Adjuvant Therapy in High-Risk Prostate Cancer

Jeffrey Shevach, MD, Parul Chaudhuri, MD, and Alicia K. Morgans, MD, MPH

The authors are affiliated with the Northwestern University Feinberg School of Medicine in Chicago, Illinois. Dr Shevach is a resident in the Department of Medicine, Dr Chaudhuri is a health system clinician in the Department of Medicine, Division of Hospital Medicine, and Dr Morgans is an associate professor of medicine and is also affiliated with the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

Corresponding author:
Alicia K. Morgans, MD, MPH
Associate Professor of Medicine
Northwestern University Feinberg School of Medicine
676 N St Clair, Suite 850
Chicago, IL 60611
Tel: (312) 695-2381
Fax: (312) 695-6189
E-mail: alicia.morgans@northwestern.edu

Keywords
Adjuvant therapy, CAPRA-S, Decipher, high-risk prostate cancer, localized prostate cancer

Abstract: Although the prognosis in patients with localized prostate cancer is positive overall, high-risk localized disease is responsible for significant cancer-related morbidity and mortality following local treatment failure. Despite recent medical advances in advanced prostate cancer, the role of systemic adjuvant therapy has remained relatively stagnant over the last few decades for patients with high-risk disease, consisting of only androgen deprivation therapy. Novel methods of risk stratification, however, based on traditional clinicopathologic features combined with genomic data, will allow investigators to study adjuvant therapy with more precision in high-risk populations. Additionally, the rise of novel hormonal therapies may provide oncologists with more efficacious drugs in the adjuvant setting, potentially leading to effective adjuvant therapy options for clinicians treating men with high-risk localized prostate cancer.

Introduction

Prostate cancer is the most common noncutaneous cancer diagnosed in men in the United States, and is second only to lung cancer in cancer-specific mortality.[1] It is a heterogeneous disease with significant variation in patient outcomes, even among patients diagnosed with the same stage of disease. Roughly 80% of prostate cancers are localized at time of diagnosis.[2] Owing to the high burden of adverse effects from local and systemic treatments for prostate cancer, combined with competing causes of morbidity and mortality in this aging patient population, proper risk stratification is necessary. D'Amico and colleagues provided the most significant initial contribution with their 1998 risk classification system.[3] Since then, multiple additional risk classification systems have been developed and used, most commonly relying upon data from clinical tumor stage, Gleason score (GS), and prostate-specific antigen (PSA) level. An estimated 15% of localized disease is high-risk.[4]

Effective local treatment with radical prostatectomy or radiation therapy (RT) in low-risk patients is associated with a positive long-term prognosis and prostate cancer–specific mortality rates of less than 5%.[5,6] High-risk prostate cancer, however, is associated with significantly higher disease-specific mortality despite local therapies.[6-8] Adjuvant systemic therapy approaches to address this have

remained relatively unchanged for the past few decades. Standard-of-care approaches include adjuvant treatment with androgen deprivation therapy (ADT) for patients with nodal metastases, based on a randomized trial of 100 patients by Messing and colleagues.[9] In high- and intermediate-risk patients receiving RT, neoadjuvant or adjuvant ADT is also considered standard of care, though the optimal duration of therapy is still being evaluated.[10]

This review summarizes the evidence for and against systemic adjuvant therapy in high-risk prostate cancer, and describes ongoing investigations of strategies for risk stratification for optimal targeting of adjuvant treatment.

Adjuvant Therapy Following Radical Prostatectomy

Chemotherapy

Two trials have assessed the use of systemic therapies to reduce rates of recurrence in high-risk patients in the post-prostatectomy setting. The SPCG-12 trial (Scandinavian Prostate Cancer Group 12) was a multinational phase 3 study that randomly assigned 459 patients with high-risk disease—as defined by clinical features (≥50% risk of progression by nomogram)—to receive 6 cycles of adjuvant docetaxel every 3 weeks or surveillance following prostatectomy.[11] There was no significant difference in time to biochemical recurrence (PSA >0.5 ng/mL) between the arms, and restricted mean survival time was 43 months in the docetaxel arm compared with 46 months in the surveillance arm (*P*=.06). The analysis was limited by the fact that approximately one-third of patients (30% in the docetaxel arm and 35% in the surveillance arm) did not receive lymph node dissection, which increased the risk for local recurrence in this high-risk population. Furthermore, 12% of patients received salvage radiation or hormonal therapy prior to meeting the primary endpoint, although the analysis was similar when these patients were excluded.

The VA Cooperative Studies Group Study #553 (Chemotherapy After Prostatectomy for High-Risk Prostate Carcinoma) also evaluated the efficacy of adjuvant docetaxel and prednisone vs standard follow-up after radical prostatectomy in patients with high-risk prostate cancer as identified by clinical characteristics.[12] The study accrued patients slowly, and was closed prior to reaching the target accrual. In total, 297 patients with high-risk prostate cancer were randomly assigned to receive 6 cycles of docetaxel every 3 weeks with continuous prednisone but without ADT. At a median follow-up of 62.4 months, no statistically significant difference in median progression-free survival (PFS) was found between the 2 groups (55.5 vs 45.6 months; log-rank *P*=.26). However, in subgroup analyses, patients with at least pT3b tumor staging and African American men did derive benefit from treatment with docetaxel (hazard ratio [HR], 0.58; 95% CI, 0.34-0.98; *P*=.04 and HR, 0.54; 95% CI, 0.29-1.01; *P*=.054, for ≥pT3b and African American men, respectively).

Hormone Therapy

Messing and colleagues evaluated the efficacy of adjuvant ADT in patients who underwent radical prostatectomy and lymph node dissection for nodal metastases.[9] A total of 100 patients were randomly assigned to receive either immediate ADT following surgery, or delayed ADT that was initiated after evidence of disease progression. At 11.9 years of follow-up, patients who received immediate ADT—goserelin (Zoladex, AstraZeneca) or bilateral orchiectomy—had statistically significantly improved overall survival (OS; HR, 1.84; 95% CI, 1.01-3.35; *P*=.04), prostate cancer–specific survival (PCSS; HR, 4.09; 95% CI, 1.76-9.49; *P*=.0004), and PFS (HR, 3.42; 95% CI, 1.96-5.98; *P*<.0001).

In patients with locally advanced (T3 or T4), lymph node–negative prostate cancer, adjuvant therapy following radical prostatectomy with first-generation antiandrogens was also assessed. Wirth and colleagues studied the efficacy of adjuvant flutamide in patients with locally advanced lymph node–negative prostate cancer (stage pT3-4pN0) by randomly assigning patients to 750 mg of flutamide daily vs surveillance. A total of 309 patients were evaluated after a median follow-up of 6.1 years.[13] PFS was improved in patients receiving flutamide vs surveillance (HR, 0.51; 95% CI, 0.32-0.81; *P*=.0041), but no difference in OS was seen (HR, 1.04; 95% CI, 0.53-2.02; *P*=.92). Flutamide was associated with significant toxicity, with 43% and 3% of patients withdrawing from the flutamide and placebo groups, respectively, for toxicity.

The Casodex Early Prostate Cancer Trialists' Group conducted 3 separate randomized, double-blind, placebo-controlled trials designed and powered to be analyzed together to evaluate the efficacy of early bicalutamide administration in localized or locally advanced prostate cancer.[14] The trials took place in different geographic locations, with a North American trial,[15] a Scandinavian trial,[16] and a trial recruiting patients from Australia, South Africa, Israel, Mexico, and Europe.[17] Patients in the combined analysis were randomly assigned to receive either placebo or bicalutamide at 150 mg daily in addition to standard-of-care treatment. Patients were treated for 2 years or until disease progression in the North American trial, whereas patients in the other trials received the randomized therapy until disease progression. Among the 8113 patients recruited, 4454 underwent radical prostatectomy. The primary endpoints were PFS and OS, and median follow-up was 9.7 years. In patients with locally

advanced disease (T3-4 or node-positive) who underwent prostatectomy (n=1719), there were no statistically significant differences between the bicalutamide and placebo groups with respect to PFS (HR, 0.85; 95% CI, 0.71-1.01; *P*=.065) or OS (HR, 1.03; 95% CI, 0.84-1.26; *P*=.817). Although patients with nodal metastasis were not excluded from this trial, fewer than 2% of patients in this study had node-positive disease. There did not appear to be a benefit to adjuvant treatment in postsurgical patients with negative nodal involvement in this study, in which 98% of patients were node-negative. Thus, predominantly driven by this and the Messing data, the consensus opinion regarding high-risk patients undergoing radical prostatectomy is that adjuvant ADT appears to be beneficial only in the subgroup of patients with nodal metastases.

Newer data from Hussain and colleagues suggest a potential benefit from adjuvant ADT following radical prostatectomy in a subset of patients with high-risk disease in the Southwest Oncology Group (SWOG) S9921 study (Hormone Therapy With or Without Mitoxantrone and Prednisone in Patients Who Have Undergone Radical Prostatectomy for Prostate Cancer).[18] The included men had cT1-3N0 disease and a postoperative PSA of no more than 0.02 ng/mL, with 1 or more of the following clinical features consistent with high-risk disease: GS of at least 8; pT3b, pT4, or pN+; pathologic GS of 7 and positive margins; or any of the following in patients receiving neoadjuvant ADT: PSA greater than 15 ng/mL, biopsy GS greater than 7, or PSA greater than 10 ng/mL plus biopsy GS greater than 6. In this phase 3 study, men were randomly assigned to receive 2 years of ADT with or without 6 cycles of mitoxantrone and prednisone in the postsurgical adjuvant setting. The study was ultimately discontinued early owing to an elevated incidence of acute myeloid leukemia in the mitoxantrone and prednisone group as compared with placebo.[19] At a median follow-up of 11.2 years, 10-year OS was 87% in the ADT/mitoxantrone arm and 86% in the ADT-alone arm, which is greater than the estimated survival calculated based on historical controls (50%) for 2 years of ADT. However, owing to the lack of an arm receiving no treatment, no definitive conclusions can be drawn regarding the benefit from ADT alone in the adjuvant setting.

Like S9921, TAX-3501 (Adjuvant Leuprolide With or Without Docetaxel in High Risk Prostate Cancer After Radical Prostatectomy) also evaluated combined adjuvant chemotherapy and ADT.[18,20] TAX-3501 was a 2 × 2 factorial study that randomly assigned 228 of a planned 1696 patients to receive immediate adjuvant or deferred leuprolide with or without docetaxel following radical prostatectomy. The study was stopped prematurely owing to poor accrual. No significant difference in PFS among any of the 4 groups (immediate hormone therapy without docetaxel, immediate hormone therapy with docetaxel, delayed hormone therapy without docetaxel, and delayed hormone therapy with docetaxel) was seen after a median follow-up of 3.4 years, although the study was substantially underpowered.

Adjuvant Therapy Following Radiation Therapy

Hormone Therapy: Radiation Therapy Alone vs Combined Therapy

Several randomized trials have assessed the benefits of adjuvant ADT in patients receiving RT for high-risk prostate cancer. The trials have heterogeneous patient populations, with different definitions of high-risk disease, and several include patients with high-risk localized and locally advanced prostate cancer in a single study. The European Organisation for Research and Treatment of Cancer's EORTC 22863 trial (Radiation Therapy With or Without Goserelin and Cyproterone in Treating Patients With Prostate Cancer) randomly assigned 415 men undergoing definitive RT for high-risk prostate cancer (T1-2 and World Health Organization histologic grade 3 or T3-4 disease without nodal metastasis) to treatment with 3 years of ADT vs observation.[21] The primary endpoint was disease-free survival (DFS). Long-term results, with a median follow-up of 9.1 years, demonstrated superior outcomes in the arm receiving combined RT and ADT with respect to 10-year DFS (47.7% vs 22.7%; HR, 0.42; 95% CI, 0.33-0.55; *P*<.0001), 10-year OS (58.1% vs 39.8%; HR, 0.60; 95% CI, 0.45-0.80; *P*=.0004), and 10-year PCSS (30.4% vs 10.3%; HR, 0.38; 95% CI, 0.24-0.60; *P*<.0001).[22]

Simultaneously, the Radiation Therapy Oncology Group (RTOG) 85-31 trial randomly assigned 977 men with high-risk disease (cT3/pT3 disease or regional nodal metastases) but without bulky primary tumors to RT alone or RT and adjuvant goserelin starting near RT completion and continuing until disease progression.[23] The study allowed enrollment of patients who had undergone prior prostatectomy. After a median follow-up of 7.6 years, 10-year OS (49% vs 39%; *P*=.002), prostate cancer–specific mortality (16% vs 22%; *P*=.0052), local failure rate (23% vs 38%; *P*<.0001), and distant failure rate (24% vs 39%; *P*<.0001) all favored the arm undergoing adjuvant ADT.[24]

The Casodex Early Prostate Cancer Trialists' Group study of adjuvant bicalutamide also assessed the use of ADT in the context of RT. Of the 8113 patients enrolled, 1370 underwent RT with curative intent, with 305 of those patients having locally advanced disease (T3-4 or node-positive).[14] After a median 9.7 years of follow-up,

55.3% of patients in the bicalutamide arm vs 71.5% of those in the placebo arm progressed on therapy (HR, 0.62; 95% CI, 0.47-0.83; *P*=.001). OS favored patients in the bicalutamide arm, with 44.7% of patients in the bicalutamide arm dying, compared with 56.9% of patients receiving placebo (HR, 0.70; 95% CI, 0.51-0.97; *P*=.031). Adjuvant bicalutamide made no difference in the PFS or OS in patients with localized disease, but no data were available for patients based on other risk stratification.

D'Amico and colleagues randomly assigned 206 men with intermediate- or high-risk prostate cancer (T1b-2b, PSA >10 ng/mL, GS >7, or evidence of extracapsular extension or seminal vesical invasion on endorectal magnetic resonance imaging) to receive either RT alone or 6 months of ADT with a gonadotropin-releasing hormone (GnRH) agonist and flutamide starting 2 months prior to initiation of RT.[25] After a median follow-up of 7.6 years, the mortality risk was higher in the group receiving RT alone (HR for death, 1.8; 95% CI, 1.1-2.9; *P*=.01), which was driven by prostate cancer–specific mortality (HR, 4.1; 95% CI, 1.4-12.1; *P*=.01). In a post-hoc subgroup analysis, men with high-risk disease who received RT alone trended toward worse survival (*P*=.06).[26] However, in patients with moderate or severe comorbidity, the increased risk of mortality was driven by cardiovascular disease, and among patients with minimal to no comorbid illnesses, the high-risk group experienced the greatest benefit of ADT at 7 years (88.9% vs 51.2%; *P*=.007).[25,26]

EORTC 22991 (Radiation Therapy With or Without Bicalutamide and Goserelin in Treating Patients With Prostate Cancer) randomly assigned 819 patients with intermediate- or high-risk localized prostate cancer to receive either RT alone or RT and 6 months of concurrent and adjuvant ADT with goserelin.[27] With a median follow-up of 7.2 years, treatment with combined RT and ADT was associated with significantly improved biochemical DFS (primary endpoint: HR, 0.52; 95% CI, 0.41-0.66; *P*<.001) and PFS (HR, 0.63; 95% CI, 0.48-0.84; *P*=.001). Notably, outcomes were not stratified according to disease risk classification, and OS data have not matured.

Hormone Therapy: Duration

Several additional studies have assessed the optimal duration of adjuvant ADT in each patient population receiving RT. Both RTOG 92-02 (Goserelin, Flutamine, and Radiation Therapy in Treating Patients With Locally Advanced Prostate Cancer) and DART01 (Clinical Trials of Adjuvant Androgen Deprivation in Localized Prostate Cancer) compared the benefit of ADT in the adjuvant setting in patients who received 4 months of neoadjuvant/concurrent ADT.[28,29] RTOG 92-02 randomly assigned 1554 patients with locally advanced prostate cancer (T2c-T4 or node-positive disease) who had undergone 4 months of neoadjuvant and concurrent ADT to observation following RT or 2 years of additional ADT.[30] Long-term results, with a median follow-up of 19.6 years, demonstrated that 15-year treatment outcomes favored the group receiving 2 years of ADT, including DFS (HR, 0.71; 95% CI, 0.64-0.79; *P*<.0001), PCSS (HR, 0.70; 95% CI, 0.55-0.89; *P*=.003), and OS (HR, 0.88; 95% CI, 0.79-0.98; *P*=.03).

DART01 randomly assigned 355 men with T1c-3b node-negative localized prostate cancer with intermediate- or high-risk features who completed 4 months of neoadjuvant/concurrent ADT with RT to receive observation or an additional 2 years of ADT.[29] At a median follow-up of 5 years, long-term ADT was superior to observation with respect to 5-year biochemical DFS (90% vs 81%; HR, 1.88; 95% CI, 1.12-3.15; *P*=.01), OS (95% vs 86%; HR, 2.48; 95% CI, 1.31-4.68; *P*=.009), and metastasis-free survival (94% vs 83%; HR, 2.31; 95% CI, 1.23-3.85; *P*=.01). Long-term ADT had a more prominent benefit in these outcomes in patients with high-risk disease. Taken together, RTOG 92-02 and DART01 demonstrated the benefit of long-term adjuvant ADT beyond neoadjuvant/concurrent therapy for high-risk patients.

EORTC 22961 (Hormone Therapy in Treating Patients With Advanced Prostate Cancer) included 1113 men with locally advanced, nonmetastatic prostate cancer (T1c-2b with pN1-N2 or T2c-4 N0-N2) who received 6 months of combined ADT and RT, with ADT initiated on the first day of RT.[31] Men who did not experience progression following 6 months of ADT (n=970) were randomly assigned to observation or 2.5 years of the GnRH agonist triptorelin. The trial was designed as a noninferiority study, with a noninferiority margin of 1.35. An initial analysis demonstrated that noninferiority could not be confirmed, with an HR for death of 1.43 favoring long-term ADT.[32] After 6.4 years of median follow-up, final analysis demonstrated that short-term ADT resulted in higher mortality and prostate cancer–specific mortality when compared with long-term ADT in this high-risk subgroup of patients.[31]

The above trials confirm the benefit of long-term ADT (28 to 36 months) over short-term ADT (4 to 6 months) in patients with high-risk localized prostate cancer. The PCS IV trial (Duration of Androgen Blockade Combined With Pelvic Irradiation in Prostate Cancers) attempted to determine whether duration of ADT could be limited to 18 months.[33] PCS IV randomly assigned 630 patients with high-risk, node-negative disease (T3-4, PSA >20 ng/dL or GS >8) undergoing RT to receive either 18 or 36 months of ADT with goserelin starting 4 months prior to initiation of RT. It was designed as a superiority study, with primary endpoints of OS and quality of life.

There was no significant difference between the 2 groups with respect to OS (HR, 1.02; 95% CI, 0.81-1.29; *P*=.7) or PCSS. Notably, 47% of patients in the 36-month arm did not receive the full course of ADT, and 24% of patients in that arm received 18 months or fewer of ADT, potentially biasing a difference in duration to the null.[33,34] In a post-hoc analysis, the authors performed an adjusted non–intention-to-treat analysis that identified an upper bound of 1.67, failing to meet the specified noninferiority bound. Taken as a whole, this study demonstrates that although 36 months of ADT does not appear superior to 18 months, there is work to be done in terms of firmly demonstrating noninferiority of shorter durations of ADT, particularly for the high-risk population included in this study.

RTOG 94-13 (Radiation Therapy and Hormone Therapy in Treating Patients With Prostate Cancer) compared 2 different styles of short-term ADT (4 months of neoadjuvant/concurrent vs 4 months of post-RT adjuvant therapy) and whole-pelvis vs prostate RT in a 2 × 2 factorial trial.[35] A total of 1323 patients with a risk of nodal involvement of at least 15% or tumors of T2c-4 and GS of at least 6 were randomly assigned to treatment. There were no statistically significant differences in OS, PFS, local failure rate, or distant metastasis rate between neoadjuvant or adjuvant ADT. Additionally, there were no statistically significant differences among the 4 randomized groups, although the authors noted that the study was not powered to detect such differences.

Chemotherapy

Although the role of adjuvant ADT in patients receiving definitive RT has been demonstrated, the role of adjuvant chemotherapy has not been established. The RTOG 05-21 trial (Hormone Therapy and Radiation Therapy or Hormone Therapy and Radiation Therapy Followed by Docetaxel and Prednisone in Treating Patients With Localized Prostate Cancer) assessed the addition of docetaxel and prednisone to 24 months of ADT and RT in patients with high-risk prostate cancer.[36] Docetaxel was administered every 3 weeks for 6 cycles along with daily prednisone starting 28 days after completion of RT. A total of 562 patients were randomly assigned to treatment. At a median of 5.5 years of follow-up, 5-year DFS was 73% in the chemotherapy arm vs 66% in the control arm (HR, 0.76; 95% CI, 0.57-1.00; 2-sided *P*=.05) and 4-year OS was 93% in the chemotherapy arm vs 89% in the control arm (HR, 0.68; 95% CI, 0.44-1.03; 1-sided *P*=.03). Although these are intriguing results, caution is warranted when interpreting the OS analysis because only 41% of deaths were attributable to prostate cancer, and the control arm experienced more deaths attributable to other or unknown causes than the chemotherapy arm (32 vs 20). The publication of these results in a peer-reviewed journal is pending.

The RTOG 99-02 trial (Hormone Therapy Plus Radiation Therapy With or Without Combination Chemotherapy in Treating Patients With Prostate Cancer) randomly assigned 397 patients with high-risk prostate cancer (PSA, 20-100 ng/mL and GS >7 or cT2 and GS >8) to receive RT with 24 months of ADT with or without paclitaxel, estramustine, and etoposide for 4 cycles.[37] The trial closed early owing to excess thromboembolic events in the chemotherapy arm, and the final 10-year results after a median follow-up of 9.2 years demonstrated no differences in biochemical recurrence, local or metastatic progression, DFS, or OS.

SPCG-13 (Adjuvant Treatment of Prostate Cancer With Docetaxel or Not After Radical Radiotherapy) randomly assigned 376 patients undergoing RT and ADT for intermediate- or high-risk prostate cancer to receive 6 cycles of adjuvant docetaxel every 3 weeks or observation.[38] There was no difference in the primary outcome of biochemical DFS at a median follow-up of 5 years, with 31% of patients in the chemotherapy arm experiencing biochemical recurrence compared with 30.3% of patients in the observation arm (*P*=.631). Taken together, the role of adjuvant chemotherapy in high-risk patients receiving radiation is still undetermined, though the data suggest potential benefit for carefully selected high-risk patients.

Ongoing Trials and Future Directions

Among patients with high-risk localized prostate cancer, long-term adjuvant ADT is recommended for those undergoing RT and those with node-positive disease.[10] A new and exciting era is arriving in prostate cancer treatment, with several randomized trials demonstrating a survival benefit for novel antiandrogens, biosynthesis inhibitors, and early chemotherapy treatment in hormone-sensitive and castration-resistant disease.[39-44] The multiarm STAMPEDE trial (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy) included a subset of patients without radiographically identifiable metastatic disease who may benefit from the addition of next-generation hormone therapy with abiraterone acetate. In a post-hoc subset analysis of 384 patients in the STAMPEDE trial treated with RT and ADT for high-risk localized node-positive nonmetastatic disease, the addition of abiraterone acetate improved several outcomes, including OS.[39,45] Patients with localized node-negative disease did not appear to benefit from the addition of abiraterone in this analysis, though the study was underpowered to assess this definitively. Additional clinical trials evaluating the efficacy of

Table. Ongoing Trials of Adjuvant Therapy in High-Risk Prostate Cancer

Trial Name	NCT Number	Inclusion Criteria for High-Risk Prostate Cancer	Comparison Arms		Primary Outcome(s)
			Control	Experimental	
Neoadjuvant and Adjuvant Abiraterone Acetate + Apalutamide Prostate Cancer Undergoing Prostatectomy	NCT02903368	GS ≥4 + 3 = 7 OR GS 3 + 4 = 7 AND at least 1 of the following: PSA >20 ng/dL or T3 disease (determined by MRI)	Prior to prostatectomy, 6 mo of neoadjuvant leuprolide, abiraterone acetate, and prednisone	Prior to prostatectomy, 6 mo of neoadjuvant leuprolide, abiraterone acetate, prednisone, and apalutamide	2-y minimal residual disease 2-y pathologic complete response
			Post-prostatectomy, observation	Post-prostatectomy, 12 mo of adjuvant leuprolide, abiraterone acetate, prednisone, and apalutamide	
ENZARAD	NCT02446444	GS 8-10 OR GS 4 + 3 AND clinical T2b-4 AND PSA >20 ng/mL OR N1 disease (involvement of lymph nodes at or below the bifurcation of the common iliac arteries)	RT plus traditional nonsteroidal antiandrogen for 6 mo and GnRH agonist for 24 mo from randomization	RT plus enzalutamide 160 mg daily and GnRH agonist for 24 mo from randomization	5-y overall survival
ATLAS	NCT02531516	GS ≥8 and ≤cT2c OR GS ≥7, PSA ≥20 ng/mL, and ≥cT2c	RT plus 30 mo of GnRH agonist and placebo	RT plus 30 mo of GnRH agonist and apalutamide	Metastasis-free survival
Abiraterone, Radiotherapy and Short-Term Androgen Deprivation in Unfavorable Localized Prostate Cancer	NCT01717053	GS 7 with PSA ≤20 ng/mL and clinical T1-2, OR GS 8-10, PSA ≤20 ng/mL and clinical T1-2a, OR PSA 10.1-40 ng/mL with GS <7 and clinical T1-2, OR Clinical T3 with GS <7 and PSA ≤10 ng/mL	None	RT plus 6 mo of abiraterone acetate/prednisone and GnRH agonist	Rate of undetectable PSA (<0.1 ng/mL) at 1 y
AASUR in High Risk Prostate Cancer	NCT02772588	GS 8-10 PSA ≥20 ng/mL within 2 mo prior to registration	None	Ultrafractionated stereotactic RT plus 6 mo of leuprolide, abiraterone, and apalutamide	Proportion of patients with biochemical failure
FORMULA-509	NCT03141671	GS 8-10 PSA >0.5 pN + pT3 or pT4	RP and salvage RT plus 6 mo of GnRH agonist and bicalutamide	RP and salvage RT plus 6 mo of GnRH agonist, abiraterone acetate/prednisone, and apalutamide	PSA PFS (up to 5 y)

GnRH, gonadotropin-releasing hormone; GS, Gleason score; mo, months; MRI, magnetic resonance imaging; PFS, progression-free survival; PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiation therapy; y, years.

novel hormonal therapy as adjuvant therapy in high-risk, localized prostate cancer are ongoing (Table).

Although newer pharmacotherapies hold promise in finding ways to fill in the gap of adjuvant therapy in prostate cancer, more precise methods of patient risk stratification are necessary. Basing adjuvant therapy on nodal status alone omits a significant proportion of patients whose disease will recur following radical prostatectomy, and may lead to overtreatment in other patients. One retrospective study examined several clinicopathologic factors

related to radical prostatectomy to determine their impact on metastasis free-survival in patients with biochemical recurrence.[46] At 8 years of median follow-up in this study of 450 patients, metastases developed in just over half of the patients with lymph node involvement (n=94) and almost a quarter of the patients without lymph node involvement, suggesting that other factors are driving metastatic disease in a significant proportion of men.

The CAPRA-S (UCSF Cancer of the Prostate Risk Assessment Postsurgical) score is a risk score that incorporates clinicopathologic data from the time of radical prostatectomy, including PSA, pathologic GS, surgical margin, extracapsular extension, seminal vesicle invasion, and lymph node involvement.[47] In the original study, which included 3837 patients from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database who had undergone radical prostatectomy, the mean HR for CAPRA-S was 1.54, meaning that every 2-point increase in the CAPRA-S score represented a 2.4-fold risk for recurrence following prostatectomy. The test performed well when compared with the Stephenson nomogram.[48] Three-year PFS ranged from 89.8% to 96.3% in the group scoring 0 to 2, from 63.1% to 80.7% in the group scoring 3 to 5, and 7.3% to 50.9% in the group scoring 6 or higher.[47] The score was later validated in the Shared Equal Access Regional Cancer Hospital (SEARCH) database, with a concordance index of 0.73 for predicting disease recurrence and of 0.85 for predicting prostate cancer–specific mortality.[49]

Several genome-based risk models recently have been developed to identify patients at high risk for metastasis following prostatectomy. The Decipher score is a genomic classifier comprised of 22 genomic markers initially derived from a set of 545 prostatectomy samples from the Mayo Clinic.[50] The genomic classifier outperformed a simultaneously derived clinical classifier in an initial training set (359 samples) and the validation set, with an area under the curve (AUC) of 0.75 in the training set against an AUC of 0.69 in the validation set. The GS had an AUC of 0.65 in the validation set. High Decipher scores predicted a clinically and statistically significant decrease in PCSS and OS when compared with low Decipher scores after a median of 18.2 years of follow-up. In external populations, Decipher outperformed clinicopathologic risk stratification in predicting metastasis.[51-53] Combining Decipher with validated clinical risk models, including CAPRA-S and National Comprehensive Cancer Network risk groups, has improved accuracy in predicting cancer metastasis and prostate cancer–specific mortality in patients undergoing prostatectomy.[54-56] Several other genomic-based risk models have also improved upon clinical risk stratification tools in predicting outcomes following radical prostatectomy.[57-62]

Genomic risk models may enable more precise risk stratification if their predictive value is validated in prospective, randomized controlled trials. If validated, these predictive strategies could affect adjuvant treatment decisions, leading to increased intensity of treatment for appropriate patients and de-escalation of treatment for others. Several studies examined practicing urologists' and radiation oncologists' adjuvant treatment recommendations for a series of de-identified patients before and after knowledge of genomic classifier results; 31% to 53% of patients would have had their adjuvant treatment recommendations changed by genomic classifier results.[63-65] Further efforts to validate molecular assays in prospective studies are critical.

Conclusions

High-risk, localized prostate cancer continues to carry a significant burden of morbidity and mortality, with ADT remaining the only effective adjuvant therapy to be paired with prostatectomy or RT at this time. Future use of biopsy or surgery specimen–based genomic risk stratification models may allow clinicians to select patients with the highest risk of metastasis and prostate cancer–specific mortality so that men with high-risk disease can receive effective adjuvant treatment. Through a combination of superior patient selection and more effective adjuvant therapy, we may see increased rates of cure from high-risk localized disease, and reduced morbidity and mortality from overtreatment of men with lower-risk disease.

Disclosures

Dr Morgans has received honoraria from Astellas, AstraZeneca, Bayer, Genentech, Janssen, and Sanofi for consulting services and advisory boards, and has received research funding from Bayer, Seattle Genetics, Astellas, and AstraZeneca. Drs Shevach and Chaudhuri have no conflicts of interest to report.

References

1. U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2017 submission data (1999-2015): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz. Accessed July 30, 2018.

2. Steele CB, Li J, Huang B, Weir HK. Prostate cancer survival in the United States by race and stage (2001-2009): findings from the CONCORD-2 study. *Cancer*. 2017;123(suppl 24):5160-5177.

3. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280(11): 969-974.

4. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol*. 2010;28(7): 1117-1123.

5. Kim MM, Hoffman KE, Levy LB, et al. Prostate cancer-specific mortality after definitive radiation therapy: who dies of disease? *Eur J Cancer.* 2012;48(11):1664-1671.
6. Stephenson AJ, Kattan MW, Eastham JA, et al. Prostate cancer-specific mortality after radical prostatectomy for patients treated in the prostate-specific antigen era. *J Clin Oncol*. 2009;27(26):4300-4305.
7. Fosså SD, Wiklund F, Klepp O, et al; The Scandinavian Prostate Cancer Group-7 Investigators. Ten- and 15-yr prostate cancer-specific mortality in patients with nonmetastatic locally advanced or aggressive intermediate prostate cancer, randomized to lifelong endocrine treatment alone or combined with radiotherapy: final results of The Scandinavian Prostate Cancer Group-7. *Eur Urol*. 2016;70(4):684-691.
8. Mason MD, Parulekar WR, Sydes MR, et al. Final report of the Intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. *J Clin Oncol*. 2015;33(19):2143-2150.
9. Messing EM, Manola J, Yao J, et al; Eastern Cooperative Oncology Group study EST 3886. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol*. 2006;7(6):472-479.
10. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer. v.3.2018. 2018. https://www.nccn.org/professionals/physician_gls/pdf/prostate_blocks.pdf. Updated August 8, Accessed October 16, 2018.
11. Ahlgren GM, Flodgren P, Tammela TLJ, et al; Investigators of the Scandinavian Prostate Cancer Study Number 12. Docetaxel versus surveillance after radical prostatectomy for high-risk prostate cancer: results from the prospective randomised, open-label phase 3 Scandinavian Prostate Cancer Group 12 trial. *Eur Urol*. 2018;73(6):870-876.
12. Lin D, Garzotto M, Aronson W, et al. VA CSP#553 Chemotherapy after prostatectomy (CAP) for high risk prostate carcinoma: a phase III randomized study [AUA abstract PI-LBA06]. *J Urol*. 2016;195(4)(suppl):e1071.
13. Wirth MP, Weissbach L, Marx FJ, et al. Prospective randomized trial comparing flutamide as adjuvant treatment versus observation after radical prostatectomy for locally advanced, lymph node-negative prostate cancer. *Eur Urol*. 2004;45(3):267-270.
14. Iversen P, McLeod DG, See WA, Morris T, Armstrong J, Wirth MP; Casodex Early Prostate Cancer Trialists' Group. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. *BJU Int*. 2010;105(8):1074-1081.
15. Hussain M, Tangen CM, Thompson IM Jr, et al. Phase III Intergroup trial of adjuvant androgen deprivation with or without mitoxantrone plus prednisone in patients with high-risk prostate cancer after radical prostatectomy: SWOG S9921. *J Clin Oncol*. 2018;36(15):1498-1504.
16. Flaig TW, Tangen CM, Hussain MH, et al; Southwest Oncology Group. Randomization reveals unexpected acute leukemias in Southwest Oncology Group prostate cancer trial. *J Clin Oncol*. 2008;26(9):1532-1536.
17. Schweizer MT, Huang P, Kattan MW, et al. Adjuvant leuprolide with or without docetaxel in patients with high-risk prostate cancer after radical prostatectomy (TAX-3501): important lessons for future trials. *Cancer*. 2013;119(20):3610-3618.
18. Bolla M, Gonzalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med*. 1997;337(5):295-300.
19. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*. 2010;11(11):1066-1073.
20. Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. *J Clin Oncol*. 1997;15(3):1013-1021.
21. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys*. 2005;61(5):1285-1290.
22. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA*. 2008;299(3):289-295.
23. Nguyen PL, Chen MH, Beard CJ, et al. Radiation with or without 6 months of androgen suppression therapy in intermediate- and high-risk clinically localized prostate cancer: a postrandomization analysis by risk group. *Int J Radiat Oncol Biol Phys*. 2010;77(4):1046-1052.
24. Bolla M, Maingon P, Carrie C, et al. Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: results of EORTC Trial 22991. *J Clin Oncol*. 2016;34(15):1748-1756.
25. Hanks GE, Pajak TF, Porter A, et al; Radiation Therapy Oncology Group. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol*. 2003;21(21):3972-3978.
26. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy with short-term or long-term androgen deprivation in localised prostate cancer (DART01/05 GICOR): a randomised, controlled, phase 3 trial. *Lancet Oncol*. 2015;16(3):320-327.
27. Lawton CAF, Lin X, Hanks GE, et al. Duration of androgen deprivation in locally advanced prostate cancer: long-term update of NRG Oncology RTOG 9202. *Int J Radiat Oncol Biol Phys*. 2017;98(2):296-303.
28. Bolla M, de Reijke TM, Van Tienhoven G, et al; EORTC Radiation Oncology Group and Genito-Urinary Tract Cancer Group. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009;360(24):2516-2527.
29. Bolla M, van Tienhoven G, De Reijke TM, et al. Concomitant and adjuvant androgen deprivation (ADT) with external beam irradiation (RT) for locally advanced prostate cancer: 6 months versus 3 years ADT—results of the randomized EORTC Phase III trial 22961 [ASCO abstract 5014]. *J Clin Oncol*. 2007;25(18)(suppl).
30. Nabid A, Carrier N, Martin AG, et al. Duration of androgen deprivation therapy in high-risk prostate cancer: a randomized phase III trial. *Eur Urol*. 2018;74(4):432-441.
31. Xie W, D'Amico AV. Eighteen months of androgen deprivation therapy in men with high-risk prostate cancer and the risk of death. *Eur Urol*. 2018;74(4):442-443.
32. Lawton CA, DeSilvio M, Roach M III, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys*. 2007;69(3):646-655.
33. Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521) [ASCO abstract LBA5002]. *J Clin Oncol*. 2015;33(18)(suppl).
34. Rosenthal SA, Hunt D, Sartor AO, et al. A phase 3 trial of 2 years of androgen suppression and radiation therapy with or without adjuvant chemotherapy for high-risk prostate cancer: final results of radiation therapy oncology group phase 3 randomized trial NRG Oncology RTOG 9902. *Int J Radiat Oncol Biol Phys*. 2015;93(2):294-302.
35. Kellokumpu-Lehtinen PLI, Hjälm-Eriksson M, Astrom L, et al. A randomized phase III trial between adjuvant docetaxel and surveillance after radical radiotherapy for intermediate and high risk prostate cancer: results of SPCG-13 trial [ASCO abstract 5000]. *J Clin Oncol*. 2018;36(15)(suppl).
36. James ND, de Bono JS, Spears MR, et al; STAMPEDE Investigators. Abiraterone for prostate cancer not previously treated with hormone therapy. *N Engl J Med*. 2017;377(4):338-351.
37. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med*. 2015;373(8):737-746.
38. Smith MR, Saad F, Chowdhury S, et al; SPARTAN Investigators. Apalutamide treatment and metastasis-free survival in prostate cancer. *N Engl J Med*. 2018;378(15):1408-1418.
39. James ND, Sydes MR, Clarke NW, et al; STAMPEDE investigators. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. *Lancet*. 2016;387(10024):1163-1177.
40. Fizazi K, Tran N, Fein L, et al; LATITUDE Investigators. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.
41. Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. *N Engl J Med*. 2018;378(26):2465-2474.
42. James N, de Bono J, Spears MR, et al. Adding abiraterone for patients (pts) with high-risk prostate cancer (PCa) starting long-term androgen deprivation therapy (ADT): outcomes in non-metastatic (M0) patients from STAMPEDE (NCT00268476) [ESMO abstract LBA34]. *Ann Oncol.* 2017;28(5)(suppl).

43. Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int*. 2012;109(1):32-39.
44. Cooperberg MR, Hilton JF, Carroll PR. The CAPRA-S score: A straightforward tool for improved prediction of outcomes after radical prostatectomy. *Cancer*. 2011;117(22):5039-5046.
45. Stephenson AJ, Scardino PT, Eastham JA, et al. Postoperative nomogram predicting the 10-year probability of prostate cancer recurrence after radical prostatectomy. *J Clin Oncol*. 2005;23(28):7005-7012.
46. Punnen S, Freedland SJ, Presti JC Jr, et al. Multi-institutional validation of the CAPRA-S score to predict disease recurrence and mortality after radical prostatectomy. *Eur Urol*. 2014;65(6):1171-1177.
47. Erho N, Crisan A, Vergara IA, et al. Discovery and validation of a prostate cancer genomic classifier that predicts early metastasis following radical prostatectomy. *PLoS One*. 2013;8(6):e66855.
48. Klein EA, Yousefi K, Haddad Z, et al. A genomic classifier improves prediction of metastatic disease within 5 years after surgery in node-negative high-risk prostate cancer patients managed by radical prostatectomy without adjuvant therapy. *Eur Urol*. 2015;67(4):778-786.
49. Spratt DE, Dess RT, Zhang J, et al. Development and validation of a novel clinical-genomic risk group classification for prostate cancer incorporating genomic and clinicopathologic risk [ASTRO]. *Int J Radiat Oncol Biol Phys*. 2017;99(2):S97.
50. Spratt DE, Yousefi K, Deheshi S, et al. Individual patient-level meta-analysis of the performance of the decipher genomic classifier in high-risk men after prostatectomy to predict development of metastatic disease. *J Clin Oncol*. 2017;35(18):1991-1998.
51. Ross AE, Johnson MH, Yousefi K, et al. Tissue-based genomics augments post-prostatectomy risk stratification in a natural history cohort of intermediate- and high-risk men. *Eur Urol*. 2016;69(1):157-165.
52. Cooperberg MR, Davicioni E, Crisan A, Jenkins RB, Ghadessi M, Karnes RJ. Combined value of validated clinical and genomic risk stratification tools for predicting prostate cancer mortality in a high-risk prostatectomy cohort. *Eur Urol*. 2015;67(2):326-333.
53. Klein EA, Haddad Z, Yousefi K, et al. Decipher genomic classifier measured on prostate biopsy predicts metastasis risk. *Urology*. 2016;90:148-152.
54. Rubicz R, Zhao S, Wright JL, et al. Gene expression panel predicts metastatic-lethal prostate cancer outcomes in men diagnosed with clinically localized prostate cancer. *Mol Oncol*. 2017;11(2):140-150.
55. Van Den Eeden SK, Lu R, Zhang N, et al. A biopsy-based 17-gene genomic prostate score as a predictor of metastases and prostate cancer death in surgically treated men with clinically localized disease. *Eur Urol*. 2018;73(1):129-138.
56. Cullen J, Rosner IL, Brand TC, et al. A biopsy-based 17-gene genomic prostate score predicts recurrence after radical prostatectomy and adverse surgical pathology in a racially diverse population of men with clinically low- and intermediate-risk prostate cancer. *Eur Urol*. 2015;68(1):123-131.
57. Klein EA, Cooperberg MR, Magi-Galluzzi C, et al. A 17-gene assay to predict prostate cancer aggressiveness in the context of Gleason grade heterogeneity, tumor multifocality, and biopsy undersampling. *Eur Urol*. 2014;66(3):550-560.
58. Levin AM, Lindquist KJ, Avila A, Witte JS, Paris PL, Rybicki BA. Performance of the Genomic Evaluators of Metastatic Prostate Cancer (GEMCaP) tumor biomarker for identifying recurrent disease in African American patients. *Cancer Epidemiol Biomarkers Prev*. 2014;23(8):1677-1682.
59. Nguyen HG, Welty C, Lindquist K, et al. Validation of GEMCaP as a DNA based biomarker to predict prostate cancer recurrence after radical prostatectomy. *J Urol*. 2018;199(3):719-725.
60. Badani K, Thompson DJ, Buerki C, et al. Impact of a genomic classifier of metastatic risk on postoperative treatment recommendations for prostate cancer patients: a report from the DECIDE study group. *Oncotarget*. 2013;4(4):600-609.
61. Badani KK, Thompson DJ, Brown G, et al. Effect of a genomic classifier test on clinical practice decisions for patients with high-risk prostate cancer after surgery. *BJU Int*. 2015;115(3):419-429.
62. Nguyen PL, Shin H, Yousefi K, et al. Impact of a genomic classifier of metastatic risk on postprostatectomy treatment recommendations by radiation oncologists and urologists. *Urology*. 2015;86(1):35-40.