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# Chemotherapy and novel therapeutics before radical prostatectomy for high-risk clinically localized prostate cancer

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**Abstract**

Although both surgery and radiation are potential curative options for men with clinically localized prostate cancer, a significant proportion of men with high-risk and locally advanced disease will demonstrate biochemical and potentially clinical progression of their disease. Neoadjuvant systemic therapy before radical prostatectomy (RP) is a logical strategy to improve treatment outcomes for men with clinically localized high-risk prostate cancer. Furthermore, delivery of chemotherapy and other systemic agents before RP affords an opportunity to explore the efficacy of these agents with pathologic end points.

Neoadjuvant chemotherapy, primarily with docetaxel (with or without androgen deprivation therapy), has demonstrated feasibility and safety in men undergoing RP, but no study to date has established the efficacy of neoadjuvant chemotherapy or neoadjuvant chemohormonal therapies. Other novel agents, such as those targeting the vascular endothelial growth factor receptor, epidermal growth factor receptor, platelet-derived growth factor receptor, clusterin, and immunomodulatory therapeutics, are currently under investigation. 

*Keywords:* High-risk prostate cancer; Neoadjuvant therapy; Chemotherapy; Novel therapeutics

## Introduction

Prostate cancer is the most common cancer and the second leading cause of cancer mortality in men in the United States, with an estimated 233,000 new cases expected in 2014 [1]. Although there are many definitions of high-risk clinically localized prostate cancer, the National Comprehensive Cancer Network definition includes men with any of the following characteristics: prostate-specific antigen (PSA) level $>20$ ng/ml, clinical stage $\geq$T3, or Gleason grade $\geq 8$ [2]. In this cohort, radical prostatectomy (RP) or definitive radiation therapy alone may provide benefit, but many patients develop disease recurrence and progression [3]. Despite advances in surgical techniques, delivery of radiation therapy, and development of novel systemic agents, outcomes of high-risk patients undergoing RP have not improved significantly over time [4].

As a result, multimodality approaches to high-risk prostate cancer have been investigated. Although trials combining radiation therapy with neoadjuvant, concurrent, and adjuvant androgen deprivation therapy (ADT) have demonstrated survival advantages over radiation alone [5], similar benefits have not yet been demonstrated for combining neoadjuvant ADT with RP [6–8].

## Neoadjuvant therapy in high-risk clinically localized prostate cancer

Treatment of patients with high-risk clinically localized prostate cancer ideally includes strategies directed toward local control of the primary tumor and eradication of microscopic metastatic disease. Toward these goals, multimodality treatment strategies have been used and investigated. The primary goal of both neoadjuvant and adjuvant therapies is to prolong survival of patients with high-risk disease. As compared with adjuvant therapy, neoadjuvant therapy offers the potential benefits of treating patients before any debilitating effects of local treatment and

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downstaging localized or locally advanced tumors, which may potentially facilitate complete resection. Furthermore, studies of neoadjuvant therapy allow for ex vivo determinations of response to systemic treatment through in vivo examination of systemic treatment response (e.g., PSA), ex vivo histopathologic evaluation of RP specimens, or examination of correlative molecular biomarkers.

Pathologic end points, such as pathologic complete response (pCR), allow for the treatment of a small number of patients with a relatively short follow-up to establish a signal of efficacy of a neoadjuvant regimen. In other malignancies, such as breast and bladder cancers, pCR following neoadjuvant chemotherapy is a significant predictor of improved clinical outcomes such as disease-free survival and overall survival [9,10]. Whether similar surrogate pathologic end points for neoadjuvant prostate cancer therapies translate into clinical benefit remains to be demonstrated.

The neoadjuvant therapy paradigm also allows an opportunity to assess tumor response through surrogate biomarkers in tissue, blood, and other biologic specimen types. Furthermore, there exists the potential to identify prognostic and predictive genetic and molecular markers of response to treatment. Potential drawbacks of evaluating systemic therapies in the neoadjuvant setting include potential delay to surgery, increased rate of complications secondary to effects of treatment, and possible overtreatment of a subset of patients who would not otherwise experience disease recurrence.

Neoadjuvant systemic therapy is widely accepted and used in the treatment of patients with localized or locally advanced high-risk solid tumor malignancies, such as breast, bladder, rectal, and esophageal cancers [10–14]. The potential benefit of neoadjuvant therapy combined with the availability of novel agents for prostate cancer has led to the evaluation of multiple regimens including hormonal and chemotherapies in this setting.

## Neoadjuvant chemotherapy with or without ADT

The rationale for the use of neoadjuvant chemotherapy in patients with high-risk clinically localized prostate cancer arises from randomized clinical trials demonstrating the improved clinical outcomes of men with metastatic castration-resistant prostate cancer (CRPC) treated with chemotherapy [15–17]. A variety of agents have been tested in phase I/II studies of neoadjuvant therapy prior to RP in patients with high-risk or locally advanced prostate cancer (Tables 1–2). These trials have significant variability in terms of defining high-risk prostate cancer/eligibility criteria, chemotherapeutic regimens, duration of treatment, inferred quality of RP, definitions of pathologic end points, use of adjuvant therapies, duration of follow-up, survival end points, and the primary end point selected for analysis.

The duration of treatment in trials evaluating neoadjuvant chemotherapy in patients with high-risk clinically localized prostate cancer has ranged from 6 weeks to 6 months (Table 1) [18–23]. Dreicer et al. [18] performed a phase II study of weekly docetaxel for 6 weeks before RP ($n = 29$), with a primary end point of surgical feasibility. Secondary end points included change in serum PSA levels, histologic effects, and time to biochemical progression. There was a statistically significant reduction in prechemotherapy vs. postchemotherapy PSA ($P < 0.03$), but there was residual carcinoma in all cases (pCR = 0%). The authors published a follow-up study with immunohistochemical analysis comparing expression levels of various biomarkers in the pretreatment biopsy and posttreatment RP specimens [19]. They speculated that the absence of meaningful differences in expression levels of various cell cycle and apoptotic biomarkers could explain the lack of clinically significant response to neoadjuvant docetaxel.

Febbo et al. [20] published a phase II study that included 19 patients treated with 6 months of docetaxel before RP. The primary study end point was pCR; no patients achieved pCR. However, there was evidence of antitumor activity, as 11 patients (58%) had PSA level reduction of more than 50% and magnetic resonance imaging (MRI) measurements of tumor volume demonstrated maximum reduction of at least 25% in 13 patients (68%) and at least 50% in 4 patients (21%). Similarly, a phase II trial of 2 cycles of neoadjuvant nab-paclitaxel weekly for 3 weeks during a 4-week cycle ($n = 19$) identified no pathologic complete responders [22].

Although these studies of neoadjuvant chemotherapy alone demonstrated feasibility and some signals of biologic efficacy, the absence of pCR and lack of evidence of improved clinical outcomes have dampened enthusiasm for this approach. Other studies have evaluated neoadjuvant chemotherapy in combination with ADT (Table 2) [24–33]. The first trial to demonstrate a pCR in high-risk prostate cancer with neoadjuvant chemohormonal therapy was reported by Prayer-Galetti et al. [28]. In their phase II study of 22 patients with high-risk prostate cancer as defined by $\geq$cT3 disease, Gleason score $\geq 8$, or PSA level $\geq$15 ng/ml, they identified 1 patient (5%) with a pCR, and 6 (32%) with "substantial" pathologic response, which was defined as involving $\leq$10% of the RP specimen. In these 6 patients, the residual tumor was confined to small foci and was comprised of single cells or small groups of glands, with prominent cytoplasmic vacuolization. At a median follow-up of 53 (range: 30–64) months, 8 patients (42%) remained free of biochemical recurrence.

The Canadian Uro-Oncology Group conducted the largest phase II trial of neoadjuvant chemohormonal therapy and reported on 72 men with high-risk prostate cancer [29]. These patients were treated with docetaxel (weekly for 6 weeks in an 8-week cycle for 3 cycles) and ADT (buserelin acetate every 8 weeks for 3 doses and nilutamide for the first 4 weeks) followed by RP. Of the 64 patients completing