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Current Role of Neoadjuvant and Adjuvant Systemic Therapy for High-risk Localized Prostate Cancer

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Abstract

Purpose of review—While most men are diagnosed with readily curable localized prostate cancer, those with high risk features face a significant mortality risk. Androgen deprivation therapy (ADT) is a standard adjunct to radiotherapy for high-risk prostate cancer, but its role around prostatectomy has not been as clearly defined, and concerns over cardiovascular toxicity have led to decreasing use. The use of chemotherapy for localized disease remains experimental. We review the most recently published trials of neoadjuvant or adjuvant systemic therapy for prostate cancer.

Recent findings—The optimal duration of ADT with higher-dose modern radiation techniques is under active investigation, but current data support the use of longer duration as standard. PSA and MRI changes may be useful in future studies optimizing duration of neoadjuvant ADT. Two years of combined ADT after prostatectomy is associated with a lower risk of disease recurrence and better PCSM than predicted. Persistence of intraprostatic androgens during neoadjuvant ADT may contribute to resistance.

Summary—Androgen deprivation added to definitive radiation or surgery improves outcomes for high-risk prostate cancer, while the role of chemotherapy remains undefined. Molecular classification is needed to improve risk stratification.

Keywords

High-Risk Localized Prostate Cancer; Androgen Deprivation Therapy; Chemotherapy

Introduction

In the era of prostate-specific antigen (PSA) screening, most men are diagnosed with early stage prostate cancer (PC) and have an excellent prospect of cure with single modality therapy. However, men diagnosed with localized disease, but categorized as high-risk due to

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high Gleason score, PSA or advanced stage face a significant risk of mortality. Androgen deprivation therapy (ADT) is very effective in controlling metastatic PC, and improves survival when added to radiation for localized disease. However, concerns over metabolic complications including cardiovascular morbidity have led investigators to question how much ADT is necessary to improve outcomes, especially as escalated radiation doses are utilized. While ADT adjunctive to radical prostatectomy (RP) has shown some promise, the optimal course and magnitude of benefit is uncertain. The incorporation of chemotherapy remains experimental, though feasible. Neoadjuvant studies are contributing information about systemic therapy by illuminating the gene and protein changes that occur after exposure. We performed a PubMed search for (neo)adjuvant chemotherapy or (neo)adjuvant ADT and PC published after 2011. This review describes the results, focusing on the questions of greatest current clinical interest.

How should androgen deprivation be added to definitive radiation therapy to improve outcomes for high-risk prostate cancer patients?

Large randomized trials such as RTOG 8531 established a significant improvement in survival when goserelin was added to radiation therapy for high-risk PC¹. Subsequently RTOG 9202² identified that longer duration of ADT was associated with improved disease-free survival. Concerns have emerged regarding increased incidence of diabetes and cardiovascular mortality in patients treated with ADT from both observational and prospective randomized cohorts.^{3,4} A SEER analysis found that use of ADT increased throughout the 1990's followed by decline leading up to 2005⁵. A population-based study in Canada found similar patterns⁶. These declines in ADT usage may be related to toxicity concerns. A recent meta-analysis including 8 randomized trials in high-risk localized PC found no difference in cardiovascular mortality when ADT was used, and noted lower all-cause mortality with ADT⁷. These reassuring new data ensure that ADT will continue to be added to radiation. Nevertheless, determining the optimal duration remains important, since some toxicities are likely duration-dependent, and recovery of testicular function declines with prolonged ADT.

A recently published Japanese series of 75 men with high-risk PC treated with radiation found that 24 months of ADT was associated with 93.9% biochemical recurrence-free survival (RFS) compared to 70% for those treated with <24 months ($p=0.0053$)⁸. While these data are consistent with those from RTOG 92-02, these patients received a relatively low dose (70-74 Gy) with 3D-conformal radiotherapy, calling into question the generalizability of these findings to patients being treated today, with higher doses administered using intensity-modulated radiation and image guidance. Data estimating the importance of ADT, even with higher doses of radiation, are beginning to emerge. One example, from a series of 306 men with high-risk disease treated in Spain, found a significant reduction in biochemical recurrence with the addition of 2 years of adjuvant ADT after neoadjuvant and concurrent ADT with >79 Gy radiation⁹. A second series from Memorial Sloan Kettering found a persistent benefit of ADT despite the use of 81 Gy as the standard¹⁰. The series included 2551 patients, of whom 906 were high-risk, and found a 55% recurrence-free survival with ADT compared to 36% without.

The timing of ADT in conjunction with radiation for PC is another important question, since preclinical work has shown that castration before radiation results in better tumor control than castration after the start of radiation¹¹ and radiation may be more effective at treating smaller volumes. In a series of 20 men on combined androgen blockade prior to radiation therapy followed with repeat CT scans every 3 months, the biggest reduction in prostate volume occurred during the first 3 months, reaching maximum at 6 months¹². This led the authors to conclude that 6 months was an optimal duration for neoadjuvant ADT, though for men with small prostate volume 3 months may be adequate. The prospective Trans-Tasman Radiation Oncology Group 96.01 trial randomized men to radiation alone (66 Gy) or to 3 or 6 months neoadjuvant ADT (combined blockade, goserelin plus flutamide) with radiation. Updated data showed that 3 months of neoadjuvant ADT did not improve outcomes, whereas 6 months resulted in improved PC-specific mortality (HR 0.49, $p=0.0008$) and all-cause mortality (HR 0.63, $p=0.0008$)¹³. Whether the administration of therapy as a neoadjuvant was important, or whether the duration itself was responsible for the advantage is unclear. Further data to clarify these questions are awaited from the EORTC22991, RTOG 0815, and MRC RT01 trials.

What is the significance of PSA kinetics and radiographic changes during neoadjuvant androgen deprivation?

Retrospective series of men with PC being treated with radiation therapy have identified PSA kinetics during neoadjuvant ADT as a prognostic marker. A Canadian series of 64 patients with baseline PSA >40 ng/mL found that the nadir value before initiating radiation (0.1 vs >0.1 ng/mL) was significantly associated with biochemical RFS and overall survival¹⁴. This finding was not confirmed in a larger series of 117 intermediate and high-risk patients, although PSA halving time was found to be a significant prognosticator¹⁵. Men whose PSA halving time was ≤ 2 weeks had a 93% biochemical RFS at 4 years compared to 70% for those with >2 week halving times, and the difference remained statistically significant in multivariate analysis.

Advances in magnetic resonance imaging (MRI) have yielded additional insights into the dynamics of response to neoadjuvant ADT. Using susceptibility and relaxivity contrast enhanced MRI, ADT was shown to reduce tumor blood flow significantly within the first month, without additional reduction over the next 2 months¹⁶. In addition, permeability of vasculature measured as transfer of contrast was shown to decrease rapidly in the first month, with continued decline over the next 2 months. These pilot data generate many interesting hypotheses which can be incorporated into neoadjuvant protocols as we attempt to better define the optimal duration of systemic therapy.

Can we achieve pathologic complete response with neoadjuvant systemic therapy in prostate cancer? And is that an important goal?

In many solid tumors, pathologic complete response (pCR) has been an important biomarker of improved survival from neoadjuvant therapy. However, for prostate cancer the rate of pCR has been low and its association with survival is undefined (Table 1). The duration and

intensity of neoadjuvant ADT may be important. A series of 68 men of all risk groups treated with ADT using combined blockade prior to prostatectomy in Japan identified a strikingly high pCR rate of 35%²³. The pCR group had received a longer median duration of ADT (9 months) compared to the men who did not achieve pCR (7.5 months). The duration of ADT given after PSA nadir <0.2 ng/mL was also statistically significantly associated with pCR; favoring men who received ADT for 10 months after reaching nadir. Though the applicability of this study is clearly limited by size, retrospective nature, and the inclusion of lower risk patients it raises the hypothesis that duration of neoadjuvant ADT may be relevant. As a case in point, the single-arm phase II prospective trial SWOG 9109 (using combined blockade for 4 months in men with clinical T3 or T4 prostate cancer, of whom 67% had Gleason Score 7) found only 1 pCR out of 50 patients¹⁷. Intensity of androgen suppression may also be critical; 25% of men treated with neoadjuvant abiraterone plus LHRH agonist achieved pCR, and higher rates were observed in those treated for 24 weeks (34%) versus 12 weeks (15%) $p=0.09$ ¹⁸. Preliminary data suggest that pCR is associated with longer biochemical RFS, but additional data from trials with higher pCR rates are needed.

The incorporation of neoadjuvant chemotherapy has been evaluated for high-risk PC. Although few patients achieve pCR even with combined chemohormonal therapy, docetaxel appears to be associated with downstaging and is well-tolerated in the neoadjuvant setting. The Prostate Cancer Clinical Trials Consortium study testing docetaxel plus bevacizumab dosed once every 21 days reported only 3 (7%) significant grade 3 toxicities and 3 patients with febrile neutropenia¹⁹. Weekly docetaxel with estramustine was also well-tolerated, with a solitary grade 3 toxicity (elevated transaminases) of 18 patients treated²⁰. The combination of docetaxel with ketoconazole resulted in 72% incidence of grade 3 and 4 toxicity, despite using a low dose of 55 mg/m² docetaxel every 3 weeks²¹. Still, only 2 cases (9%) of febrile neutropenia were reported, and much of the toxicity may have been attributable to ketoconazole. Until larger randomized studies identify significant improvement in outcomes, the use of chemotherapy for localized PC will remain experimental and toxicity must be closely examined.

Molecular Outcomes of neoadjuvant systemic therapy

Advances in pathology, as well as our genetic and molecular understanding of prostate cancer, have expanded the types of data being obtained from neoadjuvant clinical trials. One intriguing finding is that intraprostatic DHEA, androstenedione, and androstenediol levels remain elevated whereas tissue testosterone and dihydrotestosterone levels drop during neoadjuvant castration therapy²⁴. Improved suppression of intratumoral androgens with abiraterone may thus explain the higher pCR rate seen in the neoadjuvant trial¹⁸.

Protein and gene expression studies are exploring patterns of changes induced by treatment to enhance our understanding of PC subtypes and therapeutic resistance. Tumors containing the TMPRSS2-ERG fusion were found to have higher expression of proliferation-related genes at baseline, which was significantly reduced by ADT, suggesting androgen dependence despite the fusion event²⁵. In contrast Bcl-2 protein expression in PC was found to increase after exposure to ADT, though this occurred despite a lack of increase in mRNA

levels for the gene²⁶. A study comparing tissue from patients exposed to neoadjuvant chemohormonal therapy to untreated prostatectomy specimens found that androgen receptor expression was not different, but steroidogenic enzyme expression (CYP17, SRD5A1) was increased²⁷. Pretreated specimens had lower vascular endothelial growth factor expression and higher insulin-like growth factor expression, suggesting the importance of alternative mediators of PC survival.

Interactions between cancer and the host, including immune system responses, are of increasing interest. Neoadjuvant ADT was found to increase expression of interleukin-7 and interferon- λ in the normal prostate epithelium in a group of 76 patients who were compared to 50 men untreated with neoadjuvant ADT²⁸. The cytokine changes were accompanied by increases in both cytotoxic T-cells and regulatory T-cells, and the authors postulated that the lack of a shift in T-cell subset ratios may contribute to the lack of recurrence-free survival benefit induced by neoadjuvant ADT.

Clinical outcomes of adjuvant systemic therapy

ECOG 3886, which randomized men with lymph-node positive PC to immediate ADT after RP, or to observation, reported a profound survival advantage at an early interim analysis²⁹. SWOG 9921 was predicated on these findings; this study randomized men with high risk prostate cancer (defined as node positive for the highest risk group, Gleason 8-10 or stage T3b for the intermediate risk group, and Gleason 7 with positive margins or PSA >10 for the lowest risk group) to adjuvant ADT for 2 years alone or with mitoxantrone. The trial closed early due to the finding of excess acute leukemia diagnoses in the mitoxantrone arm³⁰. The statistical design predicted that median overall survival would be 10 years for the ADT arm. Results from SWOG 9921 are shown in Table 2, along with recurrence for similar populations from published series examining outcomes of RP in high-risk cohorts. Although there was no observation arm for direct comparison, the rate of recurrence and death was markedly lower³¹ than the 50% RFS at 5 years expected based on published series at the time^{32,34}. Newer retrospective series provide corroborative evidence for benefit; in 172 patients with high-risk PC, those treated with adjuvant ADT had more than double the RFS, though with 67 months median follow-up there had only been 4 PC-related deaths so no survival difference could be detected³⁶.

Are there subsets of “high risk” patients more or less likely to benefit from adjuvant ADT? A series from the University of Michigan found a persistent benefit of adjuvant ADT across multiple definitions of high-risk PC, though high Gleason score seemed to confer a worse prognosis in the face of adjuvant treatment³⁷. Given the benefit of adjuvant radiotherapy for T3 disease, clinicians may have difficulty counseling patients without nodal involvement whether to pursue adjuvant radiation, ADT, or both. The Mayo clinic experience mirrors SWOG 9921; a population of 191 men with T3bN0 prostate cancer who received ADT but not radiation were identified and compared to a matched group of men who did not receive ADT or radiation. Adjuvant ADT was associated with markedly better biochemical RFS, 60% versus 16% at 10 years, and cancer-specific survival was improved (94% versus 87%, $p=0.037$) though overall survival was equivalent³⁸. Prospective comparative data are needed to assess single modality adjuvant therapy versus combination for high risk PC patients.

What are the costs of (neo)adjuvant therapy?

Survivorship and patient-reported outcomes are increasingly recognized as important aspects of curative-intent treatment. For PC patients, one important question is whether adding systemic therapy increases the local morbidity of surgery and radiation; i.e. effects on sexual, urinary, and bowel function. According to the Irish Clinical Oncology Research Group trial 97-01, duration of neoadjuvant ADT may not affect the risk of late toxicities. In this trial 276 men were randomly assigned to 4 months or 8 months of ADT followed by external beam radiation. There was no difference in erectile function at 5 years³⁹. Additional reassuring data come from a single-arm study of adjuvant ADT and docetaxel after external beam radiation and brachytherapy for high-risk PC⁴⁰. This intense regimen was associated with only 7.7% grade 2 late genitourinary and gastrointestinal toxicities, with a notable absence of grade 3 or 4 late toxicity after median follow-up of 5.6 years. More data are needed to adequately counsel patients about risks and benefits of systemic therapy as intensified multimodal regimens are used. The longer term effects of surgery and radiation on sexual function and urinary symptomatology are not encouraging and it is likely that incorporating ADT would make longer term sexual complications even worse⁴¹.

Men receiving adjuvant ADT after definitive surgery or radiation were found to have higher rates of depression and worse quality of life compared to men on observation⁴². Although body image perception was inferior in men on ADT, this correlated weakly with depression, suggesting that there may be a direct effect of low testosterone levels on the brain. A report of quality of life from the CaPSURE database, found significant declines in the domains of physical function and vitality after exposure to ADT⁴³. Further exploration of these outcomes in the adjuvant setting is urgently needed, and interventional trials studying the potential for lifestyle modification to preserve quality of life and physical function should have high priority.

Conclusions

Strong evidence supports the use of ADT as an adjunct to radiation in high-risk localized PC, and longer courses remain standard. The role of chemotherapy remains undefined. The neoadjuvant platform provides unique opportunities for investigating novel therapies; continued exploration of molecular changes induced by systemic therapy will yield insights critical for innovating clinical trial design for high-risk localized prostate cancer.

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KEY POINTS

- Neoadjuvant and adjuvant androgen deprivation therapy improve prostate cancer outcomes when added to definitive radiotherapy for high-risk localized prostate cancer.
- Improved suppression of intratumoral androgens may result in higher rates of pathologic complete response at radical prostatectomy.
- Adjuvant androgen deprivation after radical prostatectomy is associated with 83% 5-year relapse free survival for men with lymph node positive disease, and 92% 5-year relapse free survival for men with Gleason 8-10 or stage T3b; this makes it a reasonable standard option for men with high-risk localized prostate cancer.

Table 1
Rates of pathologic response in neoadjuvant clinical trials for high-risk prostate cancer

Author (year)	N	Intervention	pCR (rate)	Other findings
Berglund (2012) SWOG 9109 ¹⁷	62	Goserelin + flutamide × 4 months	1 (2%)	40% recurrence-free estimate at 10 years
Taplin (2012) ¹⁸	58	Leuprolide plus abiraterone × 12 weeks (n= 28) or 24 weeks (n= 30)	4 (15%) 10 (34%)	
Ross (2012) ¹⁹	41	Docetaxel + bevacizumab × 6 cycles	0	29% had >50% reduction in tumor volume
Narita (2012) ²⁰	18	CAB + weekly Docetaxel + estramustine	2 (11%)	
Womble (2011) ²¹	22	Ketoconazole + Docetaxel × 4 cycles	0	36% recurrence-free at 18 mo
Kim (2011) ²²	12	Docetaxel + Estramustine ×3 months	0	45% recurrence-free at 24 months

Table 2
Recurrence and survival following adjuvant ADT in the SWOG 9921 trial, alongside published series of similar patient populations

Group	N	S9921 ³¹ 5 year Freedom from Relapse (95% CI)	S9921 5 year OS	Published series
All patients on ADT without chemotherapy	481	92.5% (90.0, 95.0)	95.9% (93.9, 97.9)	n/a
Lymph node positive	79	83.2% (73.8, 92.6)	92.3% (85.6, 99.0)	18% OS at 7 years without ADT, 77% OS with adjuvant ADT ²⁹
Gleason 8 or stage T3b	277	92.2% (88.7, 95.7)	96.8% (94.6, 99.0)	15-30% RFS at 5 years ^{32,33} 40-45% at 5 years ^{34,35}

RFS = Relapse Free Survival