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Rationale for and Review of Neoadjuvant Therapy Prior to Radical Prostatectomy for Patients with High-Risk Prostate Cancer

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Abstract

Despite state of the art local therapy a significant portion of men with high-risk prostate cancer develop progressive disease. Neoadjuvant systemic therapy prior to radical prostatectomy (RP) is an approach which can potentially maximize survival outcomes in patients with localized disease. This approach is under investigation with a wide array of agents and provides an opportunity to assess pathologic and biologic activity of novel treatments. The aim of this review is to explore the past and present role of neoadjuvant therapy prior to definitive therapy with RP in patients with high-risk localized or locally advanced disease. The results of neoadjuvant ADT, including use of newer agents such as abiraterone and enzalutamide, are promising. Neoadjuvant chemotherapy, primarily with docetaxel, with or without ADT has also demonstrated efficacy in men with high-risk disease. Other novel agents targeting the vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), platelet derived growth factor receptor (PDGFR), clusterin, and the immune system are currently under investigation and have led to variable results in early clinical trials. Despite optimistic data, approval of neoadjuvant therapy prior to RP in patients with high-risk prostate cancer will depend on positive results from well designed phase III trials.

Introduction

Prostate cancer is the most common cancer in men in the United States, with a life time risk of 16%, and the second leading cause of cancer death in this population.^[1] It is a heterogeneous disease with a variable natural history. Despite ongoing efforts, outcomes in high-risk patients undergoing RP have not significantly improved with time.^[2–4] Following RP upwards of 50% of patients with high-risk disease will experience a biochemical recurrence at 5 years.^[4] In a retrospective analysis of 379 men who developed a biochemical recurrence after RP, approximately 80–90% of patients with high-risk prostate cancer die of their disease.^[5] Consequently, new treatment strategies, including multimodality therapy, are needed to improve outcomes in high-risk patients. The aim of this review is to explore

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the role neoadjuvant therapy, including ADT, chemotherapy, and other novel agents, prior to definitive therapy with RP in patients with high-risk localized or locally advanced disease.

1. Evidence Acquisition

A critical review of the literature was performed using Medline from 1966 to December 2012. The search included, but was not limited to, the following search terms: *prostate*, *prostate cancer*, *high-risk prostate cancer*, *radical prostatectomy*, and *neoadjuvant therapy*. A manual search of meeting abstracts was performed.

2. High-Risk Prostate Cancer

Currently, the exact classification of high-risk prostate cancer remains controversial given the presence of multiple definitions in the field that encompass a heterogeneous group of patients.^[6] Pretreatment variables including clinical stage, Gleason score, and prostate specific antigen (PSA) are well-established predictors of disease extent and outcome and have been used to define high-risk patients.^[7, 8] In 1998, D'Amico *et al* defined high-risk disease as clinical stage T2c, Gleason score 8, or PSA value > 20 ng/mL.^[7] The definition of high-risk disease supported by the National Comprehensive Cancer Network (NCCN) includes those with either cT3 disease, Gleason score 8, PSA ≥ 20 ng/mL or any two of the following: cT2b–c, Gleason score 7, PSA 10–20 ng/mL.^[9] Another definition uses the Cancer of the Prostate Risk Assessment (CAPRA) score, which combines age, PSA value, clinical stage, biopsy Gleason score, and percentage of positive biopsy cores, with a calculated score of 6–10 representing high-risk disease.^[10] The Kattan nomogram predicts the probability that a man will remain free from disease recurrence at 5 years after RP and could be used to define high-risk disease.^[8] Based on the NCCN, localized disease is defined as disease T3a whereas locally advanced disease is defined as T3b–T4 disease without lymph node metastasis.

Unfortunately, our ability to accurately identify high-risk patients has been hampered by the following: 1) underestimation of clinical stage by digital rectal examination (DRE) in 30–50% of patients, 2) undergrading of the diagnostic biopsy specimen in upwards of 45% in some series, and 3) variability in serum PSA levels given degree of tumor differentiation.^[11] The lack of consensus on a clear definition for high-risk disease has led to significant variability in standard clinical practice and in patient selection for systemic neoadjuvant or adjuvant treatment. In addition, use of heterogeneous definitions in clinical trials has rendered comparative assessment of treatment outcomes difficult. Given that accurate categorization of high-risk prostate cancer remains elusive, Nguyen and colleagues evaluated outcomes of high-risk patients following RP using six different definitions of high-risk disease and showed that biochemical relapse-free survival did not significantly differ when different definitions were used.^[12] The 10-year biochemical relapse-free survival ranged from 25–41% and 31–43% for those treated from 1987–1995 and after 1995, respectively.

In the screened population, high-risk prostate cancer accounts for about 15% of newly diagnosed cases.^[13] As opposed to early in the PSA era, currently patients are more likely to be categorized as high-risk by Gleason score alone rather than elevated PSA or abnormal

DRE.^[4] In a retrospective population-based cohort study of patients with clinically localized prostate cancer treated with either ADT or observation, men with high grade cancers (Gleason score ≥ 8) had a high probability of dying from prostate cancer within 10 years of diagnosis (121 deaths per 1000 person-years).^[14] There have been several series investigating RP in men with high-risk prostate cancer.^[6] Based on a multi-institutional cohort of over 12,000 patients treated with RP, risk of 15-year prostate cancer specific mortality was 22%, 38%, and 34% for patients with pretreatment PSA > 20 ng/dL, cT3, and Gleason 8–10 disease, respectively.^[15] Another study showed that the 15-year prostate cancer specific mortality risk following RP when stratified by patient age was 26–37% for Gleason 8–10 disease, 3–10% for extraprostatic extension, 15–27% for seminal vesicle invasion, and 22%–30% for lymph node metastasis.^[16] The ultimate goal of risk stratification is to match treatment with disease aggressiveness. Promising biomarkers in development may allow for better assessment of the metastatic potential of an individual cancer and identify high-risk patients who may benefit from multimodality treatments.

3. Neoadjuvant Therapy

Treatment of patients with high-risk disease presents two therapeutic challenges: the need for local control of the primary disease site and need for systemic control of microscopic metastatic disease. These circumstances often warrant multimodality treatment strategies. The primary goal of both neoadjuvant and adjuvant therapy is to improve long-term survival outcomes for patients with high-risk disease. Unlike adjuvant therapy, neoadjuvant therapy has the benefit of down-staging localized or locally advanced malignancy, which may facilitate surgical resection, and provide *in vivo* observation of systemic treatment response.

A central tenant of neoadjuvant therapy is that local tumor response correlates with long-term outcomes such as disease-free survival (DFS) and overall survival (OS). For breast cancer, pathologic complete response (pCR) is a significant predictor of improved clinical outcomes. In a review of 6,377 breast cancer patients from seven randomized trials receiving neoadjuvant anthracycline-taxane-based chemotherapy, pCR was associated with significantly superior DFS and a trend towards improved OS.^[17] Symmans and colleagues developed a method to measure residual disease in breast cancer by combining histopathologic components of residual disease (cellularity, overall diameter, number and extent of nodal involvement) into a numerical index of residual cancer burden (RCB).^[18] In a pathologic review of 382 patients treated in two different cohorts, RCB was calculated as a continuous index for prediction of distant relapse-free survival and was independently prognostic in a multivariate model. We will be analyzing RCB as a biomarker for long term clinical response in our ongoing neoadjuvant prostate cancer trials.

Additionally, pCR is associated with improved survival in other solid malignancies. In a trial of 317 patients with muscle-invasive bladder cancer treated with neoadjuvant chemotherapy followed by cystectomy versus cystectomy alone, improved survival was associated with the absence of residual cancer in the cystectomy specimen in both treatment arms.^[19] At five years, 85% of the patients with pCR were alive. Currently, there are no standardized criteria in any cancer type in regards to pathologic methods such as sectioning and

immunohistochemical staining to determine a pCR. Given the potential importance of pCR as a surrogate marker for survival, it is crucial to develop a consensus definition.

In prostate cancer, neoadjuvant therapy changes the morphology of the residual tumor, rendering the Gleason score of the post-therapy specimen inadequate.^[20] A study of 115 patients with high-risk prostate cancer who had preoperative therapy with androgen ablation alone or in combination with chemotherapy evaluated morphologic patterns in the RP specimens that may be helpful in assessing prognosis.^[20] Based on hierarchical clustering analysis, three morphologically distinct groups were identified. On multivariate analysis, the presence of cribriform or intraductal spread morphology were strong predictors of biochemical relapse. Contemporary neoadjuvant studies will provide opportunities to validate and extend these observations.

Since pathologic staging is determined at surgery, a small number of patients and relatively short follow-up time can be used to assess the effectiveness of a neoadjuvant regimen.^[21] The ability to rapidly assess tumor response via surgical staging and surrogate markers in tumor tissue and blood provides the potential to accelerate the pace of drug development.^[21] Preoperative treatment provides a platform to evaluate pharmacodynamic endpoints of novel agents to enable the identification of signals of biological activity. In addition, it may allow for the identification of molecular and biological prognostic and predictive factors.^[21] Potential shortcomings of neoadjuvant systemic therapy include: 1) delay of surgery and thus local control if neoadjuvant therapy is ineffective, 2) increased complications from surgery secondary to effects of systemic treatment, and 3) possible overtreatment of a subset of patients not destined to relapse.

The paradigm of neoadjuvant systemic therapy is widely accepted in the treatment of patients with localized or locally advanced high-risk breast cancer and other solid tumor malignancies. In breast cancer, adjuvant chemotherapy for patients with high-risk disease has been shown to significantly improve outcomes. Preoperative therapy, initially used for inoperable locally advanced breast cancer, has become more common for patients with operable disease. The National Surgical Breast and Bowel Project (NSABP) Protocol B-18 was designed to determine whether four cycles of doxorubicin and cyclophosphamide (AC) administered preoperatively improved breast cancer DFS and OS compared with AC administered postoperatively. At a median follow-up of 16 years, there were no statistically significant differences in DFS and OS between the groups, however, there were trends in favor of preoperative chemotherapy for DFS and OS in women younger than 50 years old.^[22] A meta-analysis of nine randomized studies, including a total of 3,946 women, demonstrated that neoadjuvant therapy was equivalent to adjuvant therapy in terms of DFS and OS.^[23] Additionally, neoadjuvant therapy is routinely utilized in the treatment of bladder^[24, 25], esophageal^[5, 26, 27], and rectal cancer^[24]. Extrapolating the benefit of neoadjuvant therapy in breast and other solid tumor malignancies to prostate cancer combined with the availability of new prostate cancer drugs gives us exciting new opportunities to improve outcomes for high-risk patients.

4.1 Neoadjuvant ADT

Since the first report of efficacy by Huggins in 1941, ADT has remained the mainstay of first-line systemic therapy for patients with metastatic prostate cancer.^[28] However, clinical trials of ADT in the neoadjuvant setting performed in the 1990's did not prove effective. Table 1 provides a review of clinical trials of neoadjuvant ADT prior to RP.^[29–40] Given that most of these trials were conducted prior to the establishment of specific criteria for risk assessment, the patients included are a heterogeneous group. Patients were either treated with both combined or single androgen blockage. There was one study in which patients were treated with antiandrogen therapy alone.^[33] These trials evaluated several pathological markers, including positive surgical margin rate, as surrogates for clinically relevant outcomes. Positive surgical margins at RP have been shown to be an independent predictor of biochemical progression in patients with intermediate and high-risk disease but this did not hold true in trials of neoadjuvant ADT.^[41, 42]

The concept of utilizing neoadjuvant ADT prior to surgery emerged in an attempt to improve the rate of organ-confined disease. Labrie and colleagues^[34] were among the first to show improvement in pathologic outcomes with a randomized, prospective trial using leuprolide and flutamide for three months prior to RP compared to RP alone. The study showed that neoadjuvant combination ADT decreased positive surgical margins from 33.8% to 7.8% and resulted in down-staging in 54% in the neoadjuvant arm. In addition, pCRs were found in six RP specimens (6.7%). The authors postulated that longer duration of neoadjuvant ADT could potentially increase the degree of benefit.

Subsequently treatment durations ranging from three to eight months were evaluated.^[32, 37, 39] The Canadian Urologic Oncology Group (CUOG) conducted the largest randomized trial evaluating neoadjuvant ADT prior to RP.^[32] In this study, 547 men with cT1b–T2 were randomly assigned to treatment with leuprolide and flutamide for three or eight months before RP. Compared to the three month group, the eight month group had lower preoperative PSA (0.052 versus 0.133 ug/L, $p=0.0141$), lower positive surgical margin rate (12% versus 23%, $p=0.0106$), and higher rate of organ-confined disease (80% versus 68%, $p=0.0019$). The pCR rate was higher in the eight month group compared to the three month group, though this was not statistically significant (9.3% versus 5.1%, $p=0.0711$). There have been no reports of improvement in biochemical relapse rates or other clinical outcomes with longer ADT from this trial.

In another study with the longest follow-up to date, 62 patients with cT3 or T4 disease were treated prospectively with neoadjuvant goserelin and flutamide for 4 months followed by RP.^[43] Of the 50 patients who underwent RP, one patient had a pCR and 28 patients (56%) had organ-confined disease. Positive surgical margins were present in 26% of patients. The 10-year PFS was 40% and 10-year OS was 68%.

A meta-analysis of 10 studies of neoadjuvant ADT prior to RP showed that neoadjuvant therapy had a beneficial and statistically significant impact in lowering the pathologic T stage, increasing the organ-confined rate, lowering the positive surgical margin rate, and decreasing the number of pathologic N1 cases.^[44] The effect on positive surgical margins and organ-confined rates was significantly better with eight months of neoadjuvant

treatment as compared to only three months of treatment. Four trials included information about the pCR rate.^[32–34, 39] The beneficial effects on pathologic outcomes, including pCR rate, did not translate to improved DFS or OS. The DFS at five years, defined either as biochemical or clinical progression, remained unchanged between the treatment and control groups. Only one trial found local recurrence rates to be decreased, but this was only in a subset of patients with T2 disease.^[36] In the three studies which evaluated OS with mean follow-up periods of 4, 6, and 7 years, the meta-analysis found no significant difference in OS and no assessments with longer follow-up are available.^[29, 33, 36] Thus neoadjuvant ADT is not currently a clinical recommendation in any setting.

The discordance between the improvement in immediate pathologic endpoints and the lack of benefit in DFS or OS is likely multi-factorial in nature. These trials were underpowered to detect realistic differences between treatment arms.^[21] In addition, they included patients who did not have high-risk disease, as defined today, possibly attenuating the impact of neoadjuvant therapy on outcomes.^[21] Longer durations of follow-up may be required to appreciate significant differences in outcomes.^[21]

Markers of biological response and resistance have been reported in small studies of neoadjuvant ADT. Mostaghel *et al* evaluated the effect of 3, 6, and 9 months of neoadjuvant ADT on gene expression in RP samples from men with localized prostate cancer.^[45] Medical castration was found to reduce tissue androgens by 75% and reduce the expression of several androgen-regulated genes including *NDRG1*, *FKBP5*, *TMPRESS2*, however androgen receptor (AR) and PSA gene expression were not suppressed. These data suggest that suboptimal suppression of the AR axis at the tumoral level may lead to resistance in a low androgen environment. These studies underscore the need for novel therapies targeting complete suppression of the AR axis.

In another study, investigators evaluated the effect of androgen suppression on tissue androgens and tumor volume.^[46] In this study, 35 men with intermediate or high-risk prostate cancer were treated for three months on therapy with either: 1) goserelin and dutasteride, 2) goserelin, dutasteride, and bicalutamide, or 3) goserelin, dutasteride, bicalutamide, and ketoconazole. Data were compared to men treated with standard ADT with an LHRH agonist and bicalutamide. pCR was observed in two men and eight men had <0.2 cm³ of tumor remaining. Treatment resulted in a 30 fold decrease in tissue dihydrotestosterone and a 3–4 fold increase in tissue testosterone compared to standard ADT. There was no correlation with tissue androgens and tumor volume. Data suggest that further suppression of the AR signaling axis may result in improved local and systemic control of prostate cancer.

Promising results with a number of new ADT options in patients with metastatic disease now are providing therapeutic options in the neoadjuvant setting. Gonadotropin-releasing hormone (GnRH) antagonists offer an alternative to luteinizing hormone-releasing hormone (LHRH) agonists, as a result of immediate competitive binding to GnRH receptors.^[47] Degarelix is a third generation GnRH receptor antagonist. Given the rapid onset of testosterone and PSA suppression with degarelix, there is interest in the use of GnRH antagonists in the neoadjuvant setting. Memorial Sloan-Kettering Cancer Center is currently

conducting a trial of neoadjuvant degarelix prior to RP for patients with intermediate and high-risk prostate cancer.^[48] The primary endpoint of this trial is the change in the rate of proliferation (Ki-67) and the rate of apoptosis (cleaved caspase-3), as evaluated by immunohistochemistry in anatomically matched tumor foci from the pre-treatment diagnostic biopsy and the RP specimen.

Abiraterone, which irreversibly inhibits the CYP17 enzyme thus blocking androgen synthesis in the testis, adrenal glands, and prostatic tumor cells, was evaluated in a phase III trial of 1,195 men with metastatic castration resistant prostate cancer (CRPC) previously treated with docetaxel.^[49] After a median follow-up of 13 months, abiraterone significantly increased OS (median 14.8 versus 10.9 months, $p<0.0001$), time to PSA progression (10.2 versus 6.6 months, $p<0.0001$), radiographic progression-free survival (PFS) (5.6 versus 3.6 months, $p<0.001$), and PSA response rate (29% versus 6%, $p<0.001$) compared with placebo plus prednisone. The interim analysis of a randomized, phase III study of abiraterone in chemotherapy-naïve patients with metastatic CRPC showed that treatment with abiraterone plus prednisone produced a statistically significant improvement in radiographic PFS (hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.35–0.52, $p<0.0001$) and a strong trend for increased OS (HR 0.75, 95% CI 0.61–0.93, $p=0.0097$) over placebo plus prednisone.^[50]

We evaluated abiraterone in a phase II neoadjuvant trial in patients with high and intermediate-risk prostate cancer. Fifty-eight patients with cT3–4, Gleason 7 (4+3), PSA >10 ng/mL, or high PSA velocity, were randomized to treatment with abiraterone in combination with leuprolide and prednisone or leuprolide alone for 12 weeks.^[51] At 12 weeks, prostate biopsy was performed to obtain tissue of measurement of intraprostatic hormones, as the primary endpoint of the trial was to analyze the differential effects of abiraterone versus leuprolide in tissue hormones. After 12 weeks all patients received another 12 weeks of combination abiraterone, leuprolide and prednisone. After 24 weeks of neoadjuvant therapy, patients underwent RP (Figure 1). The hypothesis was that abiraterone (and leuprolide) would more effectively reduce tissue androgens compared to leuprolide alone. Preliminary results were presented at the 2012 ASCO meeting and showed that tissue androgens were significantly more suppressed with abiraterone and pathologic responses were favorable thus providing optimism for this approach.

Another study presented at the 2012 ASCO meeting evaluated 12 weeks of preoperative therapy with abiraterone + prednisone + an LHRH agonist compared to therapy with an LHRH agonist alone in patients with high-risk prostate cancer.^[52] The primary aim was assessing the difference in down-staging between the treatment arms. Secondary aims were to assess differences in androgen biosynthesis and androgen signaling. Down-staging and near pCR (< 6 mm of scattered cells) occurred in 60% ($n=15/25$) and 24% ($n=6/25$) of patients in the combination arm, respectively, and 33% ($n=4/12$) and 8% ($n=1/12$) of patients in the LHRH monotherapy arm. Androgen signaling and proliferation suppression was more profound in the combination arm.

Enzalutamide is a novel androgen receptor signaling inhibitor which we are evaluating in the neoadjuvant setting. Enzalutamide competitively inhibits binding of androgen to the AR,

inhibits AR nuclear translocation, and association of the AR with DNA.^[53] The AFFIRM trial is a double-blinded phase III study which evaluated the efficacy of enzalutamide versus placebo in 1,199 men with advanced prostate cancer previously treated with docetaxel.^[19] The study was stopped after a planned interim analysis showed treatment with enzalutamide was associated with improved OS (18.4 versus 13.6 months, $p<0.0001$), radiographic PFS (8.3 versus 2.9 months, $p<0.0001$), time to PSA progression (8.3 versus 3.0 months, $p<0.0001$), PSA response (54% versus 2%, $p<0.0001$), and quality of life (43% versus 18%, $p<0.0001$). The PREVAIL trial, a safety and efficacy study of enzalutamide in chemotherapy-naïve patients with CRPC, is currently ongoing.^[54]

A multi-center randomized phase II trial is currently evaluating neoadjuvant enzalutamide alone versus enzalutamide, dutasteride, and leuprolide in men with localized intermediate and high-risk prostate cancer undergoing RP (Figure 2).^[55] The primary endpoint of this trial is pCR and near pCR rate. Tissue from baseline biopsies and from RP specimens will be used for correlative assessment of mechanisms of castration resistance including selective changes in the AR and AR associated genes.

The key to new drug development and optimization of androgen suppression in patients with advanced prostate cancer lies in the identification of molecular targets and characterization of mechanisms that drive cancer growth in an androgen-depleted environment. We now know that CRPC cells maintain a degree of hormone sensitivity after initial castration and further androgen blockade of CRPC is an effective treatment option. The availability of new therapeutic compounds for CRPC provides opportunities to evaluate these agents in the neoadjuvant setting to affect a cure for a greater proportion of men who are at high risk of death from prostate cancer. As the optimal sequencing of new agents and combinations with other androgen-axis targeting agents and pathway inhibitors are developed in CRPC, we will continue to explore the efficacy of these agents in the neoadjuvant setting. While the results of recent neoadjuvant trials are promising, many questions remain unanswered including will neoadjuvant therapy improve cure rates, what is the optimal regimen and duration of therapy, and which patient population will benefit from this approach. Eventually approval of neoadjuvant therapy for localized prostate cancer will hinge on positive results from well designed phase III trials.

4.2 Neoadjuvant Chemotherapy with or without ADT

The rationale to use chemotherapy earlier in the natural history of prostate cancer stems from recent randomized trials demonstrating improvement in clinical outcomes in men with metastatic CRPC.^[56, 57] Given the lack of phase III trials, there is limited data regarding the role of neoadjuvant chemotherapy with or without ADT prior to RP in localized or locally advanced prostate cancer.^[58–72] In addition, there is significant variability among trials in regards to multiple factors including: 1) chemotherapy regimen, 2) duration of treatment, 3) surgical techniques, 4) analysis of pathologic outcomes including definitions of minimal residual disease (MRD), 5) use of adjuvant therapy, 6) duration of follow-up, 7) evaluation of survival outcomes, and 8) primary outcome assessed. Table 2 and 3 display trials of neoadjuvant chemotherapy alone or with ADT prior to RP, respectively.

In these trials, the duration of treatment ranged from as little as six weeks to six months. Dreicer and colleagues^[60] evaluated the role of weekly docetaxel for six weeks followed by RP in a phase II study. The primary endpoint was feasibility of RP after six weeks of treatment. They showed a statistically significant reduction in pre- versus post-chemotherapy PSA ($p<0.03$) with 79% of patients experiencing some reduction and 24% of patients experiencing $>50\%$ reduction in PSA. Pathologic analysis demonstrated residual carcinoma in all cases with only 3 patients (11%) with organ-confined disease. The positive surgical margin rate was 3.5%. In a phase II study, 19 patients with high-risk disease received weekly docetaxel for six months followed by RP.^[61] The primary endpoint of the trial was to define the pCR rate of docetaxel chemotherapy in patients with untreated, high-risk prostate cancer. PSA declines of $>50\%$ were seen in 11 patients (58%) and endorectal coil MRI showed maximum tumor volume reduction of at least 25% in 13 patients (68%) and at least 50% in 4 patients. No patients achieved a pCR. Microarray analysis identified upregulation of genes involved in androgen metabolism in response to chemotherapy, specifically genes that decrease cellular levels of bioactive androgens.

Although studies of neoadjuvant chemotherapy alone show feasibility and some biological activity, the lack of pCR and definitive evidence of improved clinical outcomes quells the enthusiasm for chemotherapy regimens without ADT.^[21] Neoadjuvant chemotherapy in combination with ADT has also been evaluated. Prayer-Galetti and colleagues^[69] were the first to document a pCR with neoadjuvant chemohormonal therapy. In this study of 22 high-risk patients, neoadjuvant docetaxel and estramustine was prescribed following PSA nadir with triptorelin (a GnRH agonist). Investigators observed one patient (5%) with a pCR and six patients (31.5%) with MRD, defined as residual tumor confined to $\leq 10\%$ of prostate volume. The mean five-year DFS at 53 months was 80% for patients with $\leq 10\%$ residual cancer in the gland and 20% for those with $>10\%$. The significance of tumor volume as an independent predictor of disease recurrence is unclear with variable results in the literature.^[73–75] The impact of tumor volume is more subtle because of its significant correlation with serum PSA, capsular penetration, seminal vesicle invasion, and positive surgical margins. In addition, tumor volume is difficult to measure accurately.

The CUOG conducted the largest phase II trial of combined neoadjuvant chemotherapy with ADT.^[58] In this trial, 72 men with high-risk disease were treated with docetaxel (weekly for 6 of 8 weeks for 3 cycles) and ADT (buserelin acetate every 8 weeks for 3 doses and an antiandrogen for 4 weeks) followed by RP. Median PSA before surgery was 0.14 ug/L representing a median decrease of 98.4%. Of the 64 patients completing the protocol, two (3%) had a pCR and 16 patients (25%) had $\leq 5\%$ tumor in the RP specimen. There were 34 patients (53%) with pathologic T2 disease, 17 patients (27%) with positive margins, and 4 patients (6%) with regional lymph node involvement. After a median follow up of 42.7 months, a total of 19 patients (30%) had PSA recurrence.

Currently, the Cancer and Leukemia Group B (CALGB) is conducting a multicenter, phase III, randomized trial evaluating the efficacy of neoadjuvant chemohormonal therapy.^[76] The PUNCH 90203 trial plans to enroll and randomize 750 patients to either neoadjuvant therapy with docetaxel to complete six 21-day cycles and an LHRH agonist for 18–24 weeks followed by RP with staging pelvic lymphadenectomy versus surgery alone. Eligible

patients must have one high-risk criteria defined as: a nomogram predicted probability of 60% freedom from PSA recurrence at five years or Gleason 8 disease. The primary endpoint is three-year biochemical PFS.

Based on the results of the phase III TROPIC trial, cabazitaxel is currently used for treatment of men with CRPC progressing on docetaxel.^[56] A current study is investigating the role of neoadjuvant chemohormonal therapy with cabazitaxel and ADT before RP for patients with high-risk disease, defined as cT3, Gleason 8, or PSA doubling time of < nine months.^[77]

Recently, investigators sought to characterize the prevalence of potentially therapeutically actionable mutations in patients with high-risk prostate cancer having received neoadjuvant chemotherapy with docetaxel and mitoxantrone followed by RP.^[78] Using mass spectroscopy based sequencing, 10% of evaluable tumors (n=40) had point mutations in potentially actionable cancer genes. In addition, using immunohistochemistry, 36% of evaluable tumors (n=45) had PTEN loss and 40% had ERG rearrangements. Though point mutations in cancer regulatory genes were rare, the neoadjuvant paradigm has the potential to accelerate the pace of systemic drug development.

In summary, neoadjuvant chemotherapy with or without ADT results in decreased disease burden – clinically, radiographically, pathologically, and biochemically. Whether these results translate into long-term clinically significant benefits in the phase III setting remains to be determined. Given the conflicting results between immediate pathologic endpoints and clinically meaningful overall outcomes, current guidelines recommend against neoadjuvant chemotherapy and/or ADT prior to RP in patients with localized or locally advanced prostate cancer.

4.3 Neoadjuvant Novel Therapies

The paradigm of neoadjuvant therapy with novel agents has drawn special attention given the potential to detect an early signal of biological activity in RP specimens. Various agents targeting diverse molecular mechanisms utilized by prostate cancer cells are under investigation in the neoadjuvant setting.

4.3.1 Targeting Angiogenesis and the Vascular Endothelial Growth Factor

Receptor—Given that angiogenesis is an important process for tumor growth, progression, and metastasis, VEGFR appears to be a promising target in prostate cancer.^[79] A phase II multicenter trial evaluated the efficacy of neoadjuvant docetaxel with bevacizumab in high-risk patients, defined as T3 (clinical or by MRI), Gleason 8, PSA 20 ng/mL, or PSA velocity 2 ng/mL/year.^[80] Forty-one patients were treated with docetaxel, every 21 days to complete six cycles, and bevacizumab, every 21 days for cycles 1–5. Thirty-seven patients went on to RP. The primary endpoint was partial response by endorectal MRI. Twelve patients (29%) achieved a >50% reduction in tumor volume, nine patients (22%) achieved a 50% post-treatment decline in PSA. There were no pCR. Fourteen patients (37%) had disease confined to the prostate and 68% had negative resection margins.

Sunitinib, a multi-targeted receptor tyrosine kinase with activity against VEGFR, is also being studied in the neoadjuvant setting with or without ADT. A phase II trial of neoadjuvant sunitinib with leuprolide for three months followed by RP in patients with high-risk disease, defined as cT3, Gleason 8, PSA >20 ng/mL, or cT2b–c + Gleason 7 + PSA >10 ng/mL, demonstrated a pCR rate of 4.5% (2 of 44 patients).^[81] At a median follow-up of 35 months, 15 patients (43%) were disease free.

A phase I/II study evaluated neoadjuvant thalidomide, an anti-angiogenic agent with immunomodulatory properties, for 12 weeks followed by RP in 18 patients with high-risk prostate cancer, defined as cT3 or cT1c–T2c + Gleason 7.^[82] Thalidomide was well tolerated and induced a median reduction of PSA of 41% without affecting testosterone. Modulation of vascular marker expression accompanied by a reduction in microvessel density was noted in the treated group on tissue microarray analysis. There was a transition to a less aggressive phenotype when comparing stromal-epithelial interaction markers in the treatment arm compared to the control group. A phase II neoadjuvant trial treated patients with intermediate or high-risk prostate cancer with thalidomide and granulocyte macrophage colony-stimulating factor (GM-CSF) to complete two 28-day cycles followed by RP.^[83] Although no pCRs were observed, significant post-treatment tumor T-cell and dendritic cell infiltration was noted. With a median follow up of 32 months, 19% of patients developed biochemical failure. GM-CSF alone is currently being investigated in the neoadjuvant setting prior to RP.^[84]

4.3.2 Targeting the Epidermal Growth Factor Receptor—The EGFR, which is frequently overexpressed in prostate cancer that is associated with a more aggressive clinical phenotype, is another potential target.^[85] A phase II trial investigated treatment with neoadjuvant docetaxel and gefitinib for two months before RP in high-risk patients, defined as cT2b–T3, Gleason 8, PSA >20 ng/mL. The primary endpoint was pCR. All RP specimens demonstrated residual carcinoma. Twenty-nine patients (94%) achieved a clinical partial response, 20 patients (67%) had negative surgical margins, and post-chemotherapy PSA reductions were observed in 21 patients (68%).^[86] A phase II trial of cetuximab with or without docetaxel in the neoadjuvant setting was recently closed secondary to poor accrual.^[87] Unfortunately, the data in both metastatic and neoadjuvant trials are disappointing, limiting the role of EGFR inhibition in prostate cancer.

4.3.3 Targeting Platelet Derived Growth Factor Receptor—PDGFR is expressed in high grade primary prostatic adenocarcinomas.^[88, 89] Imatinib, a tyrosine-kinase inhibitor with activity against PDGFR, has been evaluated in neoadjuvant prostate cancer trials either alone or combined with docetaxel and ADT.^[90, 91] A study of 36 men with high-risk disease, defined as cT2, Gleason 8, PSA >20 ng/mL or cT2b + Gleason 7 + PSA >10 ng/mL, scheduled patients to receive docetaxel, weekly for four weeks in a 6-week cycle, imatinib, and leuprolide to complete three cycles prior to RP.^[91] The primary objectives were to assess the clinicopathological outcomes and PFS. In this study, the positive surgical margin rate was 18%, though there were no pCR. At a median follow up of 39 months, 53% were free from progression. Unfortunately, these disappointing data parallel studies in

patients with advanced CRPC, suggesting that PDGFR inhibition has little activity in prostate cancer.

4.3.4 Targeting Clusterin—Secretory clusterin is a stress-activated cytoprotective chaperone that confers treatment resistance in many cancers, including CRPC.^[92] OGX-011 (custirsen) is a second generation oligonucleotide antisense inhibitor targeting clusterin, with activity in patients with metastatic CRPC.^[93] In the neoadjuvant setting, 25 men with high-risk prostate cancer, defined as cT3, Gleason 7, PSA > 10 ng/ml or Gleason 6 with 3 positive cores, were treated with OGX-011 on days 1, 3 and 5 and then weekly for days 8–29, combined with ADT followed by RP.^[94] OGX-011 was well tolerated, reduced clusterin expression in primary prostate tumors, and increased the apoptotic index of prostate cancer cells in a dose-dependent manner. This trial demonstrated the safety and biological efficacy of OGX-011. Future trials will investigate the clinical efficacy of this agent.

4.3.5 Immunotherapy—The efficacy of sipuleucel-T for metastatic CRPC has led to a renewed interest in immunotherapy for prostate cancer. Sipuleucel-T is an autologous active cellular immunotherapy product consisting of dendritic cells activated *in vitro* with a recombinant fusion protein consisting of the antigen prostatic acid phosphatase and GM-CSF, designed to stimulate an immune response against prostate cancer.^[95] Neo-ACT is an open-label, phase II trial of neoadjuvant sipuleucel-T administered in three infusions two weeks apart prior to RP. Preliminary results presented at the ASCO 2012 meeting showed a significant 3-fold increase in CD3+ and CD4+ T-cell populations observed at the tumor interface, compared to pre-treatment biopsy, benign RP tissue, and tumor RP tissue.^[96]

Ipilimumab, a fully human monoclonal antibody which blocks cytotoxic T-lymphocyte antigen (CTLA) 4 and potentiates an antitumor T-cell response, was recently approved for the treatment of metastatic melanoma and is being investigated in prostate cancer.^[97] M.D. Anderson Cancer Center is currently conducting a phase II clinical trial of neoadjuvant ipilimumab plus ADT in men with high-risk prostate cancer, defined as cT1-T3b and Gleason 8 or PSA 20 ng/mL, followed by RP.^[98] The primary endpoint is immunological peripheral blood and tissue variables.

Although prostate cancer was not historically considered an immune-responsive cancer, recent clinical trials have demonstrated that immunotherapy for prostate cancer can lead to improvements in efficacy. Important unresolved issues with immunotherapy include: 1) length of time required to initiate antitumor immunity, 2) defining biomarkers to recognize effectiveness of immune therapies, and 3) determining effect on clinical efficacy endpoints.

4. Conclusions

In recent years, the use of ADT and chemotherapy has expanded beyond advanced disease and is playing an ever increasing role in earlier disease stages especially in clinical trials. Neoadjuvant therapy prior to RP has not yet been established as a standard of care given the lack of testing in phase III clinical trials. However, neoadjuvant therapy followed by RP is feasible with a wide array of agents and provides a paradigm for evaluating the activity of new treatments, which may aid in the rapid development of novel therapeutic agents. The

early use of new compounds including more potent castration, immune, and chemotherapy provides an opportunity to treat and possibly cure patients with high-risk localized or locally advanced prostate cancer who are at risk of death from the disease. Over the next few years work will define an optimal neoadjuvant/adjuvant regimen, an optimal surrogate endpoint for OS, and implement a phase III trial to prove efficacy.

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Figure 1.
Schema of study of neoadjuvant abiraterone and leuprolide.

Figure 2.
Schema of study of neoadjuvant enzalutamide.

Table 1

Clinical trials of neoadjuvant ADT prior to RP.

Trial	Patients	Clinical Stage	Regimen	Outcomes (Neoadjuvant ADT + RP vs. RP alone)				Median Follow Up (Years)
				Positive Surgical Margin Rate	pCR Rate	PFS	OS	
Dalkin <i>et al</i> (1996) [30]	56	T1c–T2b	G x 3 mo	18% vs. 14%	NR	NR	NR	
Labrie <i>et al</i> (1997) [34]	161	T2–T3	L + F x 3 mo	7.8% vs. 33.8% *	6.7% vs. 0%	NR	NR	
Fair <i>et al</i> (1999) [31]	140	T1–T3	L + F x 3 mo	19% vs. 37% *	NR	No difference	NR	2.9
Van Der Kwast <i>et al</i> (1999) [39]	47	T1–T3	L + F x 3 mo vs. L + F x 6 mo	27.8% (3 mo) vs. 9.1% (6 mo) *	0 (3 mo) vs. 9% (6 mo)	NR	NR	
Schulman <i>et al</i> (2000) [36]	402	T2–T3	G + F x 3 mo	13% vs. 37% T2 * 42% vs. 61% T3	NR	74% vs. 67%	No difference	4
Gleave <i>et al</i> (2001) [32]	547	T1b–T2	L + F x 3 mo vs. L + F x 8 mo	23% (3 mo) vs. 12% (8 mo) *	5.1% (3 mo) vs. 9.3% (8 mo)	NR	NR	
Soloway <i>et al</i> (2002) [38]	303	T2b	L + F x 3 mo	18% vs. 48% *	NR	64.8% vs. 67.6%	NR	5
Selli <i>et al</i> (2002) [37]	431	T2–T3	G + B x 3 mo vs. G + B x 6 mo	27.9% vs. 53.1% (3 mo) * 29.7% vs. 53.1% (6 mo) *	NR	NR	NR	
Aus <i>et al</i> (2002) [29]	126	T1b–T3a	T x 3 mo	23.6% vs. 45.5% *	NR	49.8% vs. 51.5%	No difference	6.85
Klotz <i>et al</i> (2003) [33]	213	T1b–T2	T x 3 mo	28% vs. 65% *	0% vs. 0%	60.2% vs. 68.2% 30.5% vs. 18.8% * for PSA > 20 ng/ml	88.4% vs. 93.9%	6
Prezioso <i>et al</i> (2004) [35]	167	T1a–T2b	L + C x 3 mo	39% vs. 60% ^a	NR	NR	NR	
Yee <i>et al</i> (2009) [40]	148	T1b–T3	G + F x 3 mo	19% vs. 38% *	NR	80% vs. 78%	NR	8

* Denotes statistical significance.

G = goserelin (G); mo = months; NR = not recorded; L = leuprolide; F = flutamide; B = bicalutamide; T = triptorelin; C = cyproterone.

Table II

Clinical trials of neoadjuvant chemotherapy alone prior to RP.

Trial	Patients	Selection Criteria	Regimen	Outcomes				Median Follow Up (months)
				Positive Surgical Margin Rate	pCR Rate	PFS	OS	
Dreicer <i>et al</i> (2004) ^[60]	29	cT2b–T3, or Gleason 8, or PSA > 15 ng/mL	D (weekly x 6 weeks)	3.5%	0%	NR	NR	
Febbo <i>et al</i> (2005) ^[61]	19	cT3, or Gleason 8, or PSA 20 ng/ml, or Gleason 4+3 and SVI on MRI and/or >5 positive cores	D (weekly x 6 months)	NR	0%	NR	NR	
Friedman <i>et al</i> (2008) ^[62]	15	> cT2, or Gleason 8, or PSA > 15 ng/mL	D (weekly for 3 weeks in a 4 week cycle) and C (every 2 weeks in a 4 week cycle) x 3–6 cycles	55%	0%	NR	NR	
Shepard <i>et al</i> (2009) ^[71]	19	cT2b–T3, or Gleason 8 or any 5 component or 4+3 6 in 3 cores, or PSA 15 ng/ml, or 30% chance of BCF within 5 years	Nab-Pac (weekly for 3 weeks in a 4 week cycle x 2)	50%	0%	NR	NR	
Garzotto <i>et al</i> (2010) ^[63]	57	cT2c or surgically resectable cT3a, or Gleason 4+3 or any 5 elements, or PSA 15 ng/ml	D and escalating M (weekly for 3 weeks in a 4 week cycle x 4)	33%	0%	65.5% (2 years), 49.8% (5 years)	NR	63
Layton <i>et al</i> (2012) ^[65]	16	cT3, or Gleason 8, or PSA 20 ng/ml, or Gleason 4+3 and cT2	I (weekly x 12–16 weeks)	50%	0%	NR	NR	

D = docetaxel; NR = not recorded; SVI = seminal vesicle invasion; BCF = biochemical failure; C = capecitabine; Nab-Pac = albumin-bound paclitaxel; M = mitoxantrone, I = ixabepilone.

Table III

Clinical trials of neoadjuvant chemotherapy with ADT prior to RP.

Trial	Patients	Selection Criteria	Regimen	Outcomes				Median Follow Up (months)
				Positive Surgical Margin Rate	pCR Rate	PFS	OS	
Pettaway <i>et al</i> (2000) [68]	33	cT3, or cT1-2 and Gleason 8, or cT2b-c and Gleason 7 and PSA 10 ng/ml	KAVE + LHRH agonist + AA (weekly K + A alternating with V + E, every 6 weeks x 2)	17%	0%	69%	NR	13
Clark <i>et al</i> (2001) [59]	18	cT2b-T3, or Gleason 8, or PSA > 15 ng/ml	ET + E (orally for 3 weeks in a 4 week cycle x 3)	13%	0%	88%	NR	14
Konety <i>et al</i> (2004) [64]	36	cT3, or Gleason 8, or PSA > 20 ng/ml	C + P + E + G (4 week cycles x 4-6)	22%	0%	45%	NR	29
Prayer-Galetti <i>et al</i> (2007) [69]	22	cT3, or Gleason 8, or PSA 15 ng/ml	D + E + T (every 21 days x 4)	26.3%	5% (31.5% MRD)	42%	NR	53
Chi <i>et al</i> (2008) [58]	72	2 positive biopsies, and cT3, or Gleason 7, or PSA 20 ng/ml	D + B + AA (weekly for 6 weeks in an 8 week cycle x 3)	27%	3.1% (25% MRD)	70%	NR	42.7
Sella <i>et al</i> (2008) [70]	22	cT2c, or Gleason 8, or PSA 20 ng/ml	D + E + G + B (every 21 days x 4)	27%	0%	54.6%	NR	23.6
Mellado <i>et al</i> (2009) [66]	57	cT3, or Gleason 7 (4 + 3), or PSA > 20 ng/ml	D + E + G + F (weekly for 3 weeks in a 4 week cycle x 3)	35.3%	6% (6% MRD)	65%	NR	35
Womble <i>et al</i> (2011) [72]	22	cT3, or Gleason 8 or presence of 4 component, or PSA > 20 ng/ml	D + K (every 21 days x 4)	42%	0%	36.4%	NR	18
Narita <i>et al</i> (2012) [67]	18	cT3, or Gleason > 9, or PSA 15 ng/ml	D + E + L (weekly x 6)	0%	11.1%	77.7%	NR	18

K = ketoconazole; A = doxorubicin; V = vinblastine; E = estramustine; AA = antiandrogen; NR = not recorded; ET = etoposide; C = carboplatin; P = paclitaxel; G = goserelin; D = docetaxel; T = triptorelin; MRD = minimal residual disease; B = buserelin; F = flutamide; L = leuprolide.