this trial does not allow patients with PSA >1.0 ng/mL to even enroll on the study, given that all patients likely should be receiving ADT with a pre-SRT PSA this high and the control arm only receives a placebo. If the patient does not wish to be on trial, then I have an informed discussion of the lack of distant metastasis or survival benefit from using first-generation hormonal therapy and the associated financial and clinical toxicities of ADT.

For patients with PSA ≥0.7 ng/mL, pathologic lymph node positive disease, or numerous adverse risk factors (eg, pT3b-T4, primary pattern 5 disease), I encourage enrollment on FORMULA-509 (NCT03141671) or the soon-to-open RTOG 3506. Both of these trials recognize the negative prognostic impact of a high pre-SRT PSA and have incorporated this into their study designs. Given that these trials are enrolling patients with more aggressive disease, both the control and experimental arms use ADT with SRT, and the experimental arms add second-generation hormonal therapy. For patients with a persistently elevated PSA ≥0.2 ng/mL, I encourage enrollment on NRG GU-002 (NCT03070886), given the increased rate of distant metastasis in these patients and the potential benefit of docetaxel.

In conclusion, until there is level 1 evidence that the use of hormone therapy for men receiving early SRT improves clinically meaningful outcomes, I believe it should not be indiscriminately recommended. We should not be subjecting all of our biochemically recurrent patients to hormone therapy and the associated side effects, especially with a significant interaction test in RTOG 9601 demonstrating that men with lower PSA do not derive a clinically meaningful benefit and have a nearly identical absolute biochemical control benefit (~10%) seen from the addition of hormone therapy for low-risk intact prostate cancer. Ongoing clinical trials, such as NRG GU-006, aim to determine biologically who benefits most from hormone

Table 3 Simplified recommendations for the addition of hormone therapy with salvage RT

	Pre-RT PSA (ng/mL)			
ISUP Grade group (Gleason score)	0.1-0.5	0.6-1.0	Should say 1.0-1.5	>1.5
1 (6)	RT	RT	RT + STADT	RT + STADT
2, 3 (7)	RT	RT ± STADT*	RT + STADT	RT + LTADT
4, 5 (8-10)	RT*	RT + STADT	RT + LTADT	RT + LTADT

Abbreviations: ISUP = International Society of Urologic Pathology; LTADT = long-term androgen deprivation therapy; PSA = prostate specific antigen; RT = radiation therapy; STADT = short-term androgen deprivation therapy.

* For patients with minimal comorbidities, ≥12-year life-expectancy, and multiple high-risk features (eg, pT3b/4 and Grade group 4-5), a discussion of the harms and potential benefits of hormone therapy is warranted. Clinical trials should be recommended for men receiving early salvage RT testing the benefit of hormone therapy given that this population was excluded from a large proportion of the enrollment period in RTOG 9601.

therapy, and one day we hope that this will be the method of choice for selecting hormone therapy use.

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