European Urology Oncology Systematic Review

Optimizing Timing of Salvage Post-Prostatectomy Radiotherapy and Use of Concurrent Hormonal Therapy for Prostate Adenocarcinoma

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ABSTRACT

CONTEXT: Currently, salvage radiotherapy (SRT) is the only known curative intervention for men with recurrent disease following prostatectomy. Critical issues in the optimal selection and management of men being considered for SRT include the threshold PSA value at which to initiate treatment (i.e., pre-SRT PSA) and the role of concurrent hormonal therapy (HT).

OBJECTIVE: To review the published evidence pertaining to (a) the optimal timing for SRT and (b) the role of concurrent HT.

EVIDENCE ACQUISITION: MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, and guideline statements from professional organizations were queried January 1, 2000 through January 10, 2018.

EVIDENCE SYNTHESIS: Thirty-three independent reports, including two randomized trials evaluating HT with SRT, were identified. Retrospective data suggest that initiating SRT at lower pre-SRT levels is associated with improved clinical outcomes. Prospective data suggest an overall survival benefit to concurrent HT use that manifests with long-term follow-up, with the caveat that hypothesis-generating subgroup analyses suggest this benefit may be limited to patients with higher pre-SRT PSA levels. Patients with adverse risk factors, such as Gleason grade group 4-5 disease, are likely to benefit the most from earlier SRT initiation and/or the use of HT.

CONCLUSIONS: Given the limitations of available data, it is imperative for physicians to partake in shared decision-making with the recommendation tailored for each man's desire to maximize oncologic benefit (with a risk of overtreatment) versus potential quality of life optimization (with a risk of undertreatment). Within that framework, a significant amount of retrospective data support initiation of SRT at low pre-SRT PSAs, without an arbitrary absolute threshold. Prospective data suggest a benefit to the use of HT, but this benefit may be greatest in patients with a pre-SRT PSA that is higher than what most patients receiving "early" SRT typically have. Further research is necessary before absolute recommendations can be made.

PATIENT SUMMARY: Two ways to potentially improve outcomes following salvage radiotherapy (SRT) for prostate cancer that recurs after prostatectomy are by treating at a lower PSA level and using concurrent HT. Our review suggests that the available evidence is imperfect, but highlights that both measures are likely to improve clinical outcomes in general, but perhaps not uniformly and/or consistently for all patients. Physician-patient shared decision making and further research are critical.

1. Introduction

Prostate cancer (PCa) is the second leading cause of cancer-related death in the United States[1] and the third leading cause of cancer-related death in Europe[2]. Among men who ultimately die from their PCa, nearly 50% have potentially curable, localized disease at diagnosis that ultimately recurs after upfront treatment[3]. Therefore, effective management of men with biochemically recurrent PCa is integral in ultimately minimizing PCa-specific mortality (PCSM). Nearly 30% of men undergoing radical prostatectomy (RP) will ultimately experience a biochemical recurrence (BCR), defined by two consecutive PSA values >0.2 ng/mL.[4,5] In such patients, the only known curative intervention is salvage radiotherapy (SRT), which—on the basis of compelling but retrospective data—can offer up to a 68% relative reduction in PCSM[6]. Unfortunately, patterns of care data indicate that SRT utilization rates can be as low as 42% among patients with PSA >0.2 ng/mL after RP[7]. This underutilization is reflective of a mix of practice philosophies that place varying weight on toxicity and oncologic benefit[8]. Critical issues in the optimal selection and management of men being considered for SRT include the threshold PSA value at which to initiate treatment (i.e., pre-SRT PSA) and the role of concurrent hormonal therapy (HT). In this systematic Review, we explore the rationale and evidence pertaining to (a) the optimal timing for SRT and (b) the role of concurrent HT. We emphasize that further research is desperately needed to improve the efficacy of SRT and lessen the burden of PCSM in men with BCR after RP.

2. Evidence acquisition

2.1. Search strategy

The methods for this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement[9]. MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, and guideline statements from professional organizations were queried to identify manuscripts available from January 1, 2000 through January 10, 2018. The initial search strategy included the following different terms: “(<radiotherapy> OR <radiation>) AND <prostatectomy> AND (<salvage> OR <recurrent>)". This yielded 1443 results.

2.2. Inclusion and exclusion criteria

The 1443 identified abstracts were further analyzed per the PRISMA approach, as depicted in Figure 1. Inclusion criteria included identification based on (a) an additional search term "<PSA>", which yielded 706 results, and (b) the additional search term "(<androgen deprivation> OR <hormonal>)", which yielded 402 results. Further screening of manuscript abstracts to remove erroneous identification and abstracts without a cognate manuscript revealed 302 articles for review. These articles were then

screened in detail by single investigator (A.U.K.), with the following exclusion criteria: (a) did not present primary data, (b) did not specifically analyze the association between pre-SRT PSA or the use of HT and SRT outcomes, (c) included 50 or fewer patients, (d) reported outcomes on a patient population for whom a subsequently updated report was available, (e) were not written in English, or (f) did not have full text available. Ultimately, this yielded 16 manuscripts specifically analyzing the importance of the pre-SRT PSA level and 17 manuscripts specifically reporting the impact of concurrent HT with SRT. Outside of two randomized trials evaluating the role of HT, all other reports were retrospective in nature.

2.3. Data extraction

Patient characteristics extracted from each study included a proxy indicator of pre-SRT PSA distribution (generally median PSA), the percentage of patients with pathologic Gleason grade group (GG) 4-5 disease, the percentage of patients with pT3b or pT4 disease, and the percentage of patients with negative margins. Information on the SRT dose and field design were also extracted, along with median HT duration. Outcomes data were obtained for all reported outcomes, including BCR, progression-free investigators), distant metastasis-free survival, PCSM, and overall survival (OS). No statistical tests were performed; findings were interpreted as statistically significant if reported as such provided the p-value was <0.05.

2.4. Assessment of risk bias

The risk of bias for the two identified randomized controlled trials that were included in this Review were assessed using the Cochrane risk of bias assessment tool for randomized controlled trials[10].

3. Timing of Salvage Radiotherapy

3.1. The Rationale for Early Salvage

The EAU-ESTRO-SIOG guidelines emphasize the importance of early SRT, defined as SRT initiated at a PSA <0.5 ng/mL[11], while the 2013 ASTRO/AUA guidelines state that "patients should be informed that the effectiveness of RT for PSA recurrence is greatest when given at lower levels of PSA[12]." These recommendations are in large part driven by a systematic review of 41 studies that identified an average 2.6% decrement in BCR-free survival for each incremental 0.1 ng/mL PSA at the time of SRT[13]. However, the optimal pre-SRT PSA remains unclear. Theoretically, PSA is a proxy for disease burden and thus a low pre-SRT PSA suggests a low volume, curable disease burden that is potentially still localized. Alternatively, it is possible that the magnitude of the pre-SRT PSA itself is less important, and instead treating at lower pre-SRT PSAs simply "selects" for men with longer PSA

doubling times (PSADTs), with PSADT being a known predictor for adverse clinical outcomes following RP and SRT[14-18]. However, pre-SRT PSA and PSADT appear to be independent predictors of BCR-free survival following SRT[14], suggesting the importance of pre-SRT PSA is likely to be independent from that of PSADT. In either scenario, treating at a lower pre-SRT PSA would likely be more effective than treating at a higher pre-SRT PSA, whether directly or indirectly. On the other hand, delaying SRT may allow for improved functional recovery. Some data do indicate that prolonging the interval between RP and SRT is associated with improved erectile function and continence outcomes[19,20], but these findings are not uniform and others have reported no significant impact of SRT timing on quality-of-outcomes[21,22]. It is possible that advances in radiotherapy, such as intensity modulated radiotherapy and image guidance, may lead to improved toxicity outcomes[23-25]. A detailed discussion of the toxicity profile and quality of life effects of postoperative radiotherapy is beyond the scope of this Review, and as such, our discussion of the evidence for early SRT will instead focus on oncologic, rather than functional, outcomes.

While no prospectively obtained data are as yet available, numerous retrospective studies have investigated the importance of the timing of SRT, specifically focusing on the pre-SRT PSA as a critical variable. In the subsequent section, we summarize and critically review these studies. Of note, patients with persistently elevated PSA after RP are known to constitute a distinct, high-risk subset of patients[26,27]. For the purposes of this Review, studies including such patients were still considered for inclusion.

3.2. Retrospective Evidence: A Review

Key findings from 16 studies evaluating the importance of pre-SRT PSA are presented in Table 1. The importance of pre-SRT was originally highlighted in the widely adopted Stephenson nomogram, which was developed based off the outcomes of 1540 patients treated with SRT across 17 North American centers[14]. The authors found that along with other now canonical risk factors (e.g., GG), pre-SRT PSA was a statistically significant predictor of PFS, with 6-year PFS rates of 48% vs 26% for pre-SRT PSAs of ≤0.5 ng/mL versus >0.5 ng/mL. Tendulkar *et al*. recently developed an updated nomogram based on 2460 patients treated with SRT across 10 institutions, with a median follow-up of 5.0 years[28]. The median pre-SRT PSA was 0.5 ng/mL, with 18% having pre-SRT PSAs between 0.01-0.2 ng/mL. The median SRT dose was 66 Gy. Overall, the 5-year BCR-free survival rate was 56%; there was evidence of a clear relationship with pre-SRT PSA, with the freedom from BCR decreasing from 71% for PSAs between 0.01-0.2 ng/mL to 63%, 54%, 43%, and 37% for PSA values between 0.21-0.4, 0.51-1.0, 1.01-2.0, and >2.0 ng/mL, respectively. Similarly, the 10-year distant metastasis (DM) rates were 9%, 15%, 19%, 20%, and 37% across the same strata. Importantly, the nomogram suggests that pre-SRT PSA

would be best used as a risk factor along with (rather than instead of) other canonical risk factors. That is, higher pre-SRT PSAs may have more influence on outcomes in the presence of other risk factors.

Similarly, Stish *et al*. examined pre-SRT PSA in a cohort of 1106 patients treated with SRT at the Mayo Clinic, with a median follow-up of 8.9 years.[29] Each doubling of pre-SRT PSA was associated with an 18% increase in the relative risk of BCR and a 32% increase in relative risk of DM. The 10-year rate of PSCM was 10.4%, and overall, 22.7% of patients died by 10 years. The relative risk of PCSM and all-cause mortality increased by 40% and 12%, respectively, for each doubling of pre-SRT PSA. The authors also dichotomized pre-SRT PSA with 0.5 ng/mL as a cut-off point. Ten-year BCR rates were 60% vs. 68%, while 10-year DM and PCSM rates were 13% vs. 25% and 6% vs. 13%, respectively; all of these differences were statistically significant in favor of early SRT. All-cause mortality rates were not significantly different (17% vs. 27%).

Fossati *et al*. reported outcomes for 925 patients who received SRT at seven institutions, with a median follow-up of 8.0 years[30]. The study did include patients with PSA persistence (≥0.1 ng/ml at 1 month post-RP; 24% of patients). The investigators found that pre-SRT PSA was a significant predictor of DM on multivariable analysis (hazard ratio [HR] 1.06 per 0.1 ng/mL). Using a regression tree approach, five risk categories were developed with regards to risk of distant metastasis. Pre-SRT PSA was significantly associated with DM outcomes in all but the very low and very high risk groups (characterized by patients with GG ≤3, and tumor stage ≤pT3a disease with undetectable PSA after RP, and those with PSA persistence after RP with GG ≥4). The relationship of pre-SRT PSA and outcome was not linear and the most significant change in outcomes was seen for PSA <1 ng/mL. Of note, 30% of patients received HT. However, this finding was concordant with a prior study of patients from the same institutions, in which patients receiving concurrent HT were omitted[31].

Finally, Abugharib *et al*. recently evaluated biochemical and clinical outcomes in a cohort of 657 men treated with SRT at the University of Texas Southwestern and the University of Michigan, with a median follow-up of 9.8 years[32]. The authors operationally defined early SRT by either the time from RP to SRT (<9, 9-21, 22-47, or >48 months) or the pre-SRT PSA (0.01-0.2, 0.2-0.5, or >0.5 ng/mL). Higher pre-SRT levels were correlated with worsening outcomes, and ten-year PCSM rates were 7%, 11%, and 20%, respectively, for pre-SRT PSAs 0.01-0.2, 0.2-0.5, or >0.5 ng/mL, respectively. Corresponding 10-year DM-free survival rates were 86%, 79%, and 66%. Intriguingly, on multivariable analysis, delivering SRT at PSA values between 0.2-0.5 ng/mL was associated with increased risk of BCR (HR 1.97) and DM (HR 1.95) compared to SRT at PSAs of 0.01-0.2 ng/mL, though SRT in either stratum would be considered early. SRT at PSA >0.5 vs ≤0.2 ng/mL was associated with increased risk of BCR (HR 3.48),

DM (HR 4.45), and PCSM (HR 4.07). Importantly, when SRT was defined by time to SRT rather than pre-SRT PSA, no significant relationships were identified. This specifically addresses concerns about lead-time bias[33]. That is, if follow-up is measured from the time of SRT rather than from the time of RP, patients receiving SRT would by definition have better time-to-event outcomes than patients receiving late SRT simply due to fact that SRT was delivered at a chronologically earlier timepoint. By also evaluating outcomes based on time from RP, the authors obviate that concern.

3.3. Synthesis and Recommendation

These studies, in addition to the numerous smaller studies reviewed in Table 1, suggest at least a DM benefit to delivering SRT at lower PSAs, and possibly a PCSM benefit as well. An important caveat is that the majority of patients in these studies did not receive concurrent HT, which, as reviewed below, may improve SRT outcomes. Regardless, there does appear to be a benefit to initiating SRT at values below 0.5 ng/mL (and potentially below 0.2 ng/mL). Overall, in the absence of prospective data to guide management, we recommend that physicians partake in shared decision-making with their patients in order to understand any given patient's relative prioritization of potential oncologic benefit (with a risk of overtreatment) versus potential quality of life optimization (with a risk of undertreatment). If maximizing oncologic benefit is the primary goal, we recommend strongly considering SRT when two consecutive rising PSAs have been identified and recommend against delaying SRT until PSA has exceeded an arbitrary absolute threshold. However, we submit that certain factors, such as the kinetics of the PSA rise, the possibility of persistent benign tissue, the patient's life expectancy, and, most importantly, the patient's preferences, must be incorporated into any final treatment recommendation. We suggest that there likely exists a spectrum of benefit, with SRT offering improved outcomes if delivered at PSA values <0.2 ng/mL than if performed when PSA is between 0.2-0.5 ng/mL. The absolute benefit of such an intervention is likely to be highly dependent on other disease factors[28]. For example, in a patient with GG 1-2 disease and a positive margin, SRT could be reasonably delayed despite a rising pre-SRT above 0.2 ng/mL to aid in functional recovery. However, in patients with multiple high-risk features, such as negative margins and/or GG 4-5 disease, SRT should be considered for consecutive rising PSAs, regardless of the absolute value of the pre-SRT PSA. It should be acknowledged that in this latter scenario, the competing risk of synchronous out-of-field disease is higher than in the former, which might limit the benefit of SRT. Again, however, we recommend that shared decision-making be employed to understand whether the patient is willing to risk potential overtreatment (i.e., SRT if micrometastatic disease is present) for a potential cure. In order to discuss the baseline risk of metastasis after BCR, we strongly encourage the utilization of the aforementioned nomogram published by Tendulkar *et al*.

The interplay between the timing of SRT and SRT target volumes has not been rigorously evaluated, and a detailed analysis is beyond the scope of this Review. However, we acknowledge that inclusion of elective nodal radiation and/or the integration of advanced imaging techniques, such as positron emission tomography/computed tomography scans with fluoride-18 fluciclovine or gallium-68 prostate specific membrane antigen (PSMA) may allow improvement of SRT outcomes, regardless of pre-SRT PSA. For example, whole pelvis radiotherapy (WPRT) was previously shown to improve BCR-free survival outcomes only in patients with pre-SRT PSA ≥0.4 ng/mL, but not in those with lower PSAs[34]. However, data from a larger study found WPRT to offer a significant BCR-free survival benefit on multivariable analysis including pre-SRT PSA as a covariate[35]. Part of the variability in outcomes could reflect that the incidence of occult nodal metastases is high, and difficult to predict. A recent study of 270 patients who underwent PSMA-based imaging found that data from the PSMA scan would have changed SRT field delineation significantly in nearly 20% of patients[36]. In this study, 30.5% of patients had PSMA-positive pelvic lymph nodes and another 3.5% had extrapelvic PSMA-positive lymph nodes. Similarly, a randomized trial of 96 patients evaluating the impact of fluoride-18 fluciclovine imaging on target volume reported an essentially uniform increase in treatment volume following incorporation of information from the advanced imaging study[37]. A conceptually attractive, though unproven, strategy would be to defer SRT initiation until advanced imaging is able to identify recurrent disease. At the current time, however, this strategy cannot be endorsed outside of a clinical protocol, as the wealth of available evidence (albeit retrospective) supports early initiation of SRT.

4. The Importance of Hormonal Therapy

Multiple randomized studies have shown an OS benefit to the use of concomitant HT with RT in definitive treatment of localized PCa[38]. While the precise pathophysiologic basis of this benefit remains an active area of study, recent data have identified a direct radiosensitizing action of HT[39,40], raising the possibility that concurrent HT has both local control benefits and benefits in terms of controlling micrometastatic disease. Adjuvant HT may also be important to suppress the induction of androgen receptor-mediated signaling by radiotherapy[41]. However, HT is associated with multiple effects, including bone loss, altered metabolism, diminished muscle mass, gynecomastia, hot flashes, possibly increased cardiovascular events, renal events and cognitive-psychological disorders[42-45]. Emerging data do suggest an additive, rather than redundant, negative functional impact of RT and HT in the postoperative setting[46]. Therefore, the integration of HT with SRT must be considered carefully. In the subsequent section, we summarize and critically review both the randomized evidence and the retrospective evidence examining the use of HT with SRT.

4.1. An Overview of the Randomized Evidence: RTOG 9601 and GETUG-16

Two randomized trials, RTOG 9601 and GETUG-16, have compared outcomes following SRT with or without concurrent hormonal therapy (Table 2)[47,48]. The risk of bias assessment for these trials is presented in Figure 1. Overall, the risk of selection, detection, and reporting bias was low for both trials, and the risk of attrition bias and performance bias was low in the RTOG 9601 trial but high in the GETUG-16 trial as follow-up is relatively short and participants were not blinded. The first trial, RTOG 9601, randomized 840 men between 1998-2003 to receive 64.8 Gy of SRT to the prostate bed with or without 24 months of 150 mg daily bicalutamide (a nonsteroidal androgen receptor antagonist). Ultimately, following post-randomization screening, 760 patients were eligible for analysis. Patients were required to have either pT3 disease or pT2 disease with a positive margin, as well as a PSA between 0.2-4.0 ng/mL (initially, the lower threshold for pre-SRT PSA was 0.5 ng/mL, but as PSA assays became more sensitive, this threshold was gradually lowered to 0.2 ng/mL). Of note, 11.8% of patients had PSA persistence after surgery and 46.7% had pre-SRT PSA levels >0.7 ng/mL at trial entry. At the time of final publication, the median follow-up was 13 years[47]. Significant improvements were seen in OS, PCSM, DM, and BCR, with 12-year OS rates of 76.3% versus 71.3% with and without HT. Importantly, no significant difference was seen in the risk of non-disease-specific death, including the rate of cardiovascular deaths. The rates of hot flashes were similar between groups, but the rate of gynecomastia was significantly higher in patients receiving HT (69.7% vs. 10.9%).

The investigators did conduct a number of subgroup analyses, reporting that the OS benefit seen in the overall study population was also seen in patients with GG 2-3 disease, pre-SRT PSAs 0.7-1.5 ng/mL and >1.5 ng/mL, and positive margins; the event rate was too low in the GG 4-5 group to demonstrate a statistically significant difference in OS. Of note, however, the interaction tests failed to identify a significant differential benefit in subgroups, with the exception of PSA level, suggesting that the relative benefit is similar regardless of GG or margin status. While provocative, the results of the PSA subgroup analysis should be considered primarily as hypothesis-generating rather than definitive as the PSA threshold and direction of benefit were not pre-specified.[49]

The second trial, GETUG-16, randomized 743 patients between 2006-2010 to receive SRT with or without two 10.8 mg (i.e., three-month) injections of goserelin (a luteinizing hormone–releasing hormone agonist). Patients were required to have pT2-pT4a (bladder neck involvement) disease with an initial PSA <0.1 ng/mL following RP for at least six months, followed by consecutive rises to between 0.2-2 ng/mL. Patients with PSA persistence were thus expressly excluded, and the median PSA at inclusion was 0.3 ng/mL, with 75% having PSA <0.5 ng/mL. Patients received 66 Gy to the prostate bed,

and pelvic radiation to 46 Gy was permitted for patients with a Partin-table defined risk of pN+ disease of >15% (ultimately, 16% of patients received pelvic RT). The primary endpoint was PFS, defined to reflect biological progression or clinical progression (or both), death from any cause, or censoring at date of last follow-up. The initial intention-to-treat analysis focused on 742 patients with a median follow-up of 5.25 years[48]. A significant benefit in PFS was seen with six months of HT (5-year PFS rates of 80% vs 62%). The majority of patients with disease progression (83%) had a local progression event with or without biochemical progression. Grade 1-3 hot flashes were more common in patients receiving HT (46% vs. <1%), as was hypertension (6% vs. <1%). Rates of grade 1-3 gynecomastia were <5% in both groups. Patient-reported quality of life outcomes, including global quality of life scores, sexual activity, and sexual function scores, were similar at five years in both groups, though at an intermediate time-point of one year, sexual activity and sexual function scores were numerically lower among patients receiving HT. Notably, quality of life was not assessed at six months, which is ostensibly when the peak negative effect from HT would be present.

Two protocol-specified subgroups were selected for analysis: low-risk, defined as patients with GG <4, positive margins, PSA doubling time > 6 months, and no T3b disease, and high-risk, defined as GG 4-5, negative margins, PSA doubling time <6 months, and T3b disease. There was no evidence of significant heterogeneity of effect size between the two subgroups, with HRs of 0.40 and 0.51 in the low and high risk groups, respectively. Post-hoc subgroup analyses identified a benefit in patients with PSA ≤0.5 ng/mL and >0.5 ng/mL, but not specifically in patients with PSA ≥1 ng/mL or GG 4-5 disease (though only a minority of patients fell in the latter groups). As with the RTOG study, these subgroup analyses should be considered hypothesis-generating rather than definitive.

In contrast to the RTOG study, no differences in DM or PCSM rates were seen in the GETUG-16 study (crude incidence rates of 3.5% vs. 5.1% and 1% vs 2% with and without HT, respectively), likely due to a short follow-up time. Overall, the GETUG-16 trial enrolled a significantly lower-risk patient population than the RTOG 9601 trial, as evidenced by the median pre-SRT PSA and inclusion of patients with PSA-persistence in the RTOG study. Additionally, clinical outcome differences may only appear after longer follow-up. Notably, the RTOG trial had identified a DM-free survival benefit at a median follow-up of 7.1 years[50]. It has also been noted that the kinetics of testosterone recovery alone may explain the difference in PFS seen in the GETUG-16 trial, particularly when outcomes were defined using time from randomization and the majority of events are presumed to be from biochemical progression[51]. Therefore, the updated results of the GETUG-16 trial, which will likely be reported within a year, are eagerly anticipated.

4.2. A Review of the Retrospective Evidence

Numerous retrospective studies have investigated the association between HT and SRT, as summarized in Table 3. All of these studies are limited by significant selection bias, as in any retrospective setting, HT is likely to have been used preferentially in patients with adverse disease characteristics.

The study with the longest follow-up was recently reported by Gandaglia *et al*. and included 525 patients (178 of whom received HT) treated across six institutions with a median follow-up of 8.7 years[52]. The authors developed a multivariable model for DM-free survival based on verified prognostic factors and then calculated the 10-year DM risk for each patient in both the HT and no-HT cohort. They found that the effect of HT on the 10-year risk of DM varied according to the model-predicted risk. Specifically, HT was only associated with a significant benefit in patients with pT3b/4 and GG ≥4 or pT3b/4 and PSA ≥0.4 ng/mL. SRT dose was associated with the DM risk as well, and it is possible that the absence of a specific benefit to HT in patients with positive margins in this study (versus RTOG 9601) reflects inherent improved control from a higher SRT dose (median 66 Gy). In the setting of escalated SRT doses, the benefit of HT may be predominantly related to systemic control. In addition, the aforementioned multi-institutional study by Tendulkar *et al*. reported a significant DM benefit to the use of concurrent HT (HR 1.41 for omission of HT).

Notably, two other large retrospectives studies investigating concurrent HT did not reveal a statistically significant DM benefit. A recent multi-institutional study by Ramey *et al*. included 1861 SRT patients (267 patients with HT) and found only a trend towards statistical significance (p=0.09) for the association between HT use and DM outcomes, despite a BCR-free survival benefit[35]. A prior report from the University of Michigan, which included 680 patients receiving postoperative RT (including adjuvant radiotherapy, with 144 receiving HT) also found no significant association between HT and DM outcomes, though longer durations of HT were associated with improved DM outcomes among patients receiving HT[53]. Of note, 67% of patients treated with HT had at least one particularly high-risk feature (GG 4-5, pT3b, or pre-RT PSA ≥1 ng/mL) compared with only 48% of patients not receiving HT. Of the studies designed to examine BCR outcomes, those with reported subset analyses have similarly found HT to be most beneficial in the subset of patients with higher risk features (Table 2). The large retrospective series by Stish *et al*. from Mayo Clinic (discussed above in the context of the pre-SRT PSA level) included 180 patients treated with HT[29]. Despite the long follow-up and an improvement in BCR outcomes, HT was not significantly associated with improved DM. The studied cohort may have had less enrichment of patients with negative margins and/or high GG tumors compared with the studies showing

a DM benefit. Alternatively, if the benefit of HT stems mainly from augmenting local control, then the high median SRT dose in this study of 68 Gy may explain the relative lack of benefit to HT.

Thus far, retrospective studies have not reported evidence of a PCSM benefit to the use of HT[53]. A large report of men with recurrent PCa managed at Johns Hopkins University included 238 men who received SRT (78 with HT) with a median follow-up of six years. Men receiving concurrent HT were more likely to have GG 4-5 disease, higher pathologic T stage, negative margins, and shorter PSADTs. Despite this, PCSM outcomes were no different (crude rates of 11.3% and 11.5% without and with HT, respectively), while the rate of DM was lower (27.2% vs 19.5%).

Finally, PSADT following a BCR may be an important factor with regards to the use of HT with SRT. As briefly mentioned in the context of pre-SRT PSA, PSADT is a known poor prognostic factor following RP and SRT SRT[14-18]. Generally, patients with shorter PSADTs are likely to have more aggressive disease (whether local or systemic), and in fact SRT may be more likely to provide a PCSM benefit in patients with shorter PSADTs, even if the overall prognosis of such patients is inferior than those with longer PSADTs[6]. Whether HT has a differential benefit based on PSADT is unknown, but PSADT is considered a high-risk feature for enrollment on the FORMULA-509 trial and is a stratification factor for the SALV-ENZA trial (Table 4).

4.3. Synthesis and Recommendations

Concurrent HT with SRT has not been consistently linked with improved survival outcomes aside from the RTOG 9601 trial. While that study does provide high-level evidence to support the use of concurrent HT, the median pre-SRT PSA of patients enrolled in that study was significantly higher than what might be encountered among patients presenting for SRT under an "early SRT" paradigm (i.e., with pre-SRT PSAs <0.5 ng/mL). On the other hand, though subgroup analyses of that trial do suggest a potential interaction between PSA level and the benefit of HT, those analyses should be regarded as hypothesis-generating, rather than conclusive. While the GETUG-16 trial did identify a PFS benefit in a population with a lower median pre-SRT PSA, this benefit largely stemmed from biochemical events given the relatively short follow-up. Thus, the role of HT in the setting of early SRT remains an open question, and this constitutes an area in which further research is sorely needed. Until definitive conclusions are available, we suggest that the physicians consider enrolling patients on open clinical trials. If clinical trials are not an option, we recommend partaking in shared decision making with the patient, highlighting the paucity of available data and sharing the conclusions that can be gleaned from the totality of evidence including the hypothesis-generating subgroup analyses and retrospective data. As

with discussing the benefits and risk of treating at a lower pre-SRT PSA level, the decision ultimately rests on the patients desire to maximize oncologic benefit versus minimizing the risk of overtreatment.

With those caveats, the retrospective data along with the subgroup analyses of RTOG 9601 suggest that the clinical benefit of concurrent HT may be greatest in patients an elevated *a priori* risk of SRT failure. Adverse risk factors include elevated pre-SRT PSAs, GG 4-5 disease, negative margin status, and elevated pre-SRT PSAs. The aforementioned subgroup analysis of the RTOG trial provocatively suggests that the survival benefit conferred by HT may be reserved for patients with pre-SRT PSAs above 0.7 ng/mL. Additionally, retrospective data have thus far not consistently identified a clinical (i.e., DM or PCSM) benefit to HT use, whereas nearly all retrospective studies with sufficient follow-up have identified a benefit to early SRT for these outcomes. However, the subgroup analysis must be regarding as hypothesis-generating, rather than conclusive, and the available retrospective data focusing on HT use is likely to have been subject to selection bias, wherein the patient populations receiving HT were enriched for adverse risk features. Nonetheless, we believe it is reasonable to discuss with patients that concurrent HT may be of relatively lower added value in patients with pre-SRT PSAs <0.5 ng/mL. We suggest that, when partaking in shared decision making with the patient, physicians underscore that this is an area ripe for further investigation.

High GG lesions have been shown to benefit from HT in the RTOG trial and in multiple retrospective series. While GETUG-16 did not show a benefit in this group, that subgroup analysis was underpowered and central pathology was not performed. Therefore, concurrent HT should be strongly considered in patients with GG 4-5 disease. The influence of margin status is unclear. The RTOG study did show a robust benefit to HT in patients with positive margins, but historically, negative margins have been considered to portend a higher risk of adverse outcomes following SRT, and the overall interaction test for a significant differential effect of benefit based on margin status was negative. It is possible that HT enhances local control (with the SRT dose of 64.8 Gy otherwise less likely to control residual disease) and/or that the negative margin subgroup in the RTOG study was simply too small to observe a significant difference. GETUG-16 identified an adverse prognostic significance to having negative margins but did not specifically analyze the effect of margin status on the benefit of HT. We therefore recommend concurrent HT in patients with GG 4-5 disease and suggest that margin status itself is not necessarily an independent factor to influence the decision of using concurrent HT.

Finally, the prolonged timeframe needed to identify the survival benefit in RTOG 9601, despite the baseline high risk of the patient population, underscores the need to personalize decisions regarding the benefit of HT with careful consideration of the patient's age and other comorbidities. Patients with life

expectancies shorter than 13 years (the median follow-up on the RTOG trial) may not live to see the survival benefit of HT and could be spared of its morbidity.

Overall, these recommendations are largely in accord with a recently published framework reported by Spratt *et al*[51]. It should be noted that the optimal duration of HT is not clear; thus far, only retrospective data are available, and these do suggest a benefit to longer term HT. Once more, these data are influenced by selection bias, as patients receiving longer term HT were more likely to have other adverse prognostic features. The ongoing Radiation Therapy and Androgen Deprivation Therapy in Treating Patients Who Have Undergone Surgery for Prostate Cancer (RADICALS) trial will randomize patients receiving either adjuvant RT or SRT to receiving no HT, six months of HT, or 24 months of HT (Table 4), and will provide prospective evidence regarding the optimal duration of HT. Several other trials, are investigating the additional benefit garnered by other systemic agents in addition to conventional HT with SRT (Table 4).

The interplay between SRT dose and target volumes and the role of HT has not been rigorously evaluated, and a detailed analysis is beyond the scope of this Review. In the definitive setting, multiple randomized trials have demonstrated a clear biochemical benefit to dose-escalated radiotherapy, but none have shown a survival benefit; in contrast, multiple randomized trials have shown a survival benefit to HT[38]. Whether this is related to a larger relative benefit to HT than dose-escalation or a mixed effect of HT on both local and distant disease is unclear. Regardless, the benefit of HT in the context of dose-escalated SRT is likely to be more modest than the benefit with lower SRT doses, as any benefit in local control would be less profound. Regarding radiation volume, only a minority of patients on the GETUG-16 trial received pelvic radiotherapy, and no patient on RTOG 9601 received this. The available retrospective data suggests a synergistic rather than redundant role to pelvic radiotherapy[35]. The ongoing Short Term Androgen Deprivation with Pelvic Lymph Node or Prostate Bed Only Radiotherapy trial (RTOG 0534) will provide prospective data to guide field design.

5. Conclusions

Nearly half of patients who ultimately die of PCa initially presented with curative disease and underwent local therapy, and as such, optimizing the management of patients who have recurrent disease is critical in order to ultimately improve PCSM outcomes. SRT constitutes the only known curative intervention following a post-RP BCR, but it is widely appreciated outcomes following SRT can be quite variable. Established nomograms can assist greatly in risk stratification based on readily available clinico-pathologic data. Only retrospective data are available regarding the interplay of pre-SRT PSA and SRT outcome. On the other hand, data from prospective, randomized studies are available to guide the use of

HT with SRT, but the most mature data pertain to a population with a median pre-SRT PSA of 0.5 ng/mL (i.e., in which many patients were treated with late SRT). Given the uncertainties, we underscore that this is an area ripe for future research and strongly suggest that when clinical trials are not an option physicians partake in shared decision making with patients, in which they disclose the imperfect nature of available information. With these caveats in mind, we suggest that the preponderance of data suggests that delivering SRT at low PSAs (i.e., early SRT) is associated with improved outcomes in most groups, though the absolute benefit may be more limited in patients with an overall low-risk of adverse outcomes. Similarly, we suggest that the greatest benefit of concurrent HT is likely to be reserved for patients with a higher baseline risk of treatment failure, and particularly those who are undergoing pre-SRT at higher PSAs (i.e., late SRT). Certain high-risk groups, such as those with GG 4-5 disease, may still benefit from concurrent HT at lower PSAs. An exciting area of future research involves the use of genomic tools, such as the 22-gene Decipher genomic classifier, to better prognosticate outcomes in patients who have undergone RP[54,55]. The PAM50 classifier[56] and the PORTOS signature[57] are emerging tools that may serve as predictive biomarkers for response to HT and SRT, respectively. As these tools are being validated and more prospective data are gathered, our recommendation is to emphasize the importance of early SRT and the judicious use of concurrent HT, with an emphasis on shared decision making and the relative importance of maximizing oncologic benefit and minimizing overtreatment.

Table 1.Timing of Salvage Radiotherapy and the Importance of pre-SRT PSA: A Retrospective Synthesis

Reference	# patients	Primary Outcome	Follow-up (median, years)	Patient Risk Profile	Radiation Dose (Median, Gy)	HT Duration (median, months)	Conclusions
European Multi-Institutional[30]	925 (30% with HT)	DM	8	Median PSA: 0.3 GG≥4: 24% pT3b/4: 33% Negative Margin: 56% 24% with persistent PSA elevation	68 (no WPRT)		pre-SRT PSA level was significantly associated with DM (HR 1.06 per 0.1) This relationship remained significant in three categories: Low-risk: GG 3 and ≥pT3b Intermediate-risk: GG 4 High-risk: PSA persistence with GG 1-3
Mayo Clinic[29]	1106 (180 with HT)	BCR DM PCSM ACM	8.9	Median PSA: 0.6 GG≥4: 16.2% pT3b/4: 16% Negative Margin: 48.7%	68 (WPRT in 4%)	60%≤12** 40% >12	HT associated with reduced risk BCR (HR 0.59 and 0.26 for ≤12 mos and >12 mos), but not associated with distant metastasis or mortality Pre-SRT PSA (continuous) was associated with BCR, and each doubling of pre-SRT PSA was associated with a 32% increased risk of DM, 40% increased risk of PCSM, and 12% increased risk of ACM These relationships held true for pre-SRT PSA as a dichotomous variable (>0.5 vs ≤0.5)
US Multi-Institutional[14,28]	2460 (390 with HT)	BCR DM	5	Median PSA: 0.5 GG≥4: 19% pT3b/4: 18% Negative Margin: 40%	66 (WPRT in 17%)	6	HT significantly reduced the risk of BCR and DM (HR 1.85 and 1.41) Freedom from BCR decreased with increasing PSA 0.01-0.2: 71% 0.21-0.5: 63% 0.5-1.0: 54% 1.0-2.0: 43% >2.0: 37% DM rate increases with increasing PSA 0.01-0.2: 9% 0.21-0.5: 15% 0.5-1.0: 19% 1.0-2.0: 20% >2.0: 37% Freedom from BCR and DM significantly associated with increasing pre-SRT PSA (HR 1.88 BCR, 2.23 DM)
University of Texas Southwestern and University of Michigan[32]	657 (154 with HT)	BCR DM PCSM ACM	9.8	Median PSA: 0.4 GG≥4: 28% pT3b/4: Not reported Negative Margin: 39%	68.4 (WPRT not reported)	6	HT significantly reduced the risk of BCR (HR 0.63) SRT at PSA 0.2-0.5 vs ≤0.2 was associated with increased risk of BCR (HR 1.97) and DM (HR 1.95)

							SRT at PSA >0.5 vs ≤0.2 was associated with increased risk of BCR (HR 3.48), DM (HR 4.45), and PCSM (HR 4.07)
European Multi-Institutional[31]	716 (0 with HT)	BCR	4.75	Median PSA: 0.2 (all <0.5) GG≥4: 14% pT3b/4: 15% Negative Margin: 46%	66 (no WPRT)		pre-SRT PSA level was significantly associated with BCR (HR 4.89) However, this was only a significant effect in patients with 2 or more risk factors (pT3b-4, GG≥4, negative margins). In the high risk group, BCR increased by 10% per 0.1 increase in PSA, compared with 1.5% in lower risk patients.
Sydney[58]	189 (62 with HT)	BCR	4.17	Median PSA: 46% <0.2, 37.8% 0.2-1 GG≥4: 23.9% pT3b/4: 22.8% Negative Margin: 39.7%	69.8 Gy (WPRT not reported)		Rates of 5-year BCR varied by pre-SRT PSA <0.2: 28.3% ≥0.2 to <1.0: 44.3% ≥1.0: 73.7% Compared with PSA<0.2, BCRs were significantly more common for PSA ≥0.2 to <1.0 (HR 1.73) and >1.0 (HR 3.1)
University of Tokyo [59]	76 (12 with HT)	BCR	5.833	Median PSA: 26% <0.2, 53% 0.2-0.5, >0.5 21% GG≥4: 20% pT3b/4: 5% Negative Margin: 39.7%	Median not reported, most 66 Gy (WPRT not reported)		pre-SRT PSAs <0.2 significantly associated with decreased BCR than SRT at PSA ≥0.2; however, this may have been driven by comparing PSA <0.2 vs. PSA>0.5, not PSA 0.2-0.5
Charité Universitätsmedizin[60]	301 (0 with HT)	BCR	2.5	Median PSA: .28 GG≥4: not reported pT3b/4: 17.9% Negative Margin: 33.2%	Median not report, most 66.6 Gy (0% WPRT)		Higher PSA pre-SRT (dichotomized as >0.28 vs. ≤0.28) was significantly associated with increased BCR (OR 2.771) 2-year BCR rates of 22% vs. 39% for pre-SRT PSA ≤0.28 vs >0.28
French Multi-Institutional[61]	201 (0 with HT)	"Treatment Failure"	3.691	Median PSA: .48 GG≥4: 14.9% pT3b/4: 21.4% Negative Margin: 32.3%	Not reported		Higher pre-SRT PSAs were associated with increased risk of treatment failure (>0.5 vs. ≤0.5 having HR 1.8, and >1 vs. ≤0.5 having HR 3.44)
Aichi Cancer Center Hospital[62]	51 (6 with HT)	BCR	3	Median PSA: .25 GG≥4: 37% pT3b/4: 10% Negative Margin: 37%	60 Gy (no WPRT)	8	Pre-SRT PSA was *not* predictive of BCR (when analyzed as <0.25 vs. ≥0.25).
Karolinska[63]	184 (165 with HT)	BCR DM	4	Median PSA: .47 GG≥4: 16% pT3b/4: 22% Negative Margin: 34%	70 (no WPRT)	3	Pre-SRT PSA was a predictor of increased BCR (OR 5.48) but not DM
New York Harbor Veteran Affairs[64]	54	BCR DM	5.92	Median PSA: .45 GG≥4: 9% pT3b/4: 20% Negative Margin: 35	70.2 (WPRT in 6%)		pre-SRT PSA.>0.4 was significantly associated with worse BCR (HR 6.4)
Memorial Sloan Kettering Cancer Center[65,66]	285 (87 with HT)	BCR	5	Median PSA: 0.4 GG≥4: 24% pT3b/4: 34%	95% got 66 Gy or more (WPRT in 7%)		Both pre-SRT PSA.>0.4 and omission of HT were significantly associated with worse BCR (HRs 1.64 and 1.46)

				Negative Margin: 54%			Nearly all local failures were in patients with pre-SRT PSA>0.4
Virginia Commonwealth University/Duke/Hunter Holmes McGuire Veteran Affairs[67]	197 (0 with HT)	BCR	4.33	Median PSA: 0. GG≥4: 25% pT3b/4*:10% Negative Margin: 34%	66 (WPRT in 52%)		Higher pre-SRT PSA was significantly associated with BCR (HR 1.87) With GG≥4, 5-yr BCR was 23% vs 74% for SRT initiated at PSA ≤0.33 vs. >0.33. There was no significant difference in BCR for GG1-3 lesions.

BCR, biochemical recurrence; DM, distant metastasis; GG, Gleason grade group; HR, hazard ratio; HT, hormonal therapy; PCSM, prostate cancer-specific mortality; SRT, salvage radiotherapy; WPRT, whole pelvic radiotherapy

Table 2. Concurrent Androgen Deprivation Therapy: A Comparison of RTOG 96-01 and GETUG-AFU 16

	RTOG 96-01[47]	GETUG-AFU-16[48]
Trial Design		
# Patients Eligible For Analysis	760	742
Follow-up (years)	13	5.25
Years Active	1998-2003	2006-2010
Inclusion Criteria	pT2 with positive margin or pT3 pN0 PSA 0.2-4.0 at least 8 weeks after RP [originally, lower limit was 0.5, then decreased over time to 0.2]	pT2, pT3, pT4a (bladder neck) pN0 or pNx PSA<0.1 following surgery for 6 months consecutive PSA rises to 0.2-2
Treatment Arms	RT + 24 months of bicalutamide vs. RT alone	RT + 6 months of goserelin acetate vs RT alone
RT parameters		
Dose	64.8	66 Gy
Fields/Volumes	No nodal radiation	16% received pelvic radiation to 46 Gy (for Partin table risk of pN+ >15%) for pT3b, received 50 Gy to SV remnant
Patient Characteristics		
	Median PSA: 0.6 (46.7% ≥0.7) <0.7: 53.3% 0.7-1.5: 31.2% >1.5-4.0: 15.5%	Median PSA: 0.3 (75% 0.2-0.5) 0.2-0.3: 50% 0.2-0.5: 75% >1.0: 10%
	pT3: 67.4%	pT3a: 33.4% PT3b/4: 12.7%
	GG 1-3: 82.7% GG 4-5: 17.3%	GG 1-3: 89.1% GG 4-5: 10.9%
	Negative margins: 25.1%	Negative margins: 50%
	PSADT<6 months: Not reported	PSADT<6 months: 26.5%
Results		
Primary Endpoint	Overall survival	Progression free survival (clinical *or* biochemical progression included)
Conclusions	12-year OS: 76.3% vs 71.3%	5-year PFS: 80% vs 62%; Overall HR: 0.5
Subgroup Analyses	12-year PCSM: 5.8% vs. 13.4% (HR 0.49) 12-year DM: 14.5% vs 23.0% (HR 0.63) 12-year BCR: 44.0% vs. 67.9% (HR 0.48) HT improved 12-year OS in: GG 2-3 (HR 0.69) but not GG 1 or 4-5 PSA>1.5 (HR 0.45) and <1.5 but ≥0.7 (HR 0.61) Positive margin (HR 0.73) but not negative margins HT improved 12-year DM in: GG 4-5 (HR 0.35) but not GG 1-3 PSA>1.5 (HR 0.36) but not ≤1.5 Positive margins (HR 0.56) but not negative margins	5-year OS: 96% vs 95% PCSM: 1% vs. 2% Metastatic or local progression with BCR: 4% vs 7% HT improved PFS in: low-risk* and high-risk group (HR 0.4 and 0.51) PSA ≤0.5 and >0.5 (HR 0.55 and 0.32) PSA ≤1 (HR 0.5) but not >1 PSADT >6 mos and ≤6 mos (HR 0.42 and 0.53)

*low-risk: GG 1-3, positive margins, PSADT>6 mos, no seminal vesicle invasion

BCR, biochemical recurrence; DM, distant metastasis; GG, Gleason grade group; HR, hazard ratio; HT, hormonal therapy; PCSM, prostate cancer-specific mortality; WPRT, whole pelvic radiotherapy

Table 3. Concurrent Hormonal Therapy: A Retrospective Synthesis

Reference	# patients	Primary Outcome	Follow-up (median, years)	Patient Risk Profile	Radiation Dose (Median, Gy)	HT Duration (Median)	Conclusions
European Multi-Institutionall[52]	525 (178 HT)	DM	8.67	Median PSA: 0.42 GG≥4: 15% pT3b/4: 9% Negative margin: 58%	66 (WPRT in 21%)	15	HT was beneficial only in those with pT3b/4 and grade group ≥4 or pT3b/4 and PSA ≥0.4 ng/ml
US Mult-Institutional[35]	1861 (267 HT)	BCR DM	4.58	Median PSA: 0.5 GG≥4: 25% pT3b/4*: 21% Negative margin: 59%	66 (WPRT in 8.7-11.9%)	6	HT was beneficial on multivariate analysis, independent of WPRT (HR 1.70 for no HT vs. HT; 5-year BCR-free survival of 50% vs 55%). There was a trend towards benefit in terms of DM (HR 1.36, p=0.09) Increasing pre-SRT PSA associated with increasing HR for BCR: ≤0.2: 0.28 0.21-0.5: 0.43 0.51-1.0: 0.61 >1.0-2.0: 0.86 (in reference to >2.0) Increasing pre-SRT PSA associated with increasing HR for DM: ≤0.2: 0.20 0.21-0.5: 0.33 0.51-1.0: 0.50 >1.0-2.0: 0.69 (p=0.07) (in reference to >2.0)
Dana-Farber Cancer Institute[68]	108 (43 HT)	BCR	5.275	Median PSA: 0.24 GG≥4: 26.9% pT3b/4: 23.1% Negative margin: 44.1%	66 (WPRT not reported)	6	HT use was associated with improved BCR (HR 0.44), but on subgroup analysis, this was only significant in patients with negative margins (HR 0.27) Increasing pre-SRT PSA was significantly associated with BCR (HR 20.99)
University of Michigan[53,69]	680** (144 HT)	BCR DM	4.75	Median PSA: 0.5 no HT, 0.9 HT GG≥4: 23.3% pT3b/4*: 20.1% Negative margin: 56%	68.4 (WPRT in 15-27%)	11.9	On univariate analysis, HT use was significantly associated with improved BCR outcomes (HR 0.74), but not in DM. Among patients receiving HT, duration <12 mos was associated with increased BCR (HR 2.27) and DM (HR 2.48) vs. those with duration ≥12 mos. Following propensity score matching, the duration-dependent improvement in BCR (HR 0.39) and DM (HR 0.21) remained significant. When analyzing HT duration as a continuous variable, HT duration in

							months was significantly associated with both improved DM (HR 0.88) and PCSM (HR 0.90) outcomes.
Boramae Medical Center[70]	162 (69 with HT)	BCR DM	5	Median PSA: 0.67 GG≥4: 37.7% pT3b/4: 22.8% Negative margin: 39.9%	66 (WPRT not reported)	18	HT use was significantly associated with improved BCR (HR 0.264). On survival analysis, DM-free survival was also significantly higher at 5-years with HT (100% vs 87.3%). On subset analyses, the benefit of HT in terms of both BCR and DM outcomes was restricted to patients with pT3b or PSA ≥0.6 Pre-SRT PSA ≥0.6 was associated with significantly increased BCR (HR 3.551)
Aarhus University[71]	259 (115 with HT)	BCR	3.1	Median PSA: 47%≥0.5 GG≥4: 23% pT3b/4: 4% Negative margin: 31%	68 (no WPRT)	15	HT use was significantly associated with improved BCR outcomes (HR 0.5). On subset analysis, HT use was only correlated with BCR-free survival for pre-SRT PSA >0.2. Pre-SRT PSA levels of ≤0.5 were associated with improved BCR (HR 0.48)
Bundang Hospital[72]	212 (124 with HT)	BCR	5.29	Median PSA: 44.3%>0.5 GG≥4: 42% pT3b/4: 42.5% Negative margin: 31.6%	66 (WRPT in 25%)	15	Omitting HT was associated with significantly increased risk of BCR (HR 2.00) both overall and among patients with pre-SRT PSA≤0.5 (HR 2.611) Pre-SRT PSA >0.5 was significantly associated with increased risk of BCR (HR 3.012)
University of Pennsylvania[73]	191 (62 with HT)	BCR	5.4	Median PSA: 0.6 no HT, 0.5 HT GG≥4: 21.5% pT3b/4: 23.0% Negative margin: 50.2%	66 (WPRT in 16.2%)	11	HT was associated with a significantly higher 10-year BCR-free survival (54.2% vs. 28.5%); however, on multivariate analysis, the association was only a trend (p=0.052).
City of Hope[74]	313** (122 with HT)	BCR DM	4.58	Median PSA: 0.3 GG≥4: 22.0% pT3b/4*: 24.0% Negative margin: 47.0%	67 (WPRT in 87%)	9	HT for >6 mos was associated with improved BCR versus no HT (HR 0.39 for 6-12 mos vs none, and 0.49 for>12 vs none) Pre-SRT PSA 0.2-1.0 and PSA>1.0 associated with increased HR for BCR (HR 2.2 and 9.2) Neither HT nor pre-SRT values were associated with DM outcomes.
Ghent[75]	136 (97 with HT)	BCR Clinical recurrence	5	Median PSA: 38% <0.5, 37%>1 GG≥4: 17% pT3b/4: 22.0% Negative margin: 48%	76 (no WPRT)	6	HT use significantly decreased the risk of BCR (HR 0.33). Clinical recurrence free survival was not affected by HT
Johns Hopkins University[6]	238 (78 with HT)	PCSM DM	6	Median PSA: 0.7 without HT, 0.9 with HT GG≥4: 20.1% pT3b/4*: 13.9%	66.5-67.2 (100% WPRT)		HT use did not significantly alter the impact of SRT on PCSM (analyzing the latter relationship was the primary objective of the study)

				Negative margin: 58.8%			Crude DM incidence rate was numerically lower with HT (27.2% vs. 19.5%) but not explicitly compared
MD Anderson Cancer Center[76]	101 (59 with HT)	BCR	4.175	Median PSA: 0.4 without HT, 1.1 with HT GG≥4: 26.7% pT3b/4: 24.8% Negative margin: 38.6%	70 (small WPRT fields used)	19.8	HT use significantly improved BCR in all patients except those considered low risk (PSA <0.5 and positive margin) Lower pre-SRT PSA significantly associated with BCR (HR 1.19)
Stanford[77,78]	122 (53 with HT)	BCR	5.9	Median PSA: 1.55 without HT, 0.3 with HT GG≥4: 27.8% pT3b/4: 4% Negative margin: 34.4%	64.2-67 (42% WPRT)	4	Omission of HT associated with significantly greater BCR (HR 2.81)

*included additional patients receiving adjuvant RT

BCR, biochemical recurrence; DM, distant metastasis; GG, Gleason grade group; HR, hazard ratio; HT, hormonal therapy; PCSM, prostate cancer-specific mortality; SRT, salvage radiotherapy; WPRT, whole pelvic radiotherapy

Table 4. Ongoing Randomized Trials: Concurrent Androgen Deprivation Therapy with Salvage Radiotherapy

Trial	NCT Link	Inclusion Criteria and Arms	Primary Endpoint	RT Notes
RTOG 0534	https://clinicaltrials.gov/ct2/show/NCT00567580	pT2-3N0 GG≤9 Postoperative PSA≥0.1 and <2.0 <u>Randomizations</u>: no HT, prostate bed alone vs. prostate bed + HT vs. prostate bed + WPRT + HT	Freedom from progression (biochemical, local, regional, distant)	64.8-70.2 Gy in 36-39 fractions WPRT dose 45 Gy HT 4-6 months
MRC RADICALS-HD	https://clinicaltrials.gov/ct2/show/NCT00541047	Subrandomization of MRC RADICALS-RT <u>Randomizations</u>: no HT, 6 months of HT, or 24 months of HT	Freedom from metastasis	66 Gy in 33 fractions 52.5 Gy in 20 fractions WPRT at discretion of physician
EORTC 22043-30031*	https://clinicaltrials.gov/ct2/show/NCT00949962	pT2 with positive margins, or pT3 with or without positive margins Undetectable postoperative PSA Allows either adjuvant or early salvage (criteria not specified)* <u>Randomizations</u>: no HT or 6 months of HT	BCR-free survival	64 Gy in 32 fractions WPRT not permitted
SALV-ENZA	https://clinicaltrials.gov/ct2/show/NCT02203695	<u>Randomization</u>: no HT or 6 months of HT (enzalutamide)	PSA-progression free survival	66.6-70.2 Gy in 37-39 fractions
FORMULA-509	https://clinicaltrials.gov/ct2/show/NCT03141671	PSA ≥ 0.1 after radical prostatectomy (value w/in 3 months of registration) AND at least 1 unfavorable risk factor listed below. • GG≥4 • PSA > 0.5 • Pathologically positive lymph nodes • pT3 • PSA doubling time < 10 months • Negative margins • Post-RP PSA nadir ≥ 0.1 • Local/regional recurrence on imaging • Decipher "High risk" <u>Randomization</u>: 6 months HT (GnRH agonist+bicalutamide) vs. 6 months GnRH agonist+apalutamide+abiraterone)	PSA-progression free survival	66.6-70.2Gy in 37-39 fractions WPRT at discretion of physician
NRG GU-002	https://clinicaltrials.gov/ct2/show/NCT03070886	GG≥2 AND post-RP PSA nadir≥0.2 ng/mL <u>Randomization</u>: SRT+HT vs. SRT+HT + docetaxel	Phase II: Freedom from progression (biochemical, local, regional, distant) Phase III: Metastasis-free survival	

*terminated due to poor accrual

BCR, biochemical recurrence; DM, distant metastasis; HT, hormonal therapy; WPRT, whole pelvic radiotherapy

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