Recent Developments in Androgen Deprivation Therapy for Locally Advanced Prostate Cancer

David A Bader, BS,[1] Jasmina Z Cerne, PhD[2] and Sean E McGuire MD, PhD[3,4]

1. MD/PhD Student; 2. Post-Doctoral Fellow; 3. Assistant Professor, Department of Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas, US; 4. Assistant Professor, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, Texas, US

Abstract

Locally advanced prostate cancer (LAPC) is often managed with a combination of external beam radiation therapy (EBRT) and androgen deprivation therapy (ADT). Clinical protocols combining ADT and EBRT for the treatment of LAPC were developed based on clinical trials that used conventional-dose EBRT (~70 Gy) and luteinizing hormone-releasing hormone (LHRH) analog monotherapy. However, dose-escalated EBRT (>74 Gy) is in widespread clinical use and potent second-generation agents targeting the androgen axis have recently received US Food and Drug Administration (FDA) approval. These and other recent developments challenge the current standard of care for LAPC. Determining the optimal duration and potency of ADT in combination with dose-escalated EBRT in LAPC is an active area of clinical research seeking to balance the side-effect profile of ADT with its well-established therapeutic benefits. Prospective randomized clinical trials incorporating dose-escalated EBRT and second-generation androgen axis inhibitors are necessary to clarify the role of ADT in this new arena. Further, since biochemical response to neoadjuvant ADT predicts for efficacy of EBRT, new trials should seek to achieve maximal androgen suppression prior to EBRT to increase clinical benefit. Last, recent clinical and preclinical research efforts hold significant promise and seek to provide better predictive markers and expand the therapeutic target spectrum in prostate cancer.

Keywords

Locally advanced prostate cancer (LAPC), androgen deprivation therapy (ADT), androgen receptor (AR), dose-escalation, external beam radiotherapy (EBRT), conformal radiotherapy (CRT), continuous and intermittent ADT (CAD, IAD), prostate specific antigen (PSA), castration resistant prostate cancer (CRPC), radiotherapy synergy, luteinizing hormone-releasing hormone (LHRH) analog, androgen receptor antagonist, anti-androgen, CYP17 inhibitor, molecular and metabolic markers, biomarkers

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Correspondence: Sean E McGuire, MD, PhD, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, US. E: semcguir@mdanderson.org

Prostate cancer is the most commonly diagnosed noncutaneous cancer and second leading cause of cancer mortality in American men. The lifetime risk for prostate cancer is estimated at one in six; 30,000 men die of the disease annually in the US.[1] Prostate cancer is driven by the hormonally responsive transcription factor androgen receptor (AR) and the majority of prostate cancers are detected via serum level increase of the AR target gene prostate-specific antigen (PSA). Localized and low-risk prostate cancer is actively monitored or treated via radical prostatectomy (RP), brachytherapy, or external beam radiation therapy (EBRT).[2,3] A small but significant percentage of prostate cancer is locally advanced or metastatic at the time of initial diagnosis. The management of locally advanced prostate cancer (LAPC) is challenging and most often includes the combination of 'long-term' (24–36 months) androgen deprivation therapy (ADT) and EBRT. ADT is typically initiated in the neoadjuvant setting, given concurrently with radiotherapy, and continued in the adjuvant setting. Recent studies investigating the duration of androgen deprivation and widespread clinical use of dose-escalated EBRT challenge the role of conventional ADT in LAPC. Further, the consistent finding that biochemical response to neoadjuvant ADT predicts efficacy of subsequent EBRT is supported by recent molecular findings and begs the question as to whether potent second-generation agents targeting the AR axis should be incorporated in the neoadjuvant setting for the treatment of LAPC. However, ADT carries a significant, additive side effect profile and recent efforts to minimize ADT exposure have utilized intermittent ADT and demonstrate that it may be as effective as continuous ADT while reducing ADT-associated side effects in some patients. This review will focus on recent clinical and molecular insights, which will guide management of LAPC in a rational, evidence-based manner. We conclude with a brief section highlighting recent preclinical developments in basic prostate cancer research and novel therapeutic approaches to the treatment of the disease, which may be integrated into future clinical protocols.

Definition of Locally Advanced Prostate Cancer

LAPC has breached the prostatic capsule or invaded the seminal vesicles but has not spread to regional lymph nodes or metastatic sites (T3-4, N0-X, M0). These tumors are often bulky and most risk classification schemes (National Comprehensive Cancer Network,[3] Radiation Therapy Oncology Group,[4] and D'Amico[5]) place patients diagnosed with LAPC at high risk for disease recurrence, necessitating the need for aggressive therapeutic approaches up front to maximize the likelihood of a durable response or cure. Since extracapsular extension of the tumor often (not always—see Bonney[6] and Stephenson[7] for review of RP trials) makes these patients poor surgical candidates, the standard of care at most centers for men diagnosed with LAPC is high-dose conformal EBRT (>74 Gy[8]) combined with ADT. For these patients, ADT is generally initiated 2–6 months prior to EBRT, given concurrently with EBRT, and continued in the adjuvant setting for a total of 2–3 years.

Origins of the Standard of Care for Locally Advanced Prostate Cancer

The standard of care for LAPC has been continuously refined with contributions from multiple randomized clinical trials over the last ~30 years. A comprehensive review of all major trials is outside the scope of this review. However, recent trials that have influenced the standard of care in locally advanced and high-risk prostate cancer while setting the stage for current and future trials include the European Organisation for Research and Treatment of Cancer (EORTC) 22863 trial,[9] the Radiation Therapy Oncology Group (RTOG) 92-02 trial,[10] the Trans-Tasman Radiation Oncology Group (TROG) 96.01 trial,[11] the EORTC 22961 trial,[12] and the TROG 03.04 trial[13] (see *Table 1*). These will be briefly reviewed here.

- EORTC 22863[9] enrolled 415 men with high grade or LAPC to determine the impact of ADT concurrent with and adjuvant to EBRT (70 Gy). The addition of 36 months of adjuvant ADT improved 10-year disease-free survival by 25 % (hazard ratio [HR] 0.42; p<0.0001), overall survival by 18.3 % (HR 0.6; p=0.0004), and prostate cancer-specific mortality by 20.1 % (HR 0.38; p<0.0001) compared with EBRT alone with no measurable differences in cardiovascular mortality.
- RTOG 92-02[10] compared EBRT (65–70 Gy) with 4 or 28 months of ADT in a two-arm trial with 1,554 men. Compared with 4-month ADT, the 28-month ADT arm had decreased local progression (22.2 % versus 12.3 %; p<0.0001), distant metastasis (22.8 % versus 14.8 %; p<0.0001), and biochemical failure (68.1 % versus 51.9 %; p<0.0001). While the 28-month ADT arm had increased disease-free survival (13.2 % versus 22.5 %; p<0.0001), both groups displayed equivalent overall survival (51.6 % versus 53.9 %; p=0.36). However, in a post-hoc analysis limited to high-grade tumors (Gleason score [GS] 8–10), a significant difference in overall survival was detected (31.9 % versus 45.1 %; p=0.0061), suggesting high-grade tumors should be treated with long-term (>24 month) ADT.
- TROG 96.01[11] enrolled 818 men with T2b-T4 tumors to investigate the use of 0, 3, or 6 months of neoadjuvant ADT (NeoADT) prior to EBRT (66 Gy). The addition of NeoADT to EBRT significantly improved all study endpoints with greatest gains in the 6-month NeoADT arm. Compared with EBRT alone, 6 months of NeoADT reduced PSA progression (adjusted HR [aHR] 0.57; p<0.0001) local progression (aHR 0.45; p=0.0001), distant progression (aHR 0.49; p=0.001), all-cause mortality (aHR 0.63; p=0.0008), and prostate cancer specific mortality (aHR 0.49; p=0.0008) while improving event-free survival (aHR 0.51; p≤0.0001).
- EORTC 22961[12] is a follow up to EORTC 22863 and compared EBRT (70 Gy) supplemented with short- (6 months) or long-term (36 months) ADT with the hypothesis that short-term ADT would increase quality of life by decreasing ADT side effects while achieving therapeutic performance similar to long-term ADT. However, short-term ADT proved inferior to long-term ADT in terms of overall survival at 5 years and the study found no significant difference in overall quality of life.
- TROG 03.04[13] randomized 1,071 men to 6- or 18-month ADT (5 months of which were neoadjuvant) with or without the bisphosphonate zoledronic acid. Five-year interim analysis revealed no difference between the four treatment arms in terms of prostate cancer specific mortality but post-hoc analyses suggested reductions in PSA progression and decreased need for secondary therapeutic interventions (e.g. further androgen suppression) in the 18-month ADT plus zoledronic acid arm when the analysis was restricted to high-grade tumors (GS 8–10). No differences were detected in quality of life scores between groups.

On the basis of these and other trials,[14–16] the current standard of care at most centers for men diagnosed with LAPC is EBRT coupled with neoadjuvant (2–6 months), concurrent, and adjuvant (2–3 years) ADT. Interestingly, multiple clinical studies,[17–21] including our own,[22,23] have demonstrated that biochemical response to neoadjuvant ADT, as measured by monitoring PSA just prior to radiation, independently predicts the survival benefit conferred by combination ADT + EBRT therapy. Several factors likely contribute to this observation. For example, when combined with EBRT, neoadjuvant ADT minimizes radiation to adjacent healthy tissues because it reduces prostate size.[24] Further, neoadjuvant ADT decreases local recurrence because it inhibits repopulation of the irradiated target area,[25] and improves long-term clinical outcomes because it is synergistic with EBRT.[9,26] Several trials have likewise demonstrated a significant survival advantage is conferred by the use of ADT adjuvant to EBRT.[10,12] However, the optimal duration of ADT in the adjuvant setting remains to be defined and likely varies based on tumor grade and patient characteristics. Regardless, treating physicians must balance the clinical benefits of ADT with its side effects. While long-term adjuvant ADT appears necessary to maximize clinical benefit, there is a growing appreciation that its use is associated with increased morbidity.[27–31]

Recent Developments and Future Directions for Clinical Management of Locally Advanced Prostate Cancer

Irrespective of the agents used to accomplish castration, ADT carries a significant side-effect profile, including sexual dysfunction, hypogonadism, anemia, sarcopenia, cognitive dysfunction, increased risk for cardiovascular events, and metabolic dysfunction.[30,32,33] In an attempt to minimize these side effects, Nabid and colleagues compared EBRT combined with either 18 or 36 months of ADT. Six hundred and thirty men with high-grade (GS >7) T1c-T2a-b or T3-T4 tumors (N0-X, M0) were randomized to 18 or 36 months of ADT initiated 4 months prior to EBRT (70 Gy to the prostate; 44 Gy to pelvic lymph nodes).[34] The 10-year overall survival was 63.2 % in the 18-month ADT arm and 63.6 % in the 36-month ADT arm (p=0.429). On the surface, these results seem to indicate ADT may be safely reduced from 36 to 18 months in patients diagnosed with LAPC. However, the study is yet to fully mature and several limitations must be considered when interpreting its results.[35] First, (75.4 %) of patients in this study had localized (T1c-T2a-b) high-grade tumors (GS >7) and 24.6 % of patients had T3-T4.

Table 1: Recent Clinical Trials that have Affected the Management of Locally Advanced Prostate Cancer

Trial	EORTC 22863 (2010)	RTOG 92-02 (2008)	TROG 96.01 (2011)	EORTC 22961 (2009)	TROG 03.04 (2014)
Enrolled (Years)	415 (1987–1995)	1,554 (1992–1995)	818 (1996–2000)	970 (1997–2001)	1,071 (2003–2007)
Time to Follow-up	10 years	10 years	10 years	5 years	5 years
Stage	T1-2 with WHO histological grade 3 and M0, or T3-4 (any grade) and N0-1, M0	T2c-T4, N0, M0	T2b-T4, N0, M0	T2c-T4, N0 (91 %) T2c-T4, pN+ (6 %) T1c-T2b, pN+ (3 %) All M0	T2a, N0, M0 + Gleason >7 or T2b-4, N0, M0 any Gleason
Design	Two arms: 1. RT alone 2. RT+ concurrent and adjuvant ADT (3 years)	Two arms: (both received EBRT + 4 months ADT: LHRHa + antiandrogen) 1. No further ADT 2. Additional 2 years ADT (LHRHa monotherapy)	Three arms: 1. EBRT alone 2. EBRT + 3 months NeoADT 3. EBRT + 6 months NeoADT	Two arms: (both received EBRT + 6 months ADT: LHRHa + antiandrogen) 1. No further ADT 2. Additional 2.5 years ADT (LHRHa monotherapy)	Four arms: (all received EBRT + 6 months ADT: LHRHa monotherapy) 1. No further ADT 2. Zoledronic acid (no ADT) 3. Additional 12 months ADT 4. Additional 12 months ADT + zoledronic acid
Radiation	70 Gy (50 Gy to whole pelvis and 20 Gy prostate and seminal vesicles)	65–70 Gy to prostate, 44–50 Gy to pelvic nodes	66 Gy to prostate and seminal vesicles	70 Gy (50 Gy to whole pelvis and 20 Gy prostate and seminal vesicles)	Either 66, 70, or 74 Gy EBRT or 46 Gy EBRT + brachytherapy boost (19.5 Gy)
Androgen deprivation	3.6 mg goserelin (monthly) 50 mg cyproterone (3 x daily)	250 mg flutamide (3 x daily) 3.6 mg goserelin (monthly)	3.6 mg goserelin (monthly) 250 mg flutamide (3 x daily)	Monthly triptorelin (62 %) or goserelin (30 %) combined with 750 mg flutamide (daily) or 50 mg bicalutamide (daily)	22.5 mg leuprolin (every 3 months)
ADT initiation	Concurrent with EBRT (no NeoADT)	2 months prior to EBRT	2 or 5 months prior to EBRT	Concurrent with EBRT (no NeoADT)	ADT initiated 5 months prior to EBRT. Zoledronic acid initiated concurrently with ADT
Primary conclusion(s)	EBRT + concurrent and adjuvant ADT is superior to RT alone in terms of: overall survival disease-free survival	EBRT + 2 years ADT is superior to RT + 4 months ADT in terms of: disease-free survival local progression biochemical failure No benefit in terms of overall survival except in high-grade tumors (Gleason 8–10) (post-hoc analysis)	EBRT + 6 months NeoADT is superior to RT alone or RT + 3 months NeoADT in terms of: prostate cancer specific mortality PSA progression local progression event-free survival distant progression	EBRT + 3 years ADT is superior to RT + 6 months ADT in terms of: overall survival	No difference between treatment groups in terms of prostate cancer specific mortality at 5 years (trial not fully mature). Secondary endpoints indicate EBRT + 18 months ADT + zoledronic acid was more effective for treatment of high-grade tumors (Gleason 8–10) and RT + 18 months ADT alone was effective for low-grade tumors (Gleason ≤7)

EBRT = external beam radiation therapy; Gy = Grey; NeoADT = neoadjuvant androgen deprivation therapy; PSA = prostate-specific antigen; LHRHa = luteinizing hormone releasing hormone agonist; RT = radiation therapy; WHO = World Health Organization.

This is in contrast to the reference study, EORTC 22863, where 89.6 % of tumors were T3-T4. Second, increased patient enrollment is required to generate the statistical power necessary to confidently conclude the two arms are equivalent in terms of overall survival. Therefore, while these results are suggestive that 18 months may be sufficient duration of ADT, the standard of care for locally advanced tumors (T3-T4) should remain 2–3 years of adjuvant ADT based on RTOG 92-02 and EORTC 22961 (discussed above).

While the optimal duration of adjuvant ADT in patients with LAPC may not be conclusively defined, three principles may be drawn from these trials: 1) ADT in combination with EBRT improves outcomes (all trials), 2) ADT prior to and concurrent with EBRT improves outcomes (RTOG 86-10, TROG 96.01), and 3) ADT concurrent and adjuvant to EBRT improves outcomes (EORTC 22863, EORTC 22961). However, the extrapolation of these principles into current practice is not clear-cut owing to widespread use of dose-escalated (>74 Gy) radiotherapy,[8] recent approval of second-generation androgen axis inhibitors,[36,37] and the observation that neoadjuvant biochemical response predicts therapeutic outcomes.[21–23] To address these matters, the next generation of clinical trials must include ADT optimized to achieve maximal androgen suppression prior to the initiation of dose-escalated EBRT. For example, RTOG 1115 (NCT01546987) began enrolling patients in 2012 to compare ADT (GnRH agonist + flutamide or bicalutamide) with ADT + TAK-700 (a second-generation AR axis inhibitor targeting CYP17A1) in the context of dose-escalated EBRT. The goal of this study was to

determine whether maximal androgen suppression in combination with dose-escalated EBRT would improve LAPC outcomes compared with conventional ADT alone. Unfortunately, TAK-700 development was voluntarily terminated in May 2014 following equivocal results in two phase III clinical trials (ELM-PC4 and ELM-PC5) in men with metastatic castrate-resistant prostate cancer. At present, the future of this trial is uncertain. Nonetheless, the design of RTOG 1115 represents the next generation of clinical trials for men with LAPC and recent molecular insights are beginning to explain why achieving maximal androgen suppression results in synergistic therapeutic effects when combined with EBRT.

Finally, several trials have recently investigated the use of intermittent androgen deprivation (IAD) strategies in men with LAPC with the goal of decreasing long-term ADT-related morbidity. While IAD is traditionally used in men with metastatic castrate resistant prostate cancer, Crook and colleagues recently reported that IAD is noninferior to continuous androgen deprivation (CAD) in terms of overall survival in a group of 1,386 patients treated with EBRT who had a serum PSA level >3 ng/ml more than 1 year after EBRT. These patients were randomized to CAD (696 patients, median survival 9.1 years) or IAD (690 patients, median survival 8.8 years).[38] Notably, there were no reported differences in adverse events between groups though the IAD arm reported improvement in several quality of life factors (fatigue, hot flashes, libido, etc.) In addition to minimizing the side effects associated with CAD, it is hypothesized that IAD may also delay the emergence of castration resistance by decreasing selective pressure against hormonally responsive tumor clonal populations. Unfortunately, time to hormone resistance could not be determined due to inherent bias in the study design, although it was likely similar between groups.[38] A recent meta-analysis of nine studies totaling 5,508 patients likewise failed to detect superiority of CAD over IAD in terms of clinical benefit, but did advocate use of IAD based on cost savings and decreased exposure to androgen deprivation in IAD cohorts, which resulted in decreased side effects.[39] Because ADT is not often prescribed for >36 months in patients with LAPC, the direct applicability of these trials to patients diagnosed with LAPC is uncertain. However, IAD represents a potential mechanism to minimize ADT-related toxicities and future trials in this area may ultimately prove useful in the treatment of LAPC.

Molecular Basis for Synergy of Androgen Deprivation Therapy with External Beam Radiation Therapy

Although protocols combining radiation with androgen deprivation have been in clinical use for nearly 2 decades, the molecular mechanisms by which ADT improves radiosensitivity have remained elusive. Recent work by Polkinghorn and colleagues and Goodwin and colleagues has uncovered that activation of the AR axis increases expression of a network of DNA repair genes, including DNA-dependent protein kinase catalytic subunit (DNAPKcs—a critical component of the nonhomologous end joining machinery), enhancing radioresistance by promoting resolution of radiotherapy-induced double-stranded DNA (dsDNA) breaks.[40,41] Polkinghorn et al. demonstrated that pretreatment with R1881, a synthetic androgen, increases expression of a variety of DNA repair genes and significantly reduces the number of γ-H2AX foci (an indicator of nonresolved dsDNA breaks) induced by ionizing radiation. Conversely, Goodwin et al. demonstrated that androgen deprivation significantly increases the number of γ-H2AX foci induced by radiation.

In terms of clinical management, despite achieving castrate levels of serum testosterone (<0.5 ng/ml), conventional ADT results in a decrease of intraprostatic androgens by only ~75 %.[42,43] Residual adrenal androgens[44] and *de novo* intratumoral androgen synthesis[45] may enable a compensatory accumulation of intraprostatic androgens, initially allowing for tumor survival, but, ultimately, resulting in adaptation to castration and the emergence of castration resistant prostate cancer (CRPC) through reactivation of the AR axis as reflected by increasing PSA under castrate conditions.[46,47] Therefore, failure to efficiently inhibit the AR axis through the use of neoadjuvant and concurrent ADT may result in decreased therapeutic response to EBRT because tumor cells with an active AR axis will be primed to repair radiation-induced dsDNA breaks. Consistent with this hypothesis, animal studies have demonstrated that RT is most effective when delivered after maximal tumor shrinkage in response to ADT, an effect that is almost completely lost if the tumor is allowed to re-grow in an androgen-independent manner following initial androgen ablation.[48–50] Many clinical trials are in line with these animal studies, reporting a biochemical response to neoadjuvant ADT independently predicts the survival benefit conferred by ADT with subsequent EBRT.[17–23] In addition, multivariate analysis in our trials[22,23] revealed high-risk prostate cancer patients who achieved a pre-EBRT PSA of <0.5 ng/ml (versus >0.5 ng/ml) after neoadjuvant ADT displayed longer time to distant metastatic spread and had improved failure-free, prostate cancer-specific, and overall survival at a median follow-up of 7 years.[22,23] In sum, the clinical outcome of prostate cancer patients treated with ADT and EBRT may be closely linked to the efficacy of intratumoral androgen ablation and AR axis signaling suppression. In our experience, patients may be risk stratified as early as 3 months after initiation of ADT and those who fail to achieve a robust decrease in PSA are less likely to obtain the maximal therapeutic benefit that may be provided by the addition of EBRT. Encouragingly, both animal and clinical data support the molecular model that AR signaling supports resolution of DNA damage, highlighting an important new therapeutic angle in prostate cancer and also providing a rational explanation as to why prostate tumors treated with ADT often develop significant genomic instability.[40] In sum, active AR signaling primes cells for DNA repair and conventional ADT does not effectively abrogate AR signaling prior to EBRT initiation. Therefore, the use of potent second-generation agents in the neoadjuvant setting is expected to increase ADT-EBRT synergy, resulting in improved long-term outcomes.

Prognostic Biomarkers, Noninvasive Imaging to Diagnose and Monitor Prostate Cancer, and New Treatment Approaches

The majority of patients diagnosed with prostate cancer will die with, rather than of, the disease. The Gleason histopathologic grading system is commonly used to determine whether a tumor is likely to be aggressive (GS >8) and to guide subsequent therapy.[51] However, a reliable molecular test or biomarker panel to distinguish patients who may benefit from the addition of ADT to EBRT is lacking despite significant efforts. Analysis of tissue specimens collected in the phase III clinical trials RTOG 9202 and RTOG 8610 indicated p16, Ki-67, MDM2, Cox-2, and PKA may be useful for predicting whether a patient will benefit from long-term ADT.[52] More broadly, the search for a reliable

molecular test to differentiate indolent from lethal prostate cancer is an area of active study. Recently, Irshad et al. combined gene set enrichment analysis and a decision tree learning model to nominate a panel of three genes (*FGFR1*, *PMP22*, and *CDKN1A*) that accurately predicted the outcome of low GS tumors (GS <8) as validated by immunohistochemical staining of patient samples.[53]

Metabolic profiling reliably distinguishes benign prostate tissue from prostate cancer and may be useful for diagnosis and monitoring of prostate cancer, particularly given that certain metabolites can be detected using noninvasive magnetic resonance spectroscopic imaging[54] rather than a needle biopsy. For example, using real-time *in vivo* imaging, Nelson and colleagues determined biopsy-confirmed regions of prostate cancer take up hyperpolarized pyruvate much more rapidly than adjacent benign tissue.[55] Other compelling metabolic markers include spermine,[56] citrate,[57] sarcosine,[58] and choline.[59] In addition to diagnosis and monitoring, metabolic differences may be leveraged to enable specific therapeutic targeting of prostate cancer. Recent preclinical studies have demonstrated efficacy in targeting a broad range of metabolic targets or processes including AMPK,[60,61] amino acid trafficking,[62,63] and lipid metabolism.[64,65] Other approaches include the use of immune-activating monoclonal antibodies (e.g. ipilimumab)[66] and the alpha emitter radium-223.[67] Last, the use of mouse avatar modeling systems, in which a patient-derived prostate tumor xenograft is implanted into a cohort of immunocompromised mice, which are then treated using various regiments in an effort to guide patient therapy in real time, is beginning to emerge in so-called co-clinical trials.[68,69]

Future Clinical Directions for Combinatorial Androgen Deprivation Therapy with External Beam Radiation Therapy

ADT improves outcomes in patients diagnosed with LAPC treated with conventional dose EBRT. However, since most centers currently use dose-escalation therapy, appropriately powered prospective clinical trials are needed to clarify the role and efficacy of ADT when used in combination with dose-escalated EBRT for the treatment of high-risk or LAPC. Several high-priority questions remain to be addressed. First, whether the addition of ADT to dose-escalated EBRT improves clinical outcomes in high-risk or LAPC and whether short-term (~12–18 months) adjuvant ADT is equivalent to long-term adjuvant ADT in this cohort. Second, whether the replacement of conventional ADT (luteinizing hormone-releasing hormone [LHRH] analog monotherapy) with next-generation maximal androgen blockade (combining LHRH analogs with second-generation androgen axis inhibitors) as a first-line therapy before, during, and after dose-escalated EBRT improves disease-free and overall survival in LAPC. Last, whether neoadjuvant (3–6 month) biochemical response to ADT prior to EBRT may be used to tailor subsequent ADT. For example, patients with a robust decrease in PSA may not require (or benefit from) long-term adjuvant ADT following EBRT, patients with a moderate decline in PSA may benefit from additional neoadjuvant and longer adjuvant ADT, and patients with a marginal decline in PSA may require the addition of second-generation AR axis inhibitors prior to and following EBRT to obtain maximal clinical benefit. Randomized clinical trials will provide valuable insight to guide therapy and allow physicians and patients to accurately weigh the significant side effect profile of ADT against its proven therapeutic benefits. ■

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