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LOCALLY ADVANCED, HIGH-RISK PROSTATE CANCER

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Summary of Literature Review

Introduction/Background

Since the previous American College of Radiology (ACR) review of locally advanced, high-risk prostate cancer, a significant policy shift away from screening has been recommended by the US Preventive Services Task Force [1]. The recommendation to discontinue screening for prostate cancer reflects the decades-old Whitmore formulation: "Is cure necessary in those in whom it may be possible, and is cure possible in those in whom it is necessary?" [2]. The rationale that screening is designed to detect high-risk, potentially lethal cancers at a curable stage depends on proof of available treatment that can effectively eradicate such cancers. In the years since the 2011 review, several publications have suggested that aggressive approaches can yield high success rates, even in the most aggressive forms of prostate cancer [3].

The source of the most hopeful studies rests on the strategy of intensive local therapy. Three groups of studies support this observation. First, 3 large prospective randomized trials have demonstrated a biochemical-free survival (bFS) benefit of immediate postoperative radiation in high-risk patients and an overall survival (OS) advantage in 1 of the 3 trials [4-6]. Such immediate therapy can only improve survival if residual local disease is a subsequent source of metastasis. A second source of intensive local therapy yielding dramatically improved outcomes is the emerging combination of external beam radiation therapy (EBRT) with brachytherapy in high-risk cancers. Large retrospective studies and a recently presented randomized trial (ASCENDE-RT) comparing combination therapy to EBRT alone in such patients suggest incompletely eradicated cancers can subsequently spread and are preventable with sufficiently aggressive local therapy. Third, randomized prospective trials have demonstrated that the combination of androgen deprivation therapy (ADT) and radiation therapy (RT) provides better disease control than RT alone or ADT alone. Although ADT is often referred to as systemic therapy, profound local tumor responses to ADT suggest a major contribution to the ADT benefit may be local tumor cytoreduction prior to definitive EBRT [7]. Also supporting a dominant local effect for ADT is the surgical literature, where results competitive with or exceeding EBRT plus hormone therapy are accomplished without ADT [8]. Thus, improved local control has led to improved overall and disease-specific survival [9,10].

In spite of this progress, there remain additional trials to conduct that could facilitate improving the management of men with high-risk, localized prostate cancer. Multiple large patient series and randomized clinical trials within each treatment modality are available and are summarized below. The review of the current literature available can assist clinicians in deciding on the best treatment strategies for those with locally advanced, high-risk prostate cancer.

Definition of High-Risk Prostate Cancer

Though several risk stratification definitions exist in current practice, the most commonly utilized definition of risk groups is outlined in the National Comprehensive Cancer Network (NCCN) consensus of early 2015 [11].

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This definition separates high-risk patients in 2 strata: high and very high. Patients defined as "high risk" have a clinical stage of T3a or biopsy Gleason score (GS) of 8–10 or pretreatment prostate-specific antigen (PSA) >20 ng/mL. Those defined as "very high risk" are patients with clinical T3b-T4 without the presence of metastatic disease (including bone and lymph nodes). The NCCN guidelines also state that patients with multiple adverse factors can be shifted to the next highest risk group. These guidelines also recommend a staging bone scan for all high-risk patients and a staging pelvic computed tomography (CT) or magnetic resonance image (MRI) scan for any patient with T3 or T4 disease or for a patient with T1 or T2 disease and a nomogram that predicts involvement of lymph node metastasis >10%. Because the vast majority of clinical trials and series included in this report do not distinguish between high- and very high-risk prostate cancer, those risk groups will be considered jointly. Treatment era is also important to consider when analyzing results from the literature, likely stemming from inclusion of PSA-screened patients in most modern series. The historical high-risk patients can be expected to have a 10-year cause-specific survival (CSS) rate of 64%–90%, whereas the contemporary high-risk patients will have an 8- to 12-year CSS of 87%–96% [12-17]. Stage migration to less advanced cancers within the high-risk category combined with improved treatments may account for this improved CSS.

In addition to pretreatment PSA, biopsy GS, and tumor stage, there are multiple other factors that are correlated with outcome. For example, the percentage of positive cores, increasing GS, African-American race, and, in some but not all series, the presence of perineural invasion has been associated with poorer outcomes [18-21]. The presence of Gleason pattern 5 (GP5) prostate cancer has been demonstrated to be one of the worst prognostic factors and is associated with an increased risk of recurrence and metastasis following radical prostatectomy (RP) and salvage radiation, definitive EBRT, and brachytherapy [18,22,23]. In fact, studies of high-risk prostate cancer have identified the presence of GP5 as the strongest prognostic factor for all clinical endpoints, suggesting that the presence of GP5 constitutes a very high-risk subgroup requiring aggressive treatment strategies [22,23] (see Variant 1 and Variant 2). In summary, a population of patients within the NCCN high-risk subgroup with extremely high-risk features can be defined as those with T3/T4 tumor stage, GP5, high percentage of positive cores, or a combination of these risk factors (see Variant 3).

External Beam Radiation Therapy

EBRT is the treatment modality with the greatest volume of outcome literature available. The randomized studies within this modality help define the benefit of EBRT added to ADT, the timing and duration of ADT, the role of pelvic field irradiation, and the importance of dose-escalated EBRT. The first salient point from this extensive literature is the benefit of the addition of EBRT to ADT, which has been assessed in 2 randomized studies, each demonstrating a large OS advantage with the addition of EBRT [9,10,24]. OS went from 61% to 70% at 10 years in the Widmark et al [10] study and went from 49% to 55% at 10 years in the Mason et al [24] study.

The optimal timing and duration of ADT with EBRT has been addressed in multiple randomized trials that are summarized in Table 1. In general, these trials have established a significant OS benefit with the addition of long-term ADT (>2 years) or short-term ADT (≤6 months) compared to no ADT; however, only a CSS benefit without an OS benefit was demonstrated when comparing long-term ADT to short-term ADT in most trials [12-14,25-29]. In contrast to those studies, a recently reported Spanish trial compared 28 months versus 4 months of ADT with dose-escalated EBRT for men with intermediate- or high-risk prostate cancer and demonstrated a bFS, metastasis-free survival, and OS improvement with long-term ADT [30], although cautious interpretation of these findings is recommended [31]. Though only reported in abstract form at the time of this publication, a recent trial from Quebec randomizing 630 high-risk patients to 18 months versus 36 months of ADT showed no significant differences in OS, CSS, or any other assessed endpoint, raising the possibility that for some men with high-risk prostate cancer, 18 months of ADT may be sufficient [32]. However, the 95% confidence interval around the hazard ratio for death for 18 versus 36 months of ADT was wide (hazard ratio=1.15 [95% CI, 0.83–1.59], P=0.398) and so this study does not yet exclude the possibility of a clinically significant difference in survival between the 2 arms. Therefore, further evaluation of this study with longer follow-up is necessary in order to determine whether it provides sufficient data to alter practice recommendations. The toxicity of long-term ADT and the likelihood of a patient's ability to complete a course of ADT must not be overlooked. In 2 clinical trials evaluating long-term ADT, only 72%–76% of men were able to complete the course [14,26]. It is likely that men treated off protocol would have even lower adherence to a full course of ADT.

The role of elective treatment of pelvic lymph nodes in the clinically node-negative (cN0) patient remains controversial. The majority of the aforementioned studies establishing the role of ADT and EBRT for men with high-risk prostate cancer used pelvic fields [9,12-14,26,29]. However, 2 randomized clinical trials specifically

addressing the role of pelvic radiation found no difference in progression-free survival with the additional coverage of pelvic lymph nodes in the RT fields [25,33]. Subgroup analysis of 1 study has suggested that there may be a group of patients who would benefit from whole-pelvis radiation provided that ADT is given in the neoadjuvant setting [25]. The lack of benefit noted in these trials might be expected given poor local control of high-risk disease within the prostate. Pommier et al [33] used doses of 66–70 Gy to the prostate, and Lawton et al [25] used 70.2 Gy calculated at the isocenter. More aggressive local disease treatment would be essential before a benefit to pelvic lymph node irradiation could be identified. In this regard, it should be noted that some retrospective studies suggest improved outcome in delivering pelvic RT in patients who have limited clinically node-positive disease. In a study by Rusthoven et al [34] examining Surveillance, Epidemiology, and End Results (SEER) data, among 796 clinically node-positive patients, the 43% who received EBRT had a significantly improved 10-year cancer-specific survival (67% versus 53%, $P<0.001$). In slight contrast to this study is another SEER analysis from Johnstone et al [35], which found no OS benefit for postoperative RT in pathologically node-positive patients. It is important to note that the inclusion of a pelvic lymph node field for patients receiving EBRT cannot be determined from SEER data. Also related to the role of pelvic RT in advanced disease are retrospective studies by Briganti et al [36] and Abdollah et al [37] in which adjuvant EBRT was associated with improved OS and CSS in patients found to have node-positive disease following prostatectomy.

The role of dose-escalated EBRT to the prostate has been extensively investigated across all risk groups. One study of particular interest as it pertains to this review is by Kuban et al [38]. This study randomized patients from all risk groups to 78 Gy versus 70 Gy in 2-Gy fractions with dose prescribed to the central axis. Among the high-risk patients in the trial (approximately one-third of the study population), significant benefits in distant metastasis-free survival and bFS were noted in patients receiving 78 Gy. However, the only interaction retaining statistical significance in the Cox model was bFS for patients with PSA >10 ng/mL [38]. Ultrahigh doses (86.4 Gy) have yielded encouraging results as well, though they have not been assessed as part of a randomized clinical trial [39]. Even with ultrahigh EBRT doses, 31% of high-risk patients in that study had a biochemical failure (BF) with 7-year follow-up, suggesting additional strategies to intensify treatment are required for these patients [39]. Unfortunately, dose-escalated EBRT (>70 Gy) was not used in the aforementioned randomized trials establishing the role of ADT with EBRT, so the benefit of ADT added to dose-escalated EBRT has not been fully investigated. It is not known how such modern doses of EBRT will affect outcome, but the assumption is that because dose escalation >72 Gy is feasible with few additional side effects; there would be an improvement with no major additional toxicity. Finally, it is worth noting that hypofractionated regimens may be equivalent to dose-escalated EBRT, as was demonstrated in a recent Italian study [40]. In a cohort of 168 high-risk cancer patients also treated with 9 months of ADT, 80 Gy in 2 Gy/fraction demonstrated similar BF and distant failure (DF) as 62 Gy in 3.1 Gy/fraction at a median follow-up of 70 months (26% versus 15% for BF [$P=0.34$]; 12% versus 8% for DF [$P=0.57$]) [40].

Novel strategies to further enhance the treatment of high-risk prostate cancer with EBRT include the addition of taxane-based chemotherapy and novel antiandrogen therapy. The Radiation Therapy Oncology Group® (RTOG) is assessing both approaches in RTOG 0521 and RTOG 1115, respectively. The RTOG 0521 trial is a phase III randomized trial assessing EBRT with ADT versus EBRT with ADT followed by docetaxel and prednisone in high-risk prostate cancer [41]. This study is closed due to the trial meeting its accrual goal, not excessive toxicity, which is encouraging because a previous trial that incorporated paclitaxel, estramustine, and etoposide after EBRT and ADT did halt accrual due to excessive toxicity [42]. These trials predominantly investigate the hypothesis that high-risk patients have systemic disease requiring more aggressive systemic approaches.

Radical Prostatectomy

The literature for RP in locally advanced prostate cancer is limited compared to the EBRT data, and treatment recommendations are predominantly based on retrospective series rather than randomized clinical trials. Patients offered RP are a select subgroup of high-risk patients, further limiting comparisons. The possible advantages of RP compared to primary EBRT for men with high-risk prostate cancer include the ability to obtain complete pathology from the surgical specimen, a decreased risk of secondary malignancy, and the possibility to avoid long-term ADT. Overall, results of RP for men with high-risk prostate cancer are comparable with EBRT outcomes. Kupelian et al [43] demonstrated in a retrospective series of all risk groups that men treated with RP, dose-escalated EBRT, brachytherapy, or a combination of brachytherapy and EBRT (combo) had no difference in bFS, though the majority of patients did not have high-risk disease. Boorjian et al [8] found no differences in 10-year CSS in a retrospective study comparing men treated with RP or EBRT with ADT (92% for both). It is

important to note that there were more patients in the EBRT with ADT cohort with T3/T4 tumor stage (43% versus 33%) and GS 8–10 (48% versus 38%). The median radiation dose of 72 Gy for the EBRT patients would be considered low by current standards as well [8]. In slight contrast to the aforementioned studies, a recent retrospective comparison of RP and EBRT for high-risk patients found a slightly increased risk of distant metastasis among men in the EBRT cohort [15]. Westover et al [44] compared RP to EBRT combined with ADT followed by a permanent brachytherapy implant in men with high-risk disease. Though the men treated with combination EBRT, ADT, and brachytherapy were more likely to have GS 9–10 (32% versus 20%) and a higher T stage (77% T1 in the RP cohort versus 44% in the combo cohort), there was no difference in prostate cancer deaths (15 deaths in the RP arm versus 6 in the combination arm, P=0.3). A retrospective study by Aizer et al [45] demonstrated that men with high-risk disease had improved bFS when treated with EBRT and ADT compared to RP. Ellis et al [46] specifically analyzed the results of RP for men with GS 9–10 prostate cancer. Of 259 men with a biopsy GS of 9–10, they found a low rate of organ-confined disease on final surgical pathology (29%), a 5-year bFS of 37%, and an actuarial CSS of 61% at 10 years, further contributing to the understanding of poor outcomes for men with GP5 prostate cancer [46]. These results were much lower than the RP outcome predictions from the Kattan nomogram and limit the role of RP in such patients to a highly selective subset.

Finally, there are several retrospective series that show the superiority of RP over EBRT with respect to OS and/or CSS [47-51]. However, important considerations when analyzing the literature of RP for high-risk prostate cancer include assessing the rate of adjuvant and salvage EBRT and ADT, selection biases, patient comorbidities, use of ADT, and EBRT dose, as well as when the assignment of high-risk disease was made (based on presurgical biopsy or based on the surgical specimen). These considerations are major caveats to the aforementioned conclusions made by Zelefsky et al [15] as they note a 76% rate of salvage RT for the RP patients versus a 43% rate of salvage treatment for the EBRT patients. The median time to salvage was much shorter for the RP patients as well (13 months versus 69 months). Other studies describe rates of adjuvant ADT, RT, or both in 41%–48% of men who initially underwent RP for high-risk prostate cancer [8,52]. In most RP series the assignment of high-risk prostate cancer is made after assessing the surgical specimen. The importance of assigning risk group based on presurgical data when comparing RP to other treatment models is nicely demonstrated in a large RP series of 1366 men with high-risk prostate cancer [52]. They noted a higher rate of clinical to pathological upstaging (29%; cT1/T2 to ≥pT3) compared to downstaging (11%; cT3 to pT2) [52]. Variants evaluating the indications for postprostatectomy irradiation are discussed in the ACR Appropriateness Criteria for postprostatectomy irradiation and will not be addressed here [53].

Brachytherapy

Despite advances in EBRT dose and duration of ADT, outcomes remain poor for many men with high-risk prostate cancer. The addition of brachytherapy has been demonstrated to provide favorable results compared to EBRT alone or RP for men with high-risk disease. Relevant data on this topic come from the Prostate Cancer Results Group [54]. This group was formed to evaluate the comparative effectiveness of prostate cancer treatments and identified 848 abstracts, comprising over 52,000 patients, which met the study inclusion criteria. The RP series included required presurgical rather than postsurgical risk assignment, improving the comparison validity. Their analysis indicates that for high-risk patients, combination treatment with or without ADT appears superior to RP or EBRT alone [54]. A separate retrospective series assessing nearly 1000 patients treated with dose-escalated EBRT or combination therapy with a low-dose-rate (LDR) implant revealed an 8-year prostate cancer–specific mortality of 13% in the EBRT cohort and 7% in the combo cohort [55]. Additional series, both with over 7 years' median follow-up and nearly 300 high-risk patients in each, demonstrated CSS of 94% and 95% [56,57]. The ASCENDE-RT trial is a prospective study that completed accrual in 2011 and randomized intermediate- and high-risk patients to dose-escalated EBRT and 12 months of ADT with or without a brachytherapy boost, with results presented in abstract format this year. The study demonstrated improved bFS at 7 years with combination brachytherapy and EBRT compared to dose-escalated EBRT alone (86% versus 71%). In the high-risk prostate cancer patient subset, there was an 83% versus 72% bFS improvement at 7 years and a 78% versus 58% bFS improvement with combination therapy at 9 years [58]. Trimodality therapy consisting of a brachytherapy implant with supplemental EBRT and ADT has again been demonstrated to provide superior CSS when compared to bimodality treatments in men with a PSA >20 ng/mL and clinical T3 or 4 and/or GS 8–10 disease [59]. High-dose-rate (HDR) brachytherapy as part of this combination treatment has demonstrated favorable results compared to ultrahigh-dose EBRT (86.4 Gy) in a retrospective series [60]. Among the 204 men with high-risk disease (24 of whom were treated with HDR boost), the 5-year bFS improved from 71% to 93%, though this result did not reach statistical significance (P=0.23) [60].

Adding brachytherapy to the treatment of prostate cancer may be even more important for men with high-risk disease and additional adverse prognostic factors than in low- or intermediate-risk disease. Taira et al [16] recently reported outcomes for men with high-risk disease treated with LDR brachytherapy, EBRT, and ADT. The results compare quite favorably to other treatment modalities, with 10-year OS and CSS of 73% and 96%, respectively. Even men with GP5 had excellent outcomes (90% 10-year CSS) [16]. This CSS compares quite favorably to the results of the largest surgical series of patients with GP5, which noted a 10-year CSS of 61% [46]. Furthermore, another retrospective series of men with very high-risk features (GS 10, GS 8–9 with PSA >20 or >50% cores positive, clinical T3, or any PSA >40) treated with combo had CSS at 9 and 12 years of 91% and 87%, respectively [17]. Hoffman et al [61] also described an experience with brachytherapy in high-risk patients. They noted that the CSS at 5 years was 93% for brachytherapy alone and 97% for combination treatment with ADT (P=0.01). No difference was noted in OS (76.4% for brachytherapy alone and 79.6% for combination treatment with ADT, P=0.631) (see Variant 4). These retrospective data seem to show that combination therapy is at least comparable to EBRT and RP outcomes. It is not surprising that improved local control via combination therapy may lead to improved outcomes when considering the benefit of adjuvant RT following RP noted in 3 randomized clinical trials [4-6].

Other Therapies

Ablative treatments including cryotherapy and high-intensity focused ultrasound (HIFU) are other options available for men with high-risk prostate cancer, though data are limited for these modalities. In the aforementioned comparative effectiveness report by the Prostate Cancer Results Study Group, there was insufficient literature using the parameters employed for these modalities to be included in the assessment of high-risk prostate cancer, apart from 2 cryotherapy studies [54]. Only 1 of these 2 studies used the NCCN definition of high-risk disease and reported a 10-year bFS of 46%, lower than what would be expected with combination treatment, EBRT, or RP [62]. It is also important to note that many cryotherapy series use the American Society for Therapeutic Radiology and Oncology definition of BF, which is likely inappropriate for an ablative treatment, whereas a PSA threshold definition may be more appropriate [63]. The results of HIFU are similar to those of cryotherapy. Uchida et al [64] described a series of high-risk patients treated with HIFU and reported a bFS rate at 5 years of 45%. Thuroff et al [65] have recently reported a series of 704 men treated with HIFU, 40% of whom were high risk per the D'Amico staging criteria. The 10-year bFS reported in this series was 60%. The morbidity of HIFU is considerable, with rates of urinary obstruction up to 24% and impotency in previously potent men of 45% [65]. Impotency is a significant toxicity associated with cryotherapy as well, with one large series documenting only 41% and 51% potency rates 1 and 4 years after treatment, respectively, in pretreatment potent men [66].

Importance of Local Control

Though the major benefit of ADT is likely related to control of micrometastatic disease, it is important to consider evidence supporting the notion that at least some of the benefit of ADT in high-risk prostate cancer is related to improved local control. In a randomized trial of 0, 3, or 6 months of neoadjuvant ADT followed by EBRT, an approximately 50% decrease in local progression was noted in men who received the endocrine therapy [28]. Similarly, Jones et al and Laverdiere et al [67,68] demonstrated a 50% decreased rate of positive rebiopsies at 2 years following short-term ADT and EBRT. Further evidence of the local effect of ADT is demonstrated in a MRI-based response assessment at baseline and 3 months following ADT [7]. Following 3 months of ADT, a significant reduction was noted in all assessed MRI parameters of prostate tumors [7]. The effect of neoadjuvant ADT has been studied in an RP cohort of patients in which approximately 10%–20% of the study population comprised high-risk patients [69]. The results revealed a decreased rate of positive surgical margins but no benefit in disease-specific outcomes. In slight contrast to this are data from the dose-escalated EBRT literature. Higher doses of EBRT were associated with decreasing rates of positive post-treatment biopsies [70]. Of the 143 men with high-risk disease included in one study, post-treatment biopsies were positive in 51% of patients who received doses of 70.2 Gy or less, which decreased to a positive post-treatment biopsy rate of 15% if doses of ≥81 Gy were used. On multivariate analysis, a positive post-treatment biopsy was one of the strongest predictors of distant metastasis and prostate cancer death [70].

Toxicity

Robust data comparing the toxicities of the 3 main treatment modalities for high-risk prostate cancer come from the PROSTQA database and a prospective quality-of-life study from Spain with 5 years of follow-up [71-73]. These studies allow for several generalizations. RP is associated with the greatest decline in sexual function and

urinary incontinence. The addition of ADT to radiation treatments is associated with a greater sexual function decline when compared to the same treatment without ADT, although perhaps more so with ADT and EBRT as compared to ADT and brachytherapy or combination treatment. Nevertheless, it is clear that even short-course, neoadjuvant ADT is associated with immediate declines in vitality/hormonal and sexual quality of life [74]. Obstructive and irritative urinary symptoms are more prevalent with both radiation techniques but appear to be more protracted/persistent in brachytherapy patients. In the ASCENDE-RT trial greater genitourinary toxicity was observed on the combination arm and has been tied to high brachytherapy dose delivery to the sub-apex genitourinary diaphragm region, resulting in strictures, an avoidable technical flaw.

RP is associated with an improvement in obstructive or irritative urinary symptoms. Bowel dysfunction is clearly more common with radiation treatments than with RP. In a further analysis of the PROSTQA database, dose-escalated EBRT was associated with moderate/significant problems with bowel function in 11% of patients [75]. Interestingly, a comparative toxicity study of RT versus RP has recently been completed for men of all risk groups, showing no difference in 15-year toxicity though men in the RP group were older, had more comorbidities, and had higher GSs [76].

Recent data highlighting the cardiovascular toxicity of ADT yield conflicting results. A meta-analysis of 8 randomized trials evaluating ADT found no significant difference in the rates of cardiovascular death in patients receiving ADT as compared to controls [77]. However, a joint consensus statement of multiple medical societies reported by Levine et al [78] raises concern from mainly retrospective studies that ADT may be associated with excessive cardiovascular events, particularly in men with pre-existing cardiovascular morbidity. The possible cardiovascular risks of ADT may be attributable to the association of ADT with increased obesity, decreased insulin sensitivity, and adverse effects on lipid profiles [79].

Summary of Recommendations

- Recent prospective randomized trials in high-risk prostate cancer suggest aggressive local therapy (surgery followed by immediate EBRT, brachytherapy in combination with EBRT and ADT, and dose-escalated EBRT with ADT) may improve outcomes in locally advanced prostate cancer through improved local control.
- Improved cure rates in high-risk cancers are in part due to earlier detection by PSA screening and suggest a crucial role for screening associated with reports of improved outcomes.
- Studies continue to support a critical role for ADT, but large retrospective series suggest a favorable subgroup treated with combination brachytherapy and EBRT or surgery and EBRT may not require ADT. The maximum ADT duration in randomized studies with combination therapy is 12 months (ASCENDE-RT). Recent MRI response studies suggest the mechanism of ADT benefit may include profound local response of tumor as well as systemic effects.
- Controversy remains regarding the optimal subdivision of high-risk patients, with recent analyses suggesting Gleason grade 5 is the strongest predictor of mortality from locally advanced prostate cancer. Such high-grade lesions have a low level of prostate confinement and surgical clearance, a low response to conventional radiation doses, and an improved outcome with aggressive brachytherapy and EBRT approaches.
- Controversy remains regarding the role of adjuvant pelvic nodal radiation in high-risk disease. In high-risk disease with radiographically detected pelvic adenopathy, controversy remains regarding ADT duration and boost dose to gross nodal disease.
- A multidisciplinary approach to assure proper integration of component therapies is critical to improved outcomes in locally advanced cancers.

Summary of Evidence

Of the 79 references cited in the *ACR Appropriateness Criteria® Locally Advanced, High-Risk Prostate Cancer* document, 76 are categorized as therapeutic references including 30 well designed studies and 36 good quality studies. Additionally, 2 references are categorized as diagnostic references including 1 quality study that may have design limitations. There are 11 references that may not be useful as primary evidence. There is 1 reference that is a meta-analysis study.

The 79 references cited in the *ACR Appropriateness Criteria® Locally Advanced, High-Risk Prostate Cancer* document were published from 1990-2015.

Most of the references are well designed or good quality studies and provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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Table 1. Comparison of Major Studies of External Beam Radiation Therapy for High-Risk Prostate Cancer

Study	Treatment Era	Radiation Dose and Target	Endocrine Therapy	Biochemical Failure[3]	Clinical Failure[3]	Prostate Cancer–Specific Survival[3]	Overall Survival[3]
RTOG 8610; Roach et al [13]	1987–1991	44–46 Gy to pelvis + 20–25 Gy to prostate	None vs AD[1] + AA[2] for 4 months	65% vs 80% at 10 years; *P*<0.0001	35% vs 47% at 10 years; *P*=0.006	64.4% vs 76.6% at 10 years; *P*=0.009	34% vs 43% at 10 years; *P*=0.12
RTOG 8531; Pilepich et al [12]	1987–1992	44–46 Gy to pelvis + 20–25 Gy to prostate	None vs AD[1] indefinitely	69% vs 91% at 10 years; *P*<0.0001	~25% vs ~40% at 10 years; *P*<0.0001	78% vs 84% at 10 years; *P*=0.0052	39% vs 49% at 10 years; *P*=0.002
EORTC; Bolla et al [14]	1987–1995	50 Gy to pelvis + 20 Gy to prostate	None vs AD[1] for 3 years concurrent and adjuvant	N/A	30.2% vs 51% at 10 years; *P*<0.0001	69.6% vs 89.7% at 10 years; *P*<0.0001	39.8% vs 58.1% at 10 years; *P*=0.0004; however, a log-rank test was not performed and this *P* value is assumed to be a univariate comparison at 10 years
RTOG 9202; Horwitz et al [29]	1992–1995	44–50 Gy to pelvis + 20-25 Gy to prostate	AD[1] for 4 months vs AD[1] for 28 months	51.9% vs 68.1% at 10 years; *P*≤0.0001	N/A	83.9% vs 88.7% at 10 years; *P*=0.0042	51.6% vs 53.9% at 10 years; *P*=0.36
RTOG 9413; Lawton et al [25]	1995–1999	70.2 Gy to prostate only	AD[1] + AA[2] for 4 months neoadjuvantly vs adjuvantly	33% vs 41% at 5 years; *P*=0.0098[4]	N/A	93% vs 95% at 5 years; *P*=0.43[4]	77% vs 81% at 5 years; *P*=0.86
		50.4 Gy to pelvis + 19.8 Gy to prostate	AD[1] + AA[2] for 4 months neoadjuvantly vs adjuvantly	33% vs 33% at 5 years; *P* value not significant	N/A	95% vs 93% at 5 years; *P*=0.43[4]	81% vs 75% at 5 years; *P*=0.019
D'Amico et al [27]	1995–2001	70 Gy to prostate	None vs 6 months of AD[1] + AA[2] neoadjuvantly, concurrently, and adjuvantly	N/A	N/A	88% vs 97% at 8 years; *P*=0.007	60% vs 74% at 8 years; *P*=0.01
EORTC; Bolla et al [26]	1997–2001	50 Gy to pelvis + 20 Gy to prostate	AD[1] + AA[2] for 6 months vs 3 years	N/A	N/A	95.3% vs 96.8% at 5 years; *P*=0.002	81% vs 84.8% at 5 years; *P*=0.65
DART01/05 GICOR ; Zapatero et al [30]	2005–2010	78 Gy to prostate (14% of pts with 46 Gy to pelvis)	AD[1] for 4 months vs AD[1] for 28 months	10% vs 19% at 5 years; *P*=0.01	N/A	94% vs 83% at 5 years; *P*=0.01	95% vs 86% at 5 years; *P*=0.01

[1]Androgen deprivation (or luteinizing hormone–releasing hormone [LHRH]); [2]Antiandrogen (when combined with LHRH it is referred to as CAB); [3]reported as control group versus treatment group; [4]*P* value calculated from all 4 arms of the trial rather than pairwise.

Clinical Condition: **Locally Advanced, High-Risk Prostate Cancer**

Variant 1: **52-year-old man, PSA 6.8, T2a, Gleason 5+4=9 in 2/6 cores (L), 4+3 =7 in 4/6 cores (L)**.

Treatment	Rating	Comments
Endocrine Therapy Mixed with EBRT		
ADT 6 months	3	RTOG 99–10, high-grade disease but not T3.
ADT 12 months	5	
ADT 18 months	6	Final results of 36- versus 18-month study are pending. Although PCS IV looks promising, it is too early to say this is noninferior.
ADT 24–28 months	8	
ADT 36 months	8	
External Beam Pelvic Nodes Dose		
44–50.4 Gy	7	Trials testing role of whole-pelvis RT (WPRT) show no long-term benefit compared to no WPRT, but trials with long-term ADT did typically give WPRT. It remains unclear whether pelvic treatment is necessary.
None	6	
External Beam Prostate Dose (including pelvic dose) (assumes hormone therapy given)		
75–78 Gy	7	Acceptable options are 75.6 Gy at 1.8-Gy fractions or 78 Gy at 2-Gy fractions. This dose with 95% coverage, which gives higher isocenter dose than the prescription dose, is reasonable. GICOR study shows benefit in setting of 78 Gy.
>78 Gy	8	This dose refers to 79.2 Gy, extrapolating from RTOG 0126.
>82 Gy	6	This dose requires experience and special dose constraints.
Hypofractionated doses (2.5 Gy to 70 Gy or 3.1 Gy to 62 Gy)	6	
Brachytherapy		
LDR/HDR alone	3	
LDR/HDR + EBRT	5	This option may be appropriate but there was disagreement among panel members on the appropriateness rating as defined by the panel's median rating. The benefit of ADT for high-risk cases is extrapolated from EBRT literature.
LDR/HDR + EBRT + ADT (≤6 months)	6	
LDR/HDR + EBRT + ADT (12 months)	6	This option is similar to the ASCENDE-RT trial and could be reasonable since brachytherapy boost might reduce need for long-term ADT, but this is not proven prospectively with comparison to longer-term ADT.
LDR/HDR + EBRT + ADT (24 months)	8	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Locally Advanced, High-Risk Prostate Cancer**

Variant 2: **52-year-old man, PSA 24, T2b, Gleason 3+4=7 in 8/12 cores, 2-cm left obturator lymph node on staging CT abdomen/pelvis.**

Treatment	Rating	Comments
Endocrine Therapy Mixed with EBRT		
ADT 6 months	3	
ADT 12 months	3	This option should be used if given intermittently, extrapolating from the Hussain et al Intergroup Trial of intermittent ADT versus continuous.
ADT 18 months	5	A longer term (24+ months) is preferable based on randomized trials but this might be acceptable per the Montreal study; however, it is unknown for node-positive disease. There is no clear evidence for a node-positive patient to use a shorter ADT course.
ADT 24–28 months	8	
ADT 36 months	7	
External Beam Pelvic Nodes Dose		
44–50.4 Gy	8	Gross nodal disease should be treated beyond microscopic dose.
None	3	
External Beam Prostate Dose (including pelvic dose) (assumes hormone therapy given)		
75–78 Gy	7	
>78 Gy	8	
>82 Gy	6	
Hypofractionated doses (2.5 Gy to 70 Gy or 3.1 Gy to 62 Gy)	6	This dose is reasonable with extrapolation from lower-risk data and from Arcangeli et al. One trial addresses this issue.
Brachytherapy		
LDR/HDR alone	2	
LDR/HDR + EBRT	3	
LDR/HDR + EBRT + ADT (≤6 months)	5	
LDR/HDR + EBRT + ADT (12 months)	6	Lymph node–positive disease casts some doubt on shorter length of ADT.
LDR/HDR + EBRT + ADT (24 months)	7	The use of brachytherapy in lymph node–positive disease remains controversial.
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Locally Advanced, High-Risk Prostate Cancer**

Variant 3: **78-year-old man, PSA 12, T3b, Gleason 5+5=10 in 2/6 cores (R), 4+4=8 in 2/6 cores (R).**

Treatment	Rating	Comments
Endocrine Therapy Mixed with EBRT		
ADT 6 months	3	This option may be appropriate at this age if the patient has cardiovascular disease.
ADT 12 months	5	This option should be given with ADT per the ASCENDE-RT trial and other brachytherapy literature.
ADT 18 months	7	The result of a 36- versus 18-month ADT trial is pending.
ADT 24–28 months	8	
ADT 36 months	8	
External Beam Pelvic Nodes Dose		
44–50.4 Gy	8	
None	5	Nodal treatment is difficult to justify based on randomized data so it is reasonable to not do it, although some prefer to offer it. RTOG 0924 addressing this issue is ongoing.
External Beam Prostate Dose (including pelvic dose) (assumes hormone therapy given)		
75–78 Gy	7	
>78 Gy	8	
>82 Gy	6	
Hypofractionated doses (2.5 Gy to 70 Gy or 3.1 Gy to 62 Gy)	6	This dose is similar to Variant 2.
Brachytherapy		
LDR/HDR alone	3	
LDR/HDR + EBRT	3	
LDR/HDR + EBRT + ADT (≤6 months)	5	This is from a case series, as reviewed by Grimm et al.
LDR/HDR + EBRT + ADT (12 months)	6	This from the ASCENDE-RT trial.
LDR/HDR + EBRT + ADT (24 months)	8	
Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**		

Clinical Condition: **Locally Advanced, High-Risk Prostate Cancer**

Variant 4: **63-year-old man, PSA 8, T1c, Gleason 4+3=7 in 4/6 cores (R), 4+4=8 in 1/6 core (R).**

Treatment	Rating	Comments
Endocrine Therapy Mixed with EBRT		
ADT 6 months	6	There is some evidence showing that 6 months of ADT is a preferred option. Not all high-risk patients need to be treated the same.
ADT 12 months	6	
ADT 18 months	7	
ADT 24–28 months	8	
ADT 36 months	7	
External Beam Pelvic Nodes Dose		
44–50.4 Gy	5	
None	6	
External Beam Prostate Dose (including pelvic dose) (assumes hormone therapy given)		
75–78 Gy	7	
>78 Gy	8	
>82 Gy	6	
Hypofractionated doses (2.5 Gy to 70 Gy or 3.1 Gy to 62 Gy)	6	
Brachytherapy		
LDR/HDR alone	4	This option is used with MRI showing no extraprostatic extension or seminal vesicle involvement.
LDR/HDR + EBRT	5	This option is similar to Variant 1, but it is more reasonable to not give ADT because this case is lower risk in comparison.
LDR/HDR + EBRT + ADT (≤6 months)	6	
LDR/HDR + EBRT + ADT (12 months)	7	
LDR/HDR + EBRT + ADT (24 months)	7	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		