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Multimodality Therapies for Localized Prostate Cancer

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Abstract

Purpose of Review—Multimodality therapy including radical prostatectomy, radiation therapy, and hormone therapy are frequently deployed in the management of localized prostate cancer. We sought to perform a critical appraisal of the most contemporary literature focusing on the multimodality management of localized prostate cancer.

Recent Findings—Men who are ideal candidates for multimodality therapy include those with unfavorable intermediate-risk disease, high-risk disease, and very high-risk disease. Enhancements in both systemic agents (including second-generation antiandrogens) as well as localized therapies (such as stereotactic body radiotherapy and brachytherapy) are refining the optimal balance between the use of systemic and local therapies for localized prostate cancer. Genomic predictors are emerging as critical tools for more precisely allocating treatment intensification with multimodality therapies as well as treatment de-intensification.

Summary—Close collaboration among medical oncologists, surgeons, and radiation oncologists will be critical for coordinating evidence-based multimodality therapies when clearly indicated and for supporting shared decision-making in areas where the evidence is mixed.

Keywords

Localized prostate cancer; Radical prostatectomy; Surgery; Radiotherapy; Radiation; SBRT; Hormone therapy; ADT; Genomics

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Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Prostate cancer (PCa) is the leading cause of cancer and the second leading cause of cancer death in United States (US) men[1]. Most men harbor only localized disease at the time of diagnosis, for which definitive treatment is highly effective [2]. Evidence-based therapies for localized PCa include both systemic therapies that suppress androgen activity as well as local therapies that directly address disease in the prostate, including radical prostatectomy (RP) and definitive radiation therapy (RT)[3].

As our risk stratification approaches have become more refined, we have been better able to identify which PCas harbor more aggressive features and may warrant treatment with multimodality therapy rather than single-modality therapy. Multimodality therapies for PCa can deploy external beam RT (EBRT), androgen deprivation therapy (ADT), second-generation antiandrogen therapy, brachytherapy (BT), and RP, in various evidence-based combinations. Herein, we provide an overview of the latest data supporting the use of multimodality therapy for localized PCa and also highlight how recent publications have refined our understanding of how best to employ multimodality therapy for men with localized PCa.

Section 1: Multimodality Combination of EBRT and ADT

RT with first generation ADT is widely accepted as a multimodality approach localized PCa. However, the use of ADT with definitive RT is highly variable in real-world practice, as ADT has significant adverse impacts on quality of life [4]. Thus, the appropriate duration of ADT and the subgroups of patients in which ADT is most beneficial remain controversial. The MARCAP meta-analysis [5••] pooled data from 10,853 patients at 12 centers and found that the addition of ADT to RT improved metastasis-free survival (MFS, HR: 0.83 [0.77–0.89]) as did prolongation of adjuvant ADT (HR: 0.84 [0.78–0.91]) irrespective of RT dose, patient age, or National Comprehensive Cancer Network (NCCN) risk group. This suggests that even in the modern era of RT dose intensification, there appears to be a relative benefit to adding any duration of ADT to RT alone for most men with localized PCa. However, the absolute benefit of ADT does diverge for intermediate-risk (IR) vs high-risk (HR) patients, with a calculated number needed to treat in order to avert one distant metastasis (DM) event at 10 years of 8.4 (95% CI: 6.0–13.8) for HR patients compared to 18.0 (95% CI: 12.7–30.7) for IR patients.

Intermediate-Risk Patients

Even among IR patients, significant biological heterogeneity exists, such that some IR patients may benefit from multimodality addition of ADT to RT whereas others might not. Emerging data suggests ADT may be beneficial for patients with unfavorable IR (UIR) disease, whereas men with favorable IR (FIR) disease might reasonably be spared ADT. For example, a subset analysis of RTOG 9408, which originally examined the benefit of 4 months of ADT with RT, reported that ADT for FIR disease did not reduce DM, prostate cancer-specific mortality (PCSM), or all-cause mortality (ACM). On the other hand, in UIR disease, ADT did improve DM and PCSM at 15 years of follow-up [6].

If ADT is chosen for IR disease, multiple studies have demonstrated that the ideal duration of ADT that balances oncologic outcomes and quality of life in IR patients is between 4–6 months. EORTC 22,991, a randomized trial of 245 patients, found that 74 or 78 Gy RT in conjunction with 6 months of ADT improved event-free survival (EFS) [7] compared to RT alone. The PCS III study also found that 6 months of ADT improved freedom from biochemical failure (FFBF) [8], whereas RTOG 0815 showed decreased rates of the more clinically meaningful endpoint of DM [9]. Several additional studies also found that extending the duration of ADT did not improve outcomes. RTOG 9910 found 4 months versus 9 months of ADT were equivalent in terms of OS (66% vs 67%, p = 0.62), cumulative incidences of locoregional progression (6% vs 4%, p = 0.07), DM (6% vs 6%, p = 0.80), and biochemical recurrence (BCR) (27% vs 27%, p = 0.77) [10]. Likewise, DART 01/05 GICOR found that 28 months of ADT was comparable to 4 months with regard to biochemical progression-free survival (bPFS), overall survival (OS), and metastasis-free survival (MFS) [11]. While the above studies failed to demonstrate an OS benefit to 4–6 months of ADT, RTOG 9408 did demonstrate such an advantage (HR: 1.17, p = 0.03, 62% vs 57%) [12]; however, the protocol for this study employed a lower dose of RT (66.6 Gy) than would be standardly utilized today, potentially inflating the benefits of ADT in this cohort.

The timing of STADT also remains an important question for patients receiving multimodality therapy with ADT and RT. Ottawa 0101 evaluated 432 patients with IR PCa randomized to either neoadjuvant/concurrent or concurrent/ adjuvant STADT [13]. At 10 years, there was no difference in bRFS (80.5% vs 87.4%, p = 0.1) or OS (76.4 vs 73.7, p = 0.7), and no differences in RT-related grade > 3 gastrointestinal (GI) (2.5% vs 3.9%) or genitourinary (GU) toxicity (2.9% vs 2.9%). Furthermore, a recent pooled meta-analysis which included the Ottawa trial [14] found that, at 15 years, adjuvant ADT was actually superior to neoadjuvant therapy in terms of PFS (HR: 1.25, 95% CI: 1.07–1.47, p = 0.01, 36% vs 29%), BCR (HR 1.37, 95% CI: 1.12–1.68, p = 0.02, 33% vs 43%), DM (HR 1.17, 95% CI: 1.00–1.95, p = 0.04, 12% vs 18%), and MFS (HR: 1.17, 95% CI: 1.00–1.37, p = 0.05, delta 7.2%) with no difference in GI or GU toxicity. These findings reinforce the notion that adjuvant ADT may have increased efficacy in patients with localized PCa. Most recently, the superiority of concurrent/adjuvant ADT compared to neoadjuvant/concurrent ADT was confirmed by the SANDSTORM analysis [15••], though these benefits were reserved for men receiving prostate-only RT, as no benefit was observed for men who also received whole pelvis RT. Given what we understand about the protracted nature of RT-induced prostate cancer cell death, an attractive biologic explanation for the advantages of concurrent/adjuvant ADT may lie in prolonging the interruption of androgen receptor-mediated DNA repair during a period when repair of RT-induced DNA damage remains relevant.

Ongoing clinical trials seek to harness precision medicine platforms to identify IR patients who may benefit from de-escalation to RT alone vs those who benefit from treatment escalation with intensified ADT. For example, NRG GU010/GUIDANCE (NCT05050084) seeks to risk-stratify 2050 UIR patients using The Decipher Prostate Cancer Test. Patients with a Decipher score < 0.4 are randomized to RT alone or RT with 6 months of ADT with a primary endpoint of DM. A separate randomization for men with Decipher score > 0.4 will

determine if patients should undergo an intensified regimen of RT plus 6 months of ADT along with a second-generation antiandrogen, darotulamide, or standard of care RT with 6 months of ADT alone, using MFS as a primary end point. An artificial intelligence-derived digital pathology-based biomarker has also garnered recent excitement following validation [16•] of its ability to predict the benefit of ADT in cohort of IR patients enrolled on RTOG 9408. However, until such biomarkers can be prospectively validated, candidates for omission of ADT without significant compromise in oncologic outcomes are likely best identified by NCCN risk group classification, with omission preferred for FIR patients and 4–6 months of concurrent/adjuvant ADT preferred for most UIR patients.

High-Risk and Very High-Risk Patients

The value of combined modality RT + ADT in HR and very high-risk (VHR) patients has been well studied. Long-term ADT (LTADT) has consistently improved OS in multiple large, randomized trials. EORTC 22,863, a phase III trial with 415 HR patients randomized to RT alone or RT with 36 months of ADT, showed LTADT improved OS (58.1% vs 39.8%, HR: 0.60, $p < 0.0001$), PCSM (10.3% vs 30.5%, HR: 0.38, $p < 0.0001$), and did not affect cardiovascular-related death (15.1% vs 17.5%, $p = 0.60$) [17]. Similarly, RTOG 8531 showed that indefinite adjuvant ADT improved all endpoints, including OS [18]. Adding more granularity, DFCI 95–096 suggested that HR patients with no or minimal comorbidities were likely to experience an OS benefit from adding 6 months of ADT to their management [19]. The benefits of 6 months of ADT were redemonstrated in TROG 96.01 [20], particularly with regard to distant progression, PCSM, and ACM, when compared to both 3 months and 0 months of ADT. Conversely, RTOG 8610 examined the impact of 4 months of ADT and found improved PCSM, DM, and BCR compared to RT alone, although the improvements in OS did not reach statistical significance. These data suggest that while ADT is beneficial, 4 months may not be sufficient to improve OS in this HR group.

A number of studies have also explored the ideal duration of ADT in this cohort of patients. Overall, three studies report that LTADT may be more effective than STADT in HR and VHR patients. RTOG 9202 randomized 1554 patients to either 28 months or 4 months of ADT and subgroup analysis found that patients with a Gleason score 8 or higher saw improved OS (31.9% vs 45.1%, $p = 0.0061$) in the LTADT arm at 10 years [21]. Similarly, DART 01/05 showed improved OS in a subset of HR patients undergoing 28 months of ADT compared to those who received 4 months of ADT [11]. EORTC 22,961 similarly showed that patients undergoing LTADT for 36 months had improved OS over those with STADT for 6 months [22]. Several studies have also suggested that intermediate-term ADT (ITADT) is superior to STADT and may even be comparable to LTADT. In the RADAR study, IR and HR patients who were randomized to ITADT for 18 months had improved PCSM compared to those receiving STADT for 6 months [20]. PCS IV specifically sought to compare ITADT (18 months) vs LTADT (36 months) and showed equivocal OS (86% vs 91%, $p = 0.07$) with quality of life (QOL) analysis favoring ITADT [23]. However, it is worth noting that compliance was very poor in the 36-month arm, which may have contributed to the equivocal results. Moreover, this trial was designed as a superiority trial, and the implications of a negative superiority trial are distinct from a non-inferiority trial. Taken together, these data suggest that while LTADT is better than STADT in HR patients,

LTADT might be similar to ITADT in the modern dose-escalated RT treatment era, although 18 months may still be insufficient [24•].

Section 2: Multimodality Treatment Intensification with Second-Generation Antiandrogen Therapy

Given poorer outcomes in men with HR localized PCa, there has been interest in incorporating advanced antiandrogen therapy into the upfront treatment of HR PCa in conjunction with EBRT + ADT. In a recent meta-analysis of two phase 3 trials from the STAMPEDE platform protocol, 1974 HR patients (defined as node-positive disease or the presence of 2/3 of the following features: T3/T4 disease, Gleason score 8–10, or prostate-specific antigen (PSA) ≥ 40) undergoing local therapy predominately with RT were randomized to either ADT alone (control group), ADT with abiraterone and prednisolone (intervention arm of the first trial), or ADT with abiraterone, prednisolone, and enzalutamide (intervention arm of the second trial) [25••]. At 6 years, the combination arms demonstrated improved MFS (HR: 0.53 [95% CI: 0.44–0.64, $p = 0.0001$], 82% versus 69%) along with OS, PCSM, BCR, and PFS when compared to ADT alone. However, no benefit in MFS was seen when enzalutamide was added to ADT, abiraterone, and prednisolone (HR: 1.02 [95% CI: 0.70–1.50], $p = 0.91$), yet toxicity was increased. The most common adverse events in the combination therapy groups were hypertension (5% in abiraterone, 14% in abiraterone and enzalutamide, and 2% in ADT alone) and transaminitis (6% in abiraterone alone, 13% in abiraterone and enzalutamide, and 1% in ADT alone). These data would suggest that a multimodality approach with the addition of abiraterone and prednisone to ADT and definitive RT should be considered for selected HR node-negative men who meet the pre-specified STAMPEDE criteria of PSA ≥ 40 ng/ml, Gleason 8–10 disease, and cT3/T4 disease or men with N1 disease.

Ongoing studies are focused on employing The Decipher Prostate Cancer Test as a stratification method to inform management of patients with HR localized PCa. The two-pronged NRG GU009/PREDICT-RT study (NCT 04,513,717) is currently accruing 2478 HR patients with the goal of deescalating therapy in patients with a Decipher score of < 0.85 by randomizing them to 12 instead of 24 months of ADT in conjunction with RT. In contrast, the role of treatment intensification will be evaluated for patients with a Decipher of > 0.85, with patients randomized to the standard 24 months of ADT vs 24 months of ADT plus apalutamide. MFS is the primary endpoint of interests for both randomizations. Apalutamide is also under evaluation as a component of multimodality treatment intensification for men undergoing definitive RP in the PROTEUS trial (NCT03767244), where high-risk patients will receive neoadjuvant and adjuvant ADT +/− neoadjuvant and adjuvant apalutamide and pathologic complete response and MFS will be assessed as co-primary endpoints.

Section 3: Multimodality Radiation Therapy Combining EBRT with Brachytherapy Boost

There has been interest in leveraging the noninvasive ability to treat large fields with external beam RT alongside BT, which enables significant escalation in prostate dose with sharp falloff to surrounding organs at risk. In the landmark ASCENDE-RT trial [26, 27], 398 men were randomized to either standard 46 Gy EBRT to the pelvis followed by a dose-escalated EBRT boost to 78 Gy vs standard EBRT to the pelvis followed by a low-dose rate (LDR)

BT boost. Approximately two-third of the men enrolled were HR and one-third was IR. All men received 12 months of ADT, though it should thus be noted that the duration of ADT in the EBRT arm of ASCENDE-RT was suboptimal and that the sequencing (largely neoadjuvant) may also not have been optimal [15••]. Nevertheless, at a median follow-up of 6.5 years, men who received a BT boost were twice as likely to be free of biochemical failure (HR 2.04; $p = 0.004$), with 7-year bPFS estimates of 86% vs 75%. Moreover, this benefit was seen in both IR and HR groups, but no difference in the rates of DM or OS were reported. The bPFS benefits came at the expense of an increase in grade 3 GI and GU toxicity, and thus, the balance between increased toxicity and biochemical control must be weighed individually by patients considering BT boost. This nevertheless highlighted the potential benefit of deploying multiple radiation therapy modalities in the treatment of men at the higher end of the risk spectrum. Additionally, while ASCENDE-RT employed 12 months of ADT, a retrospective analysis [24•] of HR patients demonstrated that at least 12 months might be optimal for patients who undergo EBRT + BT boost, but that a minimum duration of 26 months is required to minimize distant metastases in men who underwent EBRT alone, suggesting alongside ASCENDE-RT itself that the multimodality use of EBRT + BT may allow for a curtailed duration of ADT without compromising outcomes.

In a contemporary retrospective analysis of 1809 men at the highest end of the risk spectrum with Gleason 9–10 disease, Kishan et al. demonstrated improvements in PCa-specific survival (PCSS) as well as DM-free survival who received the multimodality combination of EBRT + BT + ADT, surpassing outcomes of RP or EBRT + ADT alone in this HR population [28••]. Though retrospective in nature, the benefits of dose escalation to the primary were convincingly demonstrated. An open question is whether this local dose escalation is necessarily achieved by BT or whether dose escalation with advanced EBRT approaches such as SBRT can provide similar survival and DM-free benefits. Moreover, it is important to note that when comparing patients receiving EBRT + BT to the subgroup of EBRT patients who received optimal duration ADT (i.e., > 24 months), the observed PCSS differences were no longer statistically significant. This suggests that if ADT duration were to be optimized, outcomes may be equivalent with EBRT.

Additionally, a recent non-randomized subset analysis of patients who received optional BT on the TROG 03.04 RADAR study, men treated with a high-dose rate (HDR) BT boost combined with 46 Gy of pelvic EBRT did experience superior freedom from local progression and even superior PCSM compared to men who underwent EBRT alone at three dose-escalated prescription dose levels of 66 Gy, 70 Gy, or 74 Gy [29]. These findings emerged even after adjusting for duration of ADT use, stage, Gleason grade group, PSA, and age.

Finally, while not strictly multimodality in nature, focal EBRT boosting of the dominant intraprostatic lesion(s) aims to recapitulate some of the favorable dose-escalating properties of BT and has similarly been shown to improve outcomes including bDFS [30] at a median follow-up of 72 months, without increasing radiation-related toxicity in a randomized phase III setting.

Section 4: Multimodality Addition of Radiation Therapy +/− ADT in the Post-prostatectomy Setting

Multimodality therapy for the treatment of localized PCa is perhaps most critical in the post-RP setting. Among higher-risk men who undergo RP as definitive therapy for localized PCa, approximately 30–50% [31–33] will ultimately require treatment with a second modality due to the development of biochemical recurrence, defined by the American Urological Association as two postoperative serum PSA recordings of 0.2 ng/mL or greater [34]. Salvage radiotherapy is the only known curative intervention for these men, though the timing of treatment initiation and the role of concurrent hormone therapy have been the subject of intense study [35] and debate.

Real-World Receipt of Multimodality Therapy

Despite the documented oncologic benefits of adding RT +/− ADT as treatment modalities for HR patients following RP, the use of postoperative RT is still limited in the US. SEER [36] and NCDB [37] analyses have both demonstrated low and even declining rates of RT utilization as part of multimodality treatment of post-RP patients with adverse pathologic features. Despite the inherent limitations of retrospective national database studies, these series do offer convincing evidence that the urologic oncologic community may be unconvinced that curative multimodality therapy is needed for most patients with adverse features. This highlights the opportunity to refine and broadly communicate contemporary data which have aided in the appropriate selection of men for multimodality therapy, as well as the timing of when to initiate multimodality therapy.

Timing the Addition of Radiation Therapy

Regarding the appropriate timing of salvage RT, it has been long understood that treatment at lower PSA thresholds carries improved oncologic benefits, ostensibly owing to eradication of recurrent disease prior to systemic dissemination, for which serum PSA serves as an important marker. A systematic review of 41 studies comprising 5597 patients published in 2012 demonstrated a 2.6% decrement in biochemical RFS for each incremental increase of 0.1 ng/mL at the time of RT salvage [38]. Additionally, a 2016 update to a clinical nomogram of outcomes for salvage RT developed from 2460 patients (the “Tendulkar nomogram”) similarly demonstrated the pre-salvage PSA, in addition to several other canonical prognostic risk factors, were associated with freedom from biochemical failure on multivariable analysis [39]. Moreover, salvage at lower PSAs was also found to be associated with a lower rate of distant metastatic recurrences. Despite these studies, no universally agreed upon PSA cutoff exists and thus shared decision-making which considers the patients’ values and preferences regarding the balance between oncologic benefit and toxicity from multimodality treatment is required.

Additional clarity regarding the balance of oncologic benefit vs toxicity of multimodality treatment in the post-operative setting came with three prospective randomized trials which opened for accrual sequentially over the years of 2007–2009, as well as an accompanying meta-analysis evaluating benefits of adjuvant vs early salvage RT. In all three studies, radiotherapy was directed at the prostate bed alone using conventional fractionation to doses of 64–66 Gy, adjuvant RT was delivered within 6 months of RP, and men eligible

for inclusion had at least one or more pathologic risk factor including positive margins or pT3-T4 disease. RADICALS was the first trial to open and allowed Gleason 7–10 disease to be considered as a pathologic risk factor for inclusion. A hypofractionated radiation regimen of 52.5 Gy in 20 fractions was also allowed on this trial, and hormone therapy was permitted to accompany salvage RT either through a second randomization of 0 vs 6 vs 24 months of ADT or through receipt off-protocol for patients who chose not to undergo randomization. Designed as a superiority study with freedom from distant metastases as the primary endpoint, this study reported 5-year bPFS was no different between arms (85% for adjuvant vs 88% for early salvage), and those randomized to adjuvant RT experienced statistically significantly higher rates of self-reported urinary incontinence at 1 year and grade 3–4 urethral strictures at 2 years [40]. GETUG-AFU-17 [41] was similarly designed as a superiority trial with EFS as the primary outcome. Notably, all patients in the GETUG study received hormone therapy alongside RT. This trial similarly demonstrated no difference in event-free survival (92% for adjuvant vs 90% for early salvage, $p = 0.42$) and higher rates of late grade 2 GU toxicity and erectile dysfunction. Finally, RAVES was unique in its non-inferiority design and the absence of hormone therapy use for all patients. While early salvage RT did not meet trial-specified criteria for non-inferiority, 5-year freedom from biochemical progression was not significantly different between groups (86% for adjuvant vs 87% for early salvage, $p = 0.15$) and grade 2 or worse GU toxicity was lower in the salvage group [42]. Given the similar results of these studies, it is not surprising that the ARTISTIC meta-analysis, which pooled study-level outcomes from all three aforementioned studies, confirmed the absence of an event-free survival benefit for adjuvant multimodality therapy when compared to early salvage multimodality therapy [43••]. Taken together, the results of these mutually reinforcing studies suggest that early RT is beneficial, but it may be preferable to defer the application of multimodality therapy until PCa definitively recurs, heralded by a PSA rising to 0.2 ng/mL. This balanced approach seeks to balance oncologic benefit with the critical need to spare the late sequelae of RT, including GU toxicity and erectile dysfunction, in all men with postoperative pathologic risk factors.

Of note, despite the intention to include both IR and HR patients in these studies, the patients who enrolled had largely favorable risk profiles, and many of the outcomes reported on these studies were improved compared to historical controls. Indeed, only 15% had ISUP grade 4–5 disease and 19% had SVI. Thus, these studies may only assist in clarifying the timing of multimodality therapy for more favorable subsets of men, in turn raising the question on whether the door on adjuvant RT is truly shut for patient with more adverse risk features and thus higher risk. A 2017 study by Dalela et al.[44•] set out to assess whether the Decipher Prostate Cancer Test could augment the role of pathologic features in identifying patients appropriate for adjuvant RT. Indeed, Decipher score > 0.6, pT3b/T4 stage, lymph node positivity, and Gleason score 8–10 were independent predictors of clinical recurrence, and in patients with two or more of these risk factors, adjuvant RT was associated with decreased clinical recurrence. The application of adjuvant RT in conjunction with ADT (also termed “MaxRP”) has also been supported in patients with Gleason 9–10 disease [45••], where outcomes were found to be equivalent when compared to men treated with “MaxRT,” which consisted of EBRT, BT, and ADT.

The Addition of ADT to Post-RP Multimodality Therapy

Three studies have now suggested an oncologic benefit to the addition of ADT in the post-RP RT setting. GETUG-AFU-16 randomized 743 patients to either RT alone or RT plus a 6 month course of goserelin. At long-term follow-up of 112 months, biochemical progression was reduced in patients who received ADT. RTOG 9601 was a similarly designed phase III trial that randomized 760 post-RP patients undergoing 64.8 Gy salvage RT to either 24 months of bicalutamide or placebo. With the caveat that median PSA at study entry was high at 0.6 ng/mL and radiation dosing is lower than contemporary standards, the endpoints of overall survival, metastatic PCa, and death from PCa were all improved with the addition of long-term ADT. While these studies collectively demonstrate a benefit to the addition of ADT to postop RT, the precise duration and optimal method of ADT were not clarified by these studies. Importantly, in a post hoc subgroup analysis of patients on RTOG 9601 with PSA levels below 0.7 ng/mL, there was no 12-year overall survival benefit reported, and additional subgroup analyses have since suggested that utilization of ADT below 0.6 might even be associated with survival decrements driven by a greater than threefold increase in high-grade cardiac and neurologic events [46]. An orthogonal subgroup analysis of 760 patients from RTOG 9601 whose tumors were analyzed via the Decipher Prostate Cancer Test demonstrated that Decipher score was independently predictive of DM, PCSM, and OS [47••] and that men with PSA < 0.7 might be further sub-classified based on Decipher score to distinguish who may benefit from the addition of bicalutamide to salvage RT.

The SPPORT Trial, also known as RTOG 0534, was a recently published three-arm trial which evaluated the incremental benefit of adding ADT and whole pelvic RT to post-RP RT in the modern treatment era. Notably, their definition of biochemical failure following multimodality salvage was based upon the Phoenix definition of PSA ≥ 2.0 ng/mL above the post-treatment PSA nadir. While an incremental benefit to the addition of ADT was shown, this would be expected with their chosen primary endpoint of freedom from progression. Thus, perhaps the most useful insights gained from this study pertain to the incremental benefits of adding whole pelvic RT in patients who are receiving RT to the postop bed in conjunction with ADT. This study, in conjunction with RTOG 9601, also revealed that postoperative PSA might serve as a predictive biomarker for treatment response, as patients harboring higher PSA levels appeared to benefit the greatest from either the addition of 2 years of bicalutamide (RTOG 9601) or from treatment intensification with pelvic nodal RT (RTOG 0534), at PSA values > 1.5 and > 0.34, respectively.

While SPPORT was not able to demonstrate an improvement in MFS with the addition of STADT alone, the DADSPORT meta-analysis did successfully demonstrate a MFS advantage to 6 months of ADT when added to salvage RT [48]. RADICALS-HD [49] also demonstrated that 24 months of ADT improved MFS over 6 months, raising the question whether the outcomes on SPPORT could be further improved with longer durations of ADT.

Future Studies

Ongoing studies seek to harness genomic classification to add to our understanding of the optimal multimodality therapy in the post-RP setting. ECOG-ACRIN EA8183/ERADICATE (NCT04484818) mandates a Decipher score of at least 0.6 prior to randomization of 48

weeks of ADT + placebo vs ADT + darolutamide to evaluate the role of systemic therapy intensification in HR patients. Additionally, NRG GU 006 (NCT03371719) is a phase II, double-masked randomized study similarly designed to evaluate the benefit of a second-generation antiandrogen, apalutamide, as a treatment adjunct in conjunction with early salvage RT. After initial risk stratification based on PAM50 molecular subtype (Luminal B vs Luminal A/Basal/Unknown) using the Decipher Prostate Cancer Test, patients will be randomized 1:1 to either 6 months of daily apalutamide or placebo starting on day 1 of salvage RT. With a primary endpoint of biochemical PFS and a target accrual of 324 patients, this study will enhance our understanding of the role genomic classification might play in selecting patients for multimodality systemic therapy and RT in the salvage setting, particularly in patients with luminal B subtype disease, which represents a subgroup of PCas with poor prognosis and biological differences in AR-signaling that result in improved response to postoperative ADT. RTOG 3506/STEEL (NCT03809000) will evaluate the merits of treatment intensification with the addition of enzalutamide to 24 months of post-RP ADT and ECOG-ACRIN EA8191/INDICATE (NCT04423211) will evaluate a similar question, with the addition of a parallel randomization evaluating the role of metastasis-directed therapy for patients with evidence of extra-pelvic metastases as identified by molecular PET/CT.

The companion randomization in the RAVES study will also add clarity regarding the optimal duration of ADT, as patients were randomized to 0 vs 6 vs 24 months of ADT. And finally, in an effort to simplify the multimodality addition of RT to the post-RP setting, the EXCALIBUR trial (NCT04915508) is a phase II non-randomized study that will assess the safety and efficacy of a condensed hypofractionated course of RT delivered in 5 rather than 36–39 sessions using daily MRI guided radiotherapy.

Conclusions

- Men who are ideal candidates for multimodality therapy of localized prostate cancer include those with unfavorable intermediate-risk disease, high-risk disease, and very high-risk disease.
- Enhancements in both systemic agents (including second-generation antiandrogens) as well as localized therapies (such as stereotactic body radiotherapy and brachytherapy) are refining the optimal balance between the deployment of systemic and local therapies for localized prostate cancer.
- Genomic predictors are emerging as critical tools for more precisely allocating treatment intensification with multimodality therapies as well as treatment de-intensification.
- Close collaboration among medical oncologists, surgeons, and radiation oncologists will be critical for coordinating evidence-based multimodality therapies when clearly indicated and for supporting shared decision-making in areas where the evidence is mixed.

Conflict of Interest

Luca Valle reports no conflicts of interest, but receives research funding from the Bristol Meyers Squibb foundation for work outside of the scope of this review. Amar Kishan reports funding support from grant P50CA09213 from the National Institutes of Health Specialized Programs of Research Excellence and grant W81XWH-22-1-0044 from the Department of Defense, as well as grant RSD1836 from the Radiological Society of North America, the STOP Cancer organization, the Jonsson Comprehensive Cancer Center, and the Prostate Cancer Foundation. He also reports consulting fees, research funding, and low-value stock in ViewRay, Inc., as well as consulting fees from Varian Medical Systems.

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Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

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