Advances in the Multimodality Management of High-risk Prostate Cancer

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KEYWORDS

• Prostate cancer • Adjuvant • Gleason score • Chemotherapy • Radiation • Prostatectomy • Androgens

KEY POINTS

- Prostate cancer is a disease with a spectrum of clinical outcomes in terms of progression and response to therapy.
- Disease progression may be predicted based on risk stratification using stage, grade, and prostate-specific antigen testing.
- High-risk localized prostate cancer often requires multimodal therapy because of local disease extension and the presence of micrometastases.
- Androgen deprivation therapy improves the results of radiation and surgery in select cases.
- Current studies are focused on adjuvant chemotherapy and biologic agents in combination with surgery and radiation.

INTRODUCTION

Prostate cancer is the most common visceral cancer and the second most lethal malignancy of men in the western hemisphere.[1] In the United States, there are approximately 240,000 new cases detected each year and 28,000 deaths, which account for 9% of all male cancer deaths. Current estimates indicate that a man's lifetime risk of prostate cancer death is about 3%. Since the introduction of prostate-specific antigen (PSA) testing over the last 2 decades, lethality rates have steadily declined, resulting in a 44% overall reduction in rate of prostate cancer mortality.[2,3] During this time period, several technical innovations in local therapies have been introduced that resulted in improved local control with a reduction in treatment morbidity.[4] These initial

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successes in patient outcomes from PSA testing fueled an enthusiasm for early prostate cancer screening and treatment as a means to reduce the rate of prostate cancer mortality further. However, due to the often indolent nature of prostate cancer, the rates of diagnosis and treatment of clinically insignificant disease (ie, overdiagnosis and overtreatment) during this time period were calculated to be significant.[5,6] It is estimated that since the introduction of PSA testing, 1.3 million additional men have been diagnosed with prostate cancer, with younger patients experiencing the greatest relative increase compared with the pre-PSA era.[5]

PROSTATE CANCER SCREENING AND DETECTION

The effectiveness of population-based screening for the detection of prostate cancer has been studied in 2 large randomized trials but remains an area of major controversy. A randomized screening trial in Europe enrolling 182,000 men showed a 21% reduction in the rate of prostate cancer mortality at 11 years, increasing to 29% after adjusting for noncompliance.[7] In contrast, a US-based study of 77,000 men showed no survival benefit to PSA screening in comparison to controls.[8] Important limitations of this study that have been cited include a high rate of cross-contamination with frequent PSA screening in the control group and a follow-up period that was too short to assess rate of mortality.[9] A critical limitation of both of these trials was that, of the prostate cancer cases detected, 60% to 65% were low grade and thus had a reduced biologic potential for the development of clinically significant disease.[8,10] Based on the interim results from these trials, the US Preventative Services Task Force currently recommends against the use of PSA screening for prostate cancer detection.[11] Other health policy and professional organizations, including the American Society of Clinical Oncology, the National Comprehensive Cancer Network, and the American Cancer Society, recommend an informed and shared decision process toward prostate cancer screening.[12,13] Given the lack of consensus in this area, a personalized approach seems warranted in which the risks and benefits of screening are each carefully weighed with the individual patient's health concerns in mind.

These studies highlight the need for improved methods of screening, which preferentially identify potentially lethal prostate cancer. Novel strategies such as these would optimize the efficiency of the screening process and ultimately direct the most suitable patients into evidence-based treatment pathways. Several biopsy prediction tools are currently available that demonstrate the capacity for the prediction of high-grade prostate cancer on biopsy (**Table 1**).[14–17] These prediction tools incorporate several readily available clinical biomarkers that can be used to improve risk assessment for the detection of lethal cancer. These strategies help to reduce the number of unnecessary biopsies and reduce the rate of overdiagnosis in men with insignificant cancers. Future studies are likely to incorporate advanced imaging and both serum and urine biomarkers into the risk assessment of patients presenting for prostate cancer screening.[18–21]

RISK FACTORS FOR AGGRESSIVE PROSTATE CANCER

Several clinical and pathologic pretreatment factors are known to predict adverse clinical outcomes in localized prostate cancer. Validated predictors of cancer recurrence and progression that are widely used include Gleason biopsy grade, tumor stage, and level of serum PSA. Tumor stage and level of PSA primarily correlate with extent of tumor burden; however, these are less robust indicators of lethal potential than tumor grade. The effect of tumor grade was clearly demonstrated by Albertsen and colleagues,[22] who showed that the risk of prostate cancer mortality after observation

Table 1
Prostate biopsy prediction tools for the detection of high-grade cancer

Reference	Prediction Tool	Population	Predictors	Accuracy	Validation
Thompson et al,[17] 2006	Logistic regression	Screening trial	Log PSA, DRE, prior biopsy, age, race	AUC = 70%	External
Nam et al,[15] 2007	Logistic regression	Referral cohort	Age, PSA, %fPSA, DRE	NA	Split sample
Ide et al,[14] 2008	Logistic regression	Referral cohort	PSA, testosterone	AUC = 70%	Split sample
Spurgeon et al,[16] 2006	Classification and regression tree analysis	Referral cohort	PSAD, prostate volume, age	Sensitivity = 92% Specificity = 36%	Split sample

Abbreviations: %fPSA, percent-free PSA; AUC, area under curve; DRE, digital rectal examination; NA, not available; PSA, prostate specific antigen; PSAD, PSA density.

alone was 16-fold higher in men with high-grade cancer compared with those with low-grade cancer. Similarly, in a Swedish trial of observation with a mean follow-up of more than 20 years for localized prostate cancer, tumor grade was highly predictive of cancer metastases and mortality.[23] During the follow-up period, 40% of patients experienced clinical progression and nearly half of these developed metastatic disease. In many cases cancer progression accelerated late in the disease course after a long period of nonprogression (10-15 years). In addition to highlighting the effect of Gleason score on cancer progression, this study also showed the need for continued vigilance and close observation in patients with prostate cancer, particularly among those with expected longevity.

A plethora of tissue markers have been studied as predictive biomarkers in prostate cancer.[24,25] These tissue biomarkers include oncogenic molecules involved in cell cycle progression, tissue invasion, metastases, cell survival, and angiogenesis. Although these hold great promise for use in patient management, to date none hae proven to be as effective or cost-efficient as current clinical predictive models. Thus, until further data are available, tissue biomarker analyses should remain the subject of ongoing research studies.

To assess and manage the patient with clinically localized prostate cancer accurately, standardized risk stratification groups have been identified that integrate clinical biomarkers used in routine patient care. These risk stratification groups offer Q7 several advantages in patient management, including the following: (1) to serve as standard nomenclature for interdisciplinary teams that comanage patients, (2) to determine the need for staging studies, (3) to compare treatments across similar treatment groups, and (4) to codify patient groups for the development of clinical trials with special target populations in mind.

RISK ASSESSMENT OF PROSTATE CANCER

There are several clinical factors that are predictive of disease recurrence that aid in the designation of patient risk groups. Although many of these variables have been examined individually, newer predictive models capable of combining several factors have resulted in refined tools that are available for routine clinical use. D'amico and colleagues[26] retrospectively developed a widely used strategy based on clinical

data from a single institution cohort undergoing either surgery or radiation with curative intent. This straightforward schema is based on biopsy Gleason score, tumor stage, and level of PSA. Rates of relapse in risk groups were as follows (**Box 1**): low-risk: less than 25%, intermediate-risk: 25% to 50%, and high-risk: greater than 50%. Risk factors that predicted a greater than 50% chance of cancer recurrence included the following: clinical stage T3–4, a PSA >20, or a Gleason score $\geq$8. These predictors have been validated in external datasets and incorporated into routine practice guidelines by the National Comprehensive Cancer Network and the European Association of Urology.[27,28] In addition, tools have been developed that give a more personalized readout in terms of predicting clinical outcomes. Nomograms have been developed that give a numeric value (as opposed to risk grouping) for risk of recurrence. These tools may be of use in informing individual patients of their progression risk in more refined terms than risk groupings provide.[29,30]

IMAGING IN PROSTATE CANCER

Patient risk stratification is the primary means of guiding the need and the type of imaging modality in the workup of newly diagnosed prostate cancer. Prostate cancer has a unique tropism for bone whereby it metastasizes in greater than 80% of patients with systemic disease. Lesions involving bone are typically osteoblastic in nature and are a harbinger of tumor progression and death. Radioisotope bone scans are generally reserved for those with high-risk prostate cancer. In lower risk patients bone scans and other imaging modalities are typically omitted. In these cases patients are subject to a higher rate of false-positive results because of the frequency of benign conditions of the skeleton in elderly men. Newer bone imaging agents such as flourine-18 (^{18}F) and ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography have shown encouraging preliminary results in terms of improved sensitivity and tumor quantitation; however, these require further study before being incorporated into regular clinical practice.[31,32] Computerized tomogram scans are of limited utility in discerning the primary tumor extent or location,[33] although these are routinely

Box 1
D'amico/National Comprehensive Cancer Network risk stratification in prostate cancer (risk of treatment failure)

Low risk (<25%):
Clinical T1–T2a
Gleason score 2–6
PSA <10 ng/mL

Intermediate risk (25%–50%):
Clinical T2b–T2c, or
Gleason score 7, or
PSA: 10–20 ng/mL

High risk (>50%):
Clinical T3–T4, or
Gleason score 8–10, or
PSA >20 ng/mL

deployed to assess regional lymph node status, especially in high-risk cases considered to be locally advanced (ie, PSA >20 ng/mL or the presence of T3–T4 cancer or if the predicted chance of lymph node disease exceeds 20%).[27,34] In the future, the use of magnetic resonance imaging[35] and ferromagnetic nanoparticles[36] are likely to improve local and regional staging, but further study is needed to bring these promising modalities into the sphere of clinical practice. At the authors' institution, the utility of shutter-speed image analysis for discriminating benign from malignant prostate tissues using shutter-speed modeling is currently being evaluated.[19] This technique has shown encouraging results in early phase testing but requires large-scale prospective testing, which is in the planning stages.

SURGERY IMPROVES SURVIVAL IN PROSTATE CANCER

Radical prostatectomy is considered to be a primary treatment option for appropriate cases of localized prostate cancer.[27,28] This concept is strongly supported by the results of randomized controlled trials demonstrating significant improvements in oncologic outcomes compared with observation alone. The direct impact of curative therapy on the natural history of prostate cancer was first demonstrated in the Scandinavian Prostate Cancer Group Study 4.[37] In this trial, 695 men with localized prostate cancer were randomized to either observation alone or radical prostatectomy. At baseline, the mean PSA was about 13 ng/mL with half of all patients having PSA values greater than 10 ng/mL. With a median follow-up of 12.8 years, significant improvements in cancer outcomes have been reported for men entered onto the surgical intervention arm of the trial (**Table 2**). Surgery resulted in a 38% improvement in disease-specific rate of mortality and a 25% improvement in overall survival. Surgical intervention resulted in a 67% reduction in local progression and a 41% reduction in the spread of metastases. More recently, in a study of 731 men diagnosed primarily through PSA testing, surgery was compared with observation alone.[38] In the Prostate Intervention Versus Observation Trial (PIVOT), the mean PSA was lower at 7.8 ng/mL and greater than 70% of patients had low-grade tumors (Gleason 6 or less). With a median follow-up of 10.0 years, there was no benefit to subjects with Gleason 6 cancer or a preoperative PSA $\leq$10 ng/mL. However, in patients with a PSA >10 ng/mL, surgery resulted in a 21% improvement in overall survival, a 57% improvement in prostate cancer survival, and a 72% improvement in bone metastases-free survival (see **Table 2**). Similar improvements for these metrics were seen in patients with intermediate-risk and high-risk prostate cancer. Thus, based on these and other studies, surgery is considered a mainstay of therapy in

Table 2
Improvement in clinical outcome over observation in patients treated with surgery in randomized controlled trials

		PIVOT Study	
Outcome	**SPCG-4**	**PSA ≤10 Ng/mL**	**PSA >10 ng/mL**
Overall survival	25%	ns	21%
Prostate cancer survival	38%	ns	57%
Metastases-free survival	41%	ns	72%
Local control	67%	ns	NA

All numerical outcomes statistically significant (P<.05).

Abbreviations: NA, not available; ns, nonsignificant; PIVOT, Prostate Cancer Intervention Versus Observation Trial; SPCG, Swedish Prostate Cancer Group.

men with clinically significant, localized prostate cancer. This benefit seems to be greatest for men with higher levels of PSA and higher grade cancers. Because prostate cancer death is a relatively late occurrence among men with Gleason 6 cancer,[23] the PIVOT trial was poorly designed to capture these late events. Because of this, caution must be taken in making data inferences beyond 10 years in patients with a Gleason 6 or less tumor. Thus the long-term effect (>10 years) of surgery on low-grade PSA-detected prostate cancer remains unknown.

SURGERY FOR ADVANCED PROSTATE CANCER

The rate of cancer recurrence measured by PSA testing after radical prostatectomy is reported to be approximately 30% to 40%.[39–41] Data from several contemporary surgery series have shown that the increased D'amico/National Comprehensive Cancer Network (NCCN) category is associated with an increased chance of PSA recurrence and risk of prostate cancer death. In a report by Pound and colleagues[42] of patients with Gleason 8 or higher who were observed at the time of PSA recurrence after surgery, metastases-free survival at 7 years was only 29%. In a single-center experience of a cohort of men treated with either surgery or radiation, the risk of metastatic progression was 6.4-fold higher in D'amico/NCCN high-risk versus intermediate-risk or low-risk patients.[43] In addition, in a large retrospective analysis of US population-based data containing nearly 150,000 prostate cancer cases, 33% were found to be at high risk. With a mean follow-up of 60.7 months, the estimated 10-year cancer-specific rate of mortality after radical prostatectomy was 5.8% for patients less than 60 years old, increasing steadily to 21.1% in patients greater than 80 years of age.[44] Thus, prostate cancer is a fatal disease in high-risk prostate cancer and risk of death increases with advancing age.

Disease recurrence after radical prostatectomy may occur locally in the surgical site or at distant sites such as the axial bones. Imaging is of limited use in locating the anatomic source of PSA recurrences when the levels are low.[45–47] However, recent clinical trial reports show that most of these early recurrences are local within the surgical bed (ie, prostatic fossa).[48] This finding clearly highlights the need for technical improvements in the surgical procedure along with the need for effective combination therapy when indicated.

Improvements in our comprehension of prostatic anatomy and its surrounding structures as well as the pathways of disease extension have resulted in technical advancements in the surgical procedure.[49] Surgery may be performed through a standard open technique or by robotic-assisted laparoscopy. These procedural modifications must include a precise and thorough apical dissection along with the wide local excision of the neurovascular bundles in advanced disease.[50,51] Currently it is unclear which of these 2 methods is superior, because limited comparative data are available for high-risk cases.

Further improvements in the tumor staging and clinical outcomes result from the performance of an extended pelvic lymph node dissection versus a more limited pelvic dissection.[33,52] Long-term PSA-free survival is possible in 10% to 20% of patients with positive lymph nodes treated with an extended (vs limited) pelvic lymph node dissection.[33,53] Extended pelvic lymph node dissection should be performed in all patients with intermediate-risk or high-risk prostate cancer. In low-risk patients a lymph node dissection is generally omitted but should be considered on a case-by-case basis, particularly if other adverse features are present. Long-term cancer control in these node-positive cases is achievable but may require the addition adjuvant and salvage therapies.

Contemporary modifications to standard treatment have resulted in improved cancer-free rates in patients undergoing either surgery or radiation. These contemporary modifications are considered effective treatment options for low-risk to intermediate–risk prostate cancer; however, satisfactory therapeutic approaches have yet to be developed for patients with clinically localized, high-risk disease.[54]

ADJUVANT AND SALVAGE RADIATION THERAPY

Disease recurrence after radical prostatectomy or radiation therapy may occur locally in the surgical site or at distant sites. Existing or suspected subclinical, microscopic disease is below the threshold of detection of any imaging modality and may forever be.[46,47] However, recent scientific data support the concept that, despite technically adequate dissections, residual disease in the surgical bed can progress to metastases and death unless eradicated.

The benefit of maximizing local control in high-risk prostate cancer is strongly supported by controlled prospective trials of adjuvant radiotherapy after prostatectomy (**Table 3**).[55–57] In a phase III trial of adjuvant pelvic radiation versus observation after surgery for high-risk disease, postoperative radiation resulted in improved disease control.[55] The European Organization for Research and Treatment of Cancer (EORTC) reported the results of 1005 men who were randomized to receive postoperative radiation if they had 1 of 3 well-known prognostic factors for disease recurrence after radical prostatectomy: positive margins, extracapsular extension, or seminal vesicle invasion. After a median follow-up of 5.0 years, the group treated with adjuvant radiotherapy after prostatectomy had a 52% reduction (74% vs 53%) in either biochemical or clinical progression compared with control subjects.[55] In this study, follow-up is ongoing to assess the effects on cancer-specific and overall survival.

Accordingly, the Southwest Oncology Group (SWOG) has reported the mature results of a phase III trial of postsurgery adjuvant radiotherapy. Entry criteria in this trial are identical to the aforementioned EORTC trial, with patients requiring a minimum of 1 of 3 poor prognostic factors. The study showed that adjuvant radiation after prostatectomy resulted in a 25% reduction in metastases or death.[56,58] The SWOG trial differed from the EORTC trial mainly in that althoughonly 431 men were accrued, they were followed for a median of 10.6 years. Localized radiation reduced the risk of PSA recurrence by 57% and increased the time to PSA failure from 2.2 to 9.2 years.[56,58] In a subsequent analysis using updated trial data with an additional 2 years of median follow-up, Thompson and colleagues[56] showed that adjuvant radiation resulted in a statistically significant increase in metastasis-free survival (12.9 vs 14.7 years) and overall survival (13.3 vs 15.2 years) in the group receiving early postoperative radiation therapy. In a third phase III trial reported by Wiegel and colleagues[57] in 2009, 307 patients with pathologic T3 disease or positive margins disease after radical prostatectomy were also randomized to undergo postoperative radiation or observation. The unique feature of this trial is that all patients were required to have an undetectable PSA postprostatectomy. After only a median follow-up period of 53.7 months, they demonstrated a roughly 50% reduction in biochemical recurrence (hazard ratio = 0.53, P = .0015) and this was despite the fact that greater than 20% of the patients assigned to adjuvant radiation refused immediate radiation therapy.

Three separate phase III trials have now demonstrated significant reduction in biochemical recurrence for adjuvant radiation for patients with high-risk features after radical prostatectomy. All 3 trials meticulously captured toxicity data and demonstrated very little short-term toxicity and no significant long-term toxicity or impact

Table 3
Results of adjuvant localized radiotherapy versus observation after surgery for high-risk prostate cancer

Study	No. Subjects (Follow-up, Years)	Main Entry Criteria	Primary Endpoint	Treatment	Main Results
Thompson et al,[58] 2006	431 (10.6)	Extracapsular extension, positive surgical margin, *or* seminal vesicle invasion	Metastases-free survival	60–64 Gy to prostate fossa	Metastases or death improved in RT group (HR 0.75, 95% CI, 0.55–1.02; P = .06). Improved PSA-free survival.
Bolla et al,[57]	1005 (5.0)	Extracapsular extension, positive surgical margin, *or* seminal vesicle invasion	PSA recurrence-free survival	60 Gy treatment within 16 wk of surgery to prostate fossa	RT reduced PSA recurrence by 52% (HR 0.48, 98% CI 0.37–0.62; P = <.0001). Improved locoregional control but no difference in metastases or overall survival
Wiegel et al,[59]	307 (4.5)	Pathologic T3–T4, N0 Undetectable PSA	PSA recurrence-free survival	60 Gy treatment within 6–12 wk of surgery to prostate fossa	RT reduced PSA recurrence (HR = 0.53; 95% CI, 0.37 to 0.79; P = .0015). No difference in metastases or overall survival

Abbreviations: CI, confidence interval; Gy, Gray; HR, hazard ratio; PSA, prostate-specific antigen.

on quality-of-life measures.[59] With the body of evidence favoring adjuvant radiation, patients with high-risk features after prostatectomy should be considered for this treatment.

An alternative approach to adjuvant therapy that has been advocated by some experts is to implement early salvage radiation for a rising PSA after prostatectomy. Prostate cancer is unique from other tumor types in that a serum marker of early recurrence is readily available for assessment (ie, PSA). In untreated prostate cancer, the detection of PSA precedes the development of metastases and other clinical symptoms by many years.[42,45] Thus, close monitoring of the PSA with early treatment of recurrent disease may present an opportunity to improve the risk-benefit ratio of postoperative radiation. An important caveat of the use of early salvage therapy is that all published studies in this area are retrospective analyses of either single institution or pooled multi-institutional cohort samples. Thus, the published data reflect the wide variance in the selection characteristics for patients undergoing treatment as well as the interinstitutional treatment techniques for salvage therapy.

The largest of study to date was reported by Stephenson and colleagues[60] on 1540 patients undergoing salvage radiation therapy to the prostatic fossa for PSA-only recurrence. A complete PSA response was achieved in 55% of patients with radiotherapy alone and in 59% of those receiving androgen deprivation in combination with radiation. The benefit of salvage radiation was observed across all risk groups including those with high-risk pathologic features such as Gleason 8–10 and seminal vesicle invasion. The presence of positive surgical margins, which is a predictor of poor local control in prostate cancer and other tumor types, paradoxically predicted a better response to local radiotherapy than did the absence of surgical margins.

The 6-year PSA progression-free survival was 32% for the cohort, but improved to 48% for those with a starting PSA of 0.5 ng/mL or less. The authors of this study make the case that this reduction in PSA recurrence is similar to the proportional decrease seen with adjuvant radiation ($\approx$50%).[57,58,61] Based on these findings, some authorities advocate for determining the need for adjuvant versus planned early salvage on a case-by-case basis using a shared decision approach with the patient.[62]

Until further studies are completed, the debate between the choices of adjuvant versus salvage therapy will continue for patients with high-risk features after prostate surgery. Currently there are 2 ongoing phase III trials comparing the efficacy and safety of adjuvant versus salvage radiotherapy. The Medical Research Council is conducting a phase III trial entitled Radiotherapy and Androgen Deprivation in Combination After Local Surgery Trial, which has 2 main substudies. The first compares adjuvant to salvage radiotherapy in men who may or may not be ideal candidates for local radiation. The second substudy compares the length of androgen deprivation (0, 6, or 24 months) in men designated to have radiation (adjuvant or salvage). The primary endpoint of this study is prostate cancer–specific survival. Trial accrual is targeted for 3000 subjects and enrollment is ongoing in Europe and Canada. A second study is the Radiotherapy Adjuvant Versus Early Salvage Following Radical Prostatectomy, which is being performed by the Tasmanian Radiation Oncology Group. Men in the adjuvant radiation arm will initiate radiation within 4 months of surgery, whereas in the delayed treatment arm, radiation will begin if the PSA exceeds 0.2 ng/mL. The primary endpoint is 5-year biochemical recurrence-free survival. Accrual of 470 men with high-risk features is ongoing in Australia and New Zealand. It is hoped that these 2 studies will provide the much-needed insight as to the optimal approach for men with high-risk features after surgery.

ADJUVANT AND NEOADJUVANT ANDROGEN DEPRIVATION WITH SURGERY

The antitumoral effects of androgen deprivation on prostate cancer are well known to clinicians. However, recent studies have shown the androgen receptor (AR) to be the most important molecular target in the treatment of lethal prostate cancer.[63] It is a primary mediator of the development of prostate cancer as well as pan-resistance to multiple lines of treatment.[64,65] Many novel therapies incorporate AR targeting as a basis for improving treatment outcomes in combination with other treatments. Androgen deprivation has been studied extensively in combination with surgery in both preoperative and postoperative settings. The addition of androgen deprivation to surgery for lymph node–positive disease results in a significant improvement in cancer-specific and overall survival compared with surgery alone. In a randomized trial of early versus delayed androgen deprivation for node-positive disease, the use of early androgen deprivation resulted in a 4–fold improvement in prostate cancer–specific survival and a 2-fold improvement in overall survival.[66] In contrast, in a study of androgen deprivation alone for advanced nonoperable patients, the administration of early androgen deprivation failed to show an improvement in cancer-specific survival over delayed treatment, suggesting the potential need for surgical debulking.[67] Short-term neoadjuvant (preoperative) treatment with standard androgen deprivation has been studied in several clinical trials in Europe and North America. These trials have shown a uniform reduction in positive surgical margins and other histologic changes. Unfortunately, these studies have failed to show an effect on PSA recurrence or long-term survival.[68–72] Despite these shortcomings, newer more effective agents for AR targeting have shown promise in this area. Recently, Taplin[73] presented the results of a phase II trial of combined AR targeting with standard androgen deprivation plus the androgen biosynthesis inhibitor, abiraterone, before prostatectomy. This drug combination resulted in a 34% rate of either complete or near complete response in the prostatectomy specimens. Future studies of this and other AR targeting agents are warranted in the perioperative setting.

ANDROGEN DEPRIVATION WITH RADIOTHERAPY

Radiation is a mainstay in the treatment of prostate cancer, especially when used in conjunction with androgen deprivation. The rationale for this combination includes reducing cellular resistance to radiotherapy by reducing AR signaling and through the early treatment of micrometastatic disease. Androgen deprivation was initially combined cautiously with radiation because of concerns that testosterone suppression would induce treatment antagonism. Thus the original trial combining androgen suppression and radiation, Radiation Therapy Oncology Group (RTOG) 85-31, randomized patients to observation or androgen suppression immediately after the radiation concluded. The trial demonstrated an overall survival advantage at 10 years for patients with higher grade tumors, Gleason 7–10.[74] A contemporary trial, RTOG 86-10, asked the question directly of whether the androgen suppression would engender radiation resistance by randomizing patients to radiation alone or radiation with 4 months of hormone therapy, 2 months before the radiation and 2 months concurrent.[75] Although RTOG 86-10 did demonstrate an improvement in overall survival, it was not statistically significant. The 10-year prostate cancer–specific rate of mortality was statistically significant, however. These results were the basis for the subsequent trials testing the overall benefit of concurrent radiation and androgen deprivation (**Table 4**).[74,76–85]

One of the first trials to demonstrate a difference in overall survival as a primary endpoint was an EORTC trial of radiation alone versus radiation and concurrent

Table 4
Data summary of randomized trials demonstrating the oncologic benefits of androgen deprivation to radiotherapy in intermediate-risk and high-risk prostate cancer patients

Study	Eligibility Criteria	Years	No. of Patients	Androgen Deprivation	Radiation Dose	Significant Results
Long-term hormones vs RT alone						
RTOG 85-31[74]	cT3, pT3, or N1 M0	1987–1992	977	Adjuvant indefinite LHRH	65–70 Gy	With median f/u 7.6 all, 11 for living patients, 10-y overall survival was 49% vs 39% (P = .002) Gleason 7–10 10 prostate cancer-specific rate of mortality was 16% vs 22% (P = .0052) Gleason 8–10
Umea University[80]	T3 N0-1 M0	1986–1991	91	Orchiectomy	65 Gy	Mean f/u 9.7 y all patients, 16.5 y for survivors Overall survival advantage for androgen therapy in N1 patients No significant difference for patients with N0
EORTC 22863[77]	T1–T2 WHO grade 3, or T3–T4	1987–1995	415	Concurrent and adjuvant × 3 y	70 Gy	Median f/u was 9.1 y 10-y overall survival was 39.8% vs 58.1% (P = .0004) 10-y prostate-cancer rate of mortality was 30.4% vs 10.3% (P<.0001)

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Table 4
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Study	Eligibility Criteria	Years	No. of Patients	Androgen Deprivation	Radiation Dose	Significant Results
Short-term hormones vs RT alone						
RTOG 86-10[83]	Bulky T2–T4	1987–1991	456	Neoadjuvant 2 mo and concurrent	65–70 Gy	Median f/u for survivors between 11.9 and 13.2 y 10-y overall survival was 43% vs 34% (P = .12) 10-y prostate cancer-specific rate of mortality was 23% vs 36% (P = .01)
TROG 96-01[79]	T2b–T4 N0	1996–2000	818	Neoadjuvant 2 mo and concurrent vs Neoadjuvant 5 mo and concurrent vs RT alone	66 Gy	Median f/u 10.6 y 10-y prostate cancer-specific rate of mortality was 22% vs 18.9% vs 11.4% (P = .0008) for 0, 3, 6 mo of ADT 10-y all-cause rate of mortality was 42.5% vs 36.7% vs 29.2% (P = .0008) for 0, 3, 6 mo ADT In summary, only 6 mo of ADT, 5 neo and 1 concurrent, showed significant improvement
D'amico Trial[78]	T1b–T2b and 1 of 3 factors: PSA >10 ng/mL, <40 ng/mL, Gleason 7–10 or MRI T3	1995–2001	206	Neoadjuvant 2 mo and concurrent 4 mo	70 Gy	Median f/u 7.6 y 8-y overall survival 74% vs 61% (P = .01) 8-y prostate cancer-specific rate of mortality HR 4.1 (P = .01)
RTOG 94-08[82]	T1b–T2b, PSA <20	1994–2001	1979	Neoadjuvant 2 mo and concurrent 2 mo	66.6 Gy	Median f/u 9.1 y 10-y overall survival was 62% vs 57% (P = .03) 10-y prostate cancer-specific rate of mortality 8% vs 4% (P = .001)

Short-term vs long-term androgen deprivation with concurrent RT						
RTOG 92-02[81]	T2c–T4 N0	1992–1995	1554	Neoadjuvant 2 mo and concurrent 2 mo vs Neoadjuvant 2 mo and concurrent 24 mo	65–70 Gy	Median f/u survivors 11.31 and 11.27 y 10-y overall survival 51.6% vs 53.9% (P = .36) 10-y prostate cancer-specific survival 83.9% vs 88.7% (P = .0042) 10-y overall survival Gleason 8–10 31.9% vs 45.1% (P = .0061)
EORTC 22961[76]	T1c–T2b pN+ or T2c–cT4 N0–N1	1997–2001	970	Concurrent 6 mo vs Concurrent 36 mo	70 Gy	Median f/u 6.4 y 5-y overall rate of mortality 19.0% vs 15.2% (P = .65 noninferiority test) 5-y prostate cancer-specific rate of mortality 4.7% vs 3.2% (P = .002)
RT and long-term hormones vs long-term hormones alone						
SPCGF-7/SFUO-3[85]	T1b–T2 WHO G2–G3 M0 T3 M0	1996–2002	875	Lifelong ADT vs Neoadjuvant 3 mo, concurrent, and lifelong	70 Gy	Median f/u 7.6 y 10-y overall rate of mortality 39.4% in ADT alone vs 11.9% in ADT and RT (P = .004 at 7 y) 10-y prostate cancer-specific rate of mortality was 23.9% in ADT alone and 11.9% in ADT and RT (P<.0001 at 7 y)
NCIC CTG PR3/MRC PR07/SWOG[84]	T3–T4 or T2 PSA >40 ng/mL or PSA >20 Gleason $\geq$8	1995–2005	1205	Lifelong ADT	65–69 Gy	Median f/u 6 y 7-y overall survival 74% vs 66% (P = .03) 7-y prostate cancer-specific rate of mortality 9% vs 19% (P = .01)

androgen-deprivation therapy (ADT) for 3 years. The 10-year results demonstrated a doubling in disease-free survival, 22.7% versus 47.7%, along with an improvement in overall survival from 39.8% to 58.1%.[77,86] The use of concurrent androgen deprivation has been demonstrated to improve overall survival with only 6 months of therapy.[82,87] An RTOG study, 92-02, demonstrated an overall survival difference for patients with Gleason 8–10 cancers when subjects received more than 2 years of androgen deprivation therapy versus only 4 months.[81] An independent EORTC study demonstrated 3 years of ADT to be superior to 6 months of androgen deprivation for all patients with high-risk disease.[76] In conclusion, these trials demonstrated a significant improvement in all outcomes with androgen deprivation when added to radiation treatment. Underlying these positive results was a growing appreciation for the significance of the androgen suppression in prostate cancer and a nagging concern about whether the same benefits were achievable without the radiation.

In the last few years, 2 additional trials have been reported that asked the question of whether radiation could improve on continuous ADT alone. These 2 separate, large, randomized trials have demonstrated a large and very significant overall survival advantage for patients with high-risk disease when they receive ADT and radiation over receiving indefinite ADT by itself. Both of these trials emphatically demonstrate the synergy of multimodality therapy in prostate cancer.

INTEGRATION OF CHEMOTHERAPY INTO PRIMARY THERAPY

Disease recurrence after primary treatment may occur in the local treatment site or in distant areas such as bone or regional lymph nodes. In other cancer types the use of systemic therapies are commonly used to treat both the local tumor and the micrometastatic disease not removed with surgery. Several treatment combinations are currently under study for prostate cancer.

Adjuvant Chemotherapy

Taxane-based chemotherapies have been shown to improve overall survival in advanced prostate cancer. In phase III trials of men with metastatic castration–resistant prostate cancer, taxanes demonstrated a survival advantage over controls in both the first-line and the second-line settings.[88–90] These encouraging studies have led investigators to study these drugs after standard treatment with either surgery or radiation. Postprostatectomy docetaxel was studied in a phase II trial of 77 men with high-risk prostate cancer. For the group, the predicted time to PSA progression was 10.0 months based on tumor characteristics; however, observed time to progression was 15.7 months. The RTOG is examining the effect of radiation with androgen deprivation plus or minus docetaxel chemotherapy on overall survival in high-risk prostate cancer.[91] This trial has fully accrued its planned 600 patients and is awaiting completed follow-up. The Veterans Administration is studying the effect of docetaxel plus prednisone after prostatectomy versus surgery alone on PSA recurrence and metastases-free survival.[92] For this trial accrual is complete and follow-up is ongoing. These important studies will offer the first insights into the effect of active chemotherapy on the progression of prostate cancer in the posttreatment setting.

Neoadjuvant Chemotherapy

Taxane-based chemotherapies have been studied by several investigative groups including the authors' group in the neoadjuvant setting for high-risk prostate cancer.[54] These trials have shown that in the castration-sensitive setting, taxanes have antineoplastic activity as demonstrated by PSA changes and histologic findings in prostate

specimens; however, the effects are limited and have not met treatment thresholds to justify larger scale trials.[93–97] The use of docetaxel in combination with androgen deprivation has been studied with more promising results.[98] In a phase II study of docetaxel and androgen deprivation before prostatectomy, a complete tumor response was observed in 3% of subjects.[98] One limitation of the study was that because there was no control arm, it is unknown if these effects are due to the drug combination or to the androgen deprivation itself. Currently the effectiveness of this combination is being studied in a phase III trial comparing this regimen with surgery to surgery alone. The accrual target for this trial is 750 subjects and the primary endpoint is progression-free survival. As advanced treatments that harness the knowledge of specific molecular targets expand, the need for large-scale neoadjuvant trials will increase.

SUMMARY

In summary, numerous developments in the fields of surgery and radiation have improved treatment outcomes in high-risk prostate cancer. However, continued advancements in these monotherapies are limited by prevalence of subclinical metastases and microscopic local tumor extension. The selective addition of adjuvant treatment significantly improves survival over standard treatment. These options should be presented to the patient in a balanced manner that considers risks and benefits. Future developments in the treatment of advanced prostate cancer therapy will likely be guided by advances in the understanding of prostate cancer biology.

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin 2012;62(1):10–29.
2. Thompson IM Jr, Tangen CM. Prostate cancer–uncertainty and a way forward. N Engl J Med 2012;367(3):270–1.
3. Etzioni R, Tsodikov A, Mariotto A, et al. Quantifying the role of PSA screening in the US prostate cancer mortality decline. Cancer Causes Control 2008;19(2):175–81.
4. Walsh PC, DeWeese TL, Eisenberger MA. Clinical practice. Localized prostate cancer. N Engl J Med 2007;357(26):2696–705.
5. Welch HG, Albertsen PC. Prostate cancer diagnosis and treatment after the introduction of prostate-specific antigen screening: 1986-2005. J Natl Cancer Inst 2009;101(19):1325–9.
6. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol 2010;28(7):1117–23.
7. Schroder FH, Hugosson J, Roobol MJ, et al. Prostate-cancer mortality at 11 years of follow-up. N Engl J Med 2012;366(11):981–90.
8. Andriole GL, Crawford ED, Grubb RL 3rd, et al. Mortality results from a randomized prostate-cancer screening trial. N Engl J Med 2009;360(13):1310–9.
9. Barry MJ. Screening for prostate cancer–the controversy that refuses to die. N Engl J Med 2009;360(13):1351–4.
10. Schroder FH, Hugosson J, Roobol MJ, et al. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med 2009;360(13):1320–8.
11. Moyer VA. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2012;157(2):120–34.
12. Basch E, Oliver TK, Vickers A, et al. Screening for prostate cancer with prostate-specific antigen testing: American Society of Clinical Oncology provisional clinical opinion. J Clin Oncol 2012;30(24):3020–5.

13. Brawley OW. Prostate cancer screening: what we know, don't know, and believe. Ann Intern Med 2012;157(2):135–6.
14. Ide H, Yasuda M, Nishio K, et al. Development of a nomogram for predicting high-grade prostate cancer on biopsy: the significance of serum testosterone levels. Anticancer Res 2008;28(4C):2487–92.
15. Nam RK, Toi A, Klotz LH, et al. Assessing individual risk for prostate cancer. J Clin Oncol 2007;25(24):3582–8.
16. Spurgeon SE, Hsieh YC, Rivadinera A, et al. Classification and regression tree analysis for the prediction of aggressive prostate cancer on biopsy. J Urol 2006;175(3 Pt 1):918–22.
17. Thompson IM, Ankerst DP, Chi C, et al. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. J Natl Cancer Inst 2006;98(8):529–34.
18. Hansen J, Auprich M, Ahyai SA, et al. Initial prostate biopsy: development and internal validation of a biopsy-specific nomogram based on the prostate cancer antigen 3 assay. Eur Urol 2012. [Epub ahead of print]. Q11
19. Li X, Priest RA, Woodward WJ, et al. Feasibility of shutter-speed DCE-MRI for improved prostate cancer detection. Magn Reson Med 2012. [Epub ahead of print].
20. Litjens GJ, Hambrock T, Hulsbergen-van de Kaa C, et al. Interpatient variation in normal peripheral zone apparent diffusion coefficient: effect on the prediction of prostate cancer aggressiveness. Radiology 2012;265(1):260–6.
21. Tosoian JJ, Loeb S, Feng Z, et al. Association of [-2]proPSA with biopsy reclassification during active surveillance for prostate cancer. J Urol 2012;188(4):1131–6.
22. Albertsen PC, Hanley JA, Fine J. 20-year outcomes following conservative management of clinically localized prostate cancer. JAMA 2005;293(17):2095–101.
23. Johansson JE, Andren O, Andersson SO, et al. Natural history of early, localized prostate cancer. JAMA 2004;291(22):2713–9.
24. Bjartell A, Montironi R, Berney DM, et al. Tumour markers in prostate cancer II: diagnostic and prognostic cellular biomarkers. Acta Oncol 2011;50(Suppl 1):76–84.
25. Shariat SF, Scherr DS, Gupta A, et al. Emerging biomarkers for prostate cancer diagnosis, staging, and prognosis. Arch Esp Urol 2011;64(8):681–94.
26. 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):969–74.
27. Mohler JL. The 2010 NCCN clinical practice guidelines in oncology on prostate cancer. J Natl Compr Canc Netw 2010;8(2):145.
28. Heidenreich A, Aus G, Bolla M, et al. EAU guidelines on prostate cancer. Eur Urol 2008;53(1):68–80.
29. 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):7005–12.
30. 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):5039–46.
31. Even-Sapir E, Metser U, Mishani E, et al. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP Planar bone scintigraphy, single- and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. J Nucl Med 2006;47(2):287–97.
32. Jadvar H, Desai B, Ji L, et al. Prospective evaluation of 18F-NaF and 18F-FDG PET/CT in detection of occult metastatic disease in biochemical recurrence of prostate cancer. Clin Nucl Med 2012;37(7):637–43.

33. Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol 2009;55(6):1251–65.
34. Greene KL, Albertsen PC, Babaian RJ, et al. Prostate specific antigen best practice statement: 2009 update. J Urol 2009;182(5):2232–41.
35. Fuchsjager M, Akin O, Shukla-Dave A, et al. The role of MRI and MRSI in diagnosis, treatment selection, and post-treatment follow-up for prostate cancer. Clin Adv Hematol Oncol 2009;7(3):193–202.
36. Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003;348(25): 2491–9.
37. Bill-Axelson A, Holmberg L, Ruutu M, et al. Radical prostatectomy versus watchful waiting in early prostate cancer. N Engl J Med 2011;364(18):1708–17.
38. Wilt TJ, Brawer MK, Jones KM, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012;367(3):203–13.
39. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA 2005;294(4):433–9.
40. Han M, Partin AW, Pound CR, et al. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. Urol Clin North Am 2001;28(3):555–65.
41. Stephenson AJ, Shariat SF, Zelefsky MJ, et al. Salvage radiotherapy for recurrent prostate cancer after radical prostatectomy. JAMA 2004;291(11):1325–32.
42. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281(17):1591–7.
43. Zelefsky MJ, Eastham JA, Cronin AM, et al. Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. J Clin Oncol 2010; 28(9):1508–13.
44. Abdollah F, Sun M, Thuret R, et al. A competing-risks analysis of survival after alternative treatment modalities for prostate cancer patients: 1988-2006. Eur Urol 2011;59(1):88–95.
45. 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):32–9.
46. Hricak H, Schoder H, Pucar D, et al. Advances in imaging in the postoperative patient with a rising prostate-specific antigen level. Semin Oncol 2003;30(5): 616–34.
47. Scattoni V, Montorsi F, Picchio M, et al. Diagnosis of local recurrence after radical prostatectomy. BJU Int 2004;93(5):680–8.
48. Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. J Clin Oncol 2007;25(16):2225–9.
49. Walsh PC. 2008 Whitmore Lecture: Radical prostatectomy–where we were and where we are going. Urol Oncol 2009;27(3):246–50.
50. Hull GW, Rabbani F, Abbas F, et al. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. J Urol 2002;167(2 Pt 1):528–34.
51. Ward JF, Zincke H, Bergstralh EJ, et al. The impact of surgical approach (nerve bundle preservation versus wide local excision) on surgical margins and biochemical recurrence following radical prostatectomy. J Urol 2004;172(4 Pt 1):1328–32.
52. Wagner M, Sokoloff M, Daneshmand S. The role of pelvic lymphadenectomy for prostate cancer–therapeutic? J Urol 2008;179(2):408–13.

53. La Rochelle JC, Amling CL. Role of lymphadenectomy for prostate cancer: indications and controversies. Urol Clin North Am 2011;38(4):387–95, v.
54. Sonpavde G, Chi KN, Powles T, et al. Neoadjuvant therapy followed by prostatectomy for clinically localized prostate cancer. Cancer 2007;110(12):2628–39.
55. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet 2005; 366(9485):572–8.
56. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 2009; 181(3):956–62.
57. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. J Clin Oncol 2009;27(18):2924–30.
58. Thompson IM Jr, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA 2006; 296(19):2329–35.
59. Moinpour CM, Hayden KA, Unger JM, et al. Health-related quality of life results in pathologic stage C prostate cancer from a Southwest Oncology Group trial comparing radical prostatectomy alone with radical prostatectomy plus radiation therapy. J Clin Oncol 2008;26(1):112–20.
60. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol 2007;25(15):2035–41.
61. Bolla M. Does adjuvant androgen suppression after radiotherapy for prostate cancer improve long-term outcomes? Nat Clin Pract Urol 2005;2(11):536–7.
62. Stephenson AJ, Bolla M, Briganti A, et al. Postoperative radiation therapy for pathologically advanced prostate cancer after radical prostatectomy. Eur Urol 2012;61(3):443–51.
63. Attard G, Richards J, de Bono JS. New strategies in metastatic prostate cancer: targeting the androgen receptor signaling pathway. Clin Cancer Res 2011;17(7): 1649–57.
64. Mostaghel EA, Page ST, Lin DW, et al. Intraprostatic androgens and androgen-regulated gene expression persist after testosterone suppression: therapeutic implications for castration-resistant prostate cancer. Cancer Res 2007;67(10): 5033–41.
65. Scher HI, Sawyers CL. Biology of progressive, castration-resistant prostate cancer: directed therapies targeting the androgen-receptor signaling axis. J Clin Oncol 2005;23(32):8253–61.
66. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 2006;7(6):472–9.
67. Studer UE, Whelan P, Albrecht W, et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24(12):1868–76.
68. Aus G, Abrahamsson PA, Ahlgren G, et al. Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. BJU Int 2002;90(6):561–6.

69. Gleave ME, Goldenberg SL, Chin JL, et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. J Urol 2001;166(2):500–6 [discussion: 506–7].
70. Hurtado-coll A, Goldenberg SL, Klotz L, et al. Preoperative neoadjuvant androgen withdrawal therapy in prostate cancer: the Canadian experience. Urology 2002;60(3 Suppl 1):45–51 [discussion: 51].
71. Rabbani F, Perrotti M, Bastar A, et al. Prostate specific antigen doubling time after radical prostatectomy: effect of neoadjuvant androgen deprivation therapy. J Urol 1999;161(3):847–52.
72. Soloway MS, Pareek K, Sharifi R, et al. Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results. J Urol 2002;167(1):112–6.
73. Taplin EA. Effect of neoadjuvant abiraterone acetate (AA) plus leuprolide acetate (LHRHa) on PSA, pathological complete response (pCR), and near pCR in localized high-risk prostate cancer (LHRPC): Results of a randomized phase II study. Paper presented at: American Society of Clinical Oncology. Chicago, 2012. Q12
74. 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):1285–90.
75. Pilepich MV, Winter K, John MJ, et al. Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys 2001; 50(5):1243–52.
76. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. N Engl J Med 2009;360(24):2516–27.
77. 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):1066–73.
78. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. JAMA 2008;299(3): 289–95.
79. Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. Lancet Oncol 2011;12(5):451–9.
80. Granfors T, Modig H, Damber JE, et al. Long-term followup of a randomized study of locally advanced prostate cancer treated with combined orchiectomy and external radiotherapy versus radiotherapy alone. J Urol 2006;176(2):544–7.
81. Horwitz EM, Bae K, Hanks GE, et al. Ten-year follow-up of radiation therapy oncology group protocol 92-02: a phase III trial of the duration of elective androgen deprivation in locally advanced prostate cancer. J Clin Oncol 2008; 26(15):2497–504.
82. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365(2):107–18.
83. Roach M 3rd, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: long-term results of RTOG 8610. J Clin Oncol 2008;26(4):585–91.
84. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. Lancet 2011;378(9809):2104–11.

85. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet 2009;373(9660):301–8.
86. 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.
87. D'Amico AV, Manola J, Loffredo M, et al. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: a randomized controlled trial. JAMA 2004;292(7):821–7.
88. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351(15):1513–20.
89. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351(15): 1502–12.
90. de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376(9747): 1147–54.
91. Patel AR, Sandler HM, Pienta KJ. Radiation Therapy Oncology Group 0521: a phase III randomized trial of androgen suppression and radiation therapy versus androgen suppression and radiation therapy followed by chemotherapy with docetaxel/prednisone for localized, high-risk prostate cancer. Clin Genitourin Cancer 2005;4(3):212–4.
92. Montgomery B, Lavori P, Garzotto M, et al. Veterans Affairs Cooperative Studies Program study 553: chemotherapy after prostatectomy, a phase III randomized study of prostatectomy versus prostatectomy with adjuvant docetaxel for patients with high-risk, localized prostate cancer. Urology 2008;72(3):474–80.
93. Garzotto M, Higano CS, O'Brien C, et al. Phase 1/2 study of preoperative docetaxel and mitoxantrone for high-risk prostate cancer. Cancer 2010;116(7): 1699–708.
94. Gleave M, Kelly WK. High-risk localized prostate cancer: a case for early chemotherapy. J Clin Oncol 2005;23(32):8186–91.
95. Hussain M, Smith DC, El-Rayes BF, et al. Neoadjuvant docetaxel and estramustine chemotherapy in high-risk/locallyadvanced prostate cancer. Urology 2003; 61(4):774–80.
96. Konety BR, Eastham JA, Reuter VE, et al. Feasibility of radical prostatectomy after neoadjuvant chemohormonal therapy for patients with high risk or locally advanced prostate cancer: results of a phase I/II study. J Urol 2004;171(2 Pt 1): 709–13.
97. Dreicer R, Magi-Galluzzi C, Zhou M, et al. Phase II trial of neoadjuvant docetaxel before radical prostatectomy for locally advanced prostate cancer. Urology 2004; 63(6):1138–42.
98. Chi KN, Chin JL, Winquist E, et al. Multicenter phase II study of combined neoadjuvant docetaxel and hormone therapy before radical prostatectomy for patients with high risk localized prostate cancer. J Urol 2008;180(2):565–70 [discussion: 570].

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