Neoadjuvant Therapy in High-Risk Prostate Cancer

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ABSTRACT

High-risk prostate cancer (PCa) is associated with higher rates of biochemical recurrence, clinical recurrence, metastasis, and PCa-specific death, compared to low- and intermediate-risk disease. Herein, we review the various definitions of high-risk PCa, describe the rationale for neoadjuvant therapy prior to radical prostatectomy, and summarize the contemporary data on neoadjuvant therapies. Since the 1990s, several randomized trials of neoadjuvant androgen deprivation therapy (ADT) have consistently demonstrated improved pathological parameters, specifically tumor downstaging and reduced extraprostatic extension, seminal vesicle invasion, and positive surgical margins without improvements in cancer-specific or overall survival. These studies, however, were not exclusive to high-risk patients and were limited by suboptimal follow-up periods. Newer studies of neoadjuvant ADT in high-risk PCa show promising pathological and oncological outcomes. Recent level 1 data suggests neoadjuvant chemohormonal therapy (CHT) may improve longer-term survival in high-risk PCa. Immunologic neoadjuvant trials are in their infancy, and further study is required. Neoadjuvant therapies may be promising additions to the multimodal therapeutic landscape of high-risk and locally advanced PCa in the near future.

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men and the fourth most common cancer overall.[1] PCa guidelines have incorporated various risk stratification schemes for localized PCa as a basis for predicting risk of recurrence after definitive local therapy and guiding therapeutic recommendations.[2-4] Risk stratification is typically based on prostate specific antigen (PSA), clinical stage on digital rectal exam (DRE), and prostate biopsy Gleason score or Grade Group (GG). Despite considerable stage migration associated with widespread PSA screening, up to 1/3 of the incident PCa cases have high-risk features.[5] Low-risk PCa has an excellent 10-year cancer-specific survival of 99% in men undergoing active surveillance, radical prostatectomy (RP), or radiation therapy (RT), irrespective of the treatment strategy.[6] On the other hand, men with high-risk PCa have a higher risk of failure with a lower 10-year biochemical recurrence (BCR)-free survival (68%) and cancer-specific survival (88%–92%) after local treatment with RP or RT.[7,8] Hence, a significant portion of men with high-risk PCa will need additional adjuvant or salvage treatment following RP in the search for long-term cure.[9] The utilization of radical curative treatment for high-risk PCa has increased over the past 2 decades. Given that PCa is an inherently androgen-driven malignancy, several studies have investigated the use of androgen deprivation therapy (ADT) in men with localized PCa. While ADT is used routinely in metastatic PCa and with external beam RT for intermediate and high-risk PCa, it is not currently recommended prior to RP for nonmetastatic PCa.[2-4] While the early trials of neoadjuvant ADT (nADT) prior to RP did not demonstrate an oncological

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benefit, subset analyses in high-risk PCa have suggested a trend towards the survival benefit in this cohort. Emerging data on newer anti-androgen agents, immunotherapy, and chemotherapy in metastatic PCa has led to a renewed interest in the concept of neoadjuvant therapy prior to RP in the higher risk cohorts.

DEFINITION AND OUTCOMES FOR HIGH-RISK PROSTATE CANCER

High-risk disease generally accounts for approximately 15%–30% of all the incident PCa diagnoses. A number of risk stratification systems for PCa have been published. The most commonly used systems are from the D’Amico classification, American Urological Association (AUA)/American Society for Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO), European Association of Urology (EAU), and National Comprehensive Cancer Network (NCCN) guidelines [Table 1].

Although mostly similar, these definitions are subtly different particularly with regards to the clinical stage as assessed by DRE. While DRE is a very useful assessment tool, it lacks specificity and sensitivity. Because of the subjective nature in identifying a prostate lesion and the number of quadrants affected by the prostate lesion, the DRE assessment is limited by a significant inter-observer variability. In the European Randomized study of Screening for PCa, suspicious DRE was reported in 4%–28% of the cases and the detection of PCa in men with a suspicious DRE varied from 18% to 36%. The varying definitions for high-risk PCa can lead to significant differences in the published prevalence of high-risk disease. Further, the prognostic estimates can also vary significantly as demonstrated in a study by Yossepowitch et al., where the same population had a 49%–80% 5-year recurrence-free survival based on the different classification schemes. A systematic review and meta-analysis of RP versus RT in high-risk disease found that RT with or without ADT had worse overall and disease-specific mortality compared to RP. Similarly, a study of the Surveillance, Epidemiology, and End Results (SEER) database demonstrated that RP had improved cancer-specific survival compared to RT and ADT in high-risk PCa, with the additional benefit of significant cost savings over radiation. Another SEER database study in patients with high-risk PCa found that surgery improved the overall survival compared to RT alone, though a combination of RT and brachytherapy had improved cancer-specific survival compared to RT or RP alone. Multimodal therapy using a combination of surgery and RT is often required for the optimal management of high-risk PCa. The advantage of upfront surgery for locally advanced PCa is the potential for cure in cases of complete resection and negative surgical margins with salvage RT kept in the reserve if required. This approach is supported by the recent data from the Radiotherapy– Adjuvant Versus Early Salvage (RAVES) trial demonstrating that salvage RT is associated with fewer men getting RT and reduced genitourinary toxicity compared to adjuvant RT following RP.

NEOADJUVANT THERAPY OBJECTIVES

BCR can be seen in approximately 30%–50% of the men with high-risk PCa within 10 years of surgery. Positive surgical margins has been found to be a predictor of PSA recurrence and secondary cancer treatment including adjuvant ADT or RT. As such, neoadjuvant therapies prior to RP have been investigated in an attempt to decrease cancer volume and potentially downstage the disease before surgery. Further, the administration of therapies early in the disease course may allow the patients to benefit while...
they have minimal tumor burden, potentially improving long term cure. Systemic neoadjuvant therapy may also eliminate micrometastatic disease and reduce the risk of local recurrence and distant metastases in the future. An overview of the various types of systematic neoadjuvant therapies is shown in Table 2.

**ANDROGEN DEPRIVATION THERAPY AGENTS AND MECHANISM OF ACTION**

ADT can include surgical castration via orchietomy, or medical castration via luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, as well as androgen-receptor blockers. Bilateral orchietomy was historically performed to eliminate testicular androgen production. Serum testosterone levels after orchietomy are typically <15 ng/dL. A small amount of testosterone can still be produced by the adrenal glands. While effective, given the irreversibility of the procedure and recent pharmacological advances, medical ADT is preferred in contemporary clinical practice, medical ADT is more commonly used.

Oral antiandrogens can be nonsteroidal (bicalutamide, flutamide, and nilutamide) and steroidal (cyproterone acetate). They inhibit the binding of dihydrotestosterone (DHT) and testosterone to the androgen receptor, but the overall serum testosterone levels are not reduced. Thus, they are typically less effective as a monotherapy and are more commonly used in combination with LHRH agonists or antagonists. Abiraterone, a newer hormonal agent, is a 17-lyase inhibitor and inhibits steroid hormone synthesis in both the adrenal and the prostate glands. Clinically, it has been shown to improve survival in both the castrate-sensitive and castrate-resistant metastatic PCa.

LHRH agonists (leuprolide acetate, triptorelin pamoate, goserelin acetate, and histrelin acetate) and antagonists (degarelix) work to lower the circulating testosterone levels by suppressing the hypothalamic–pituitary–gonadal axis. Initially, the hypothalamus releases LHRH in a pulsatile fashion, which binds to the receptors in the anterior pituitary gland leading to the secretion of luteinizing and follicle-stimulating hormones. Luteinizing hormone then binds to the receptors in the Leydig cells of the testes to stimulate testosterone production. Thus, suppressing this mechanism reduces the testosterone levels. LHRH agonists stimulate the LHRH receptor continuously leading to a transient increase in luteinizing hormone and testosterone levels leading to an increase in PSA (“flare” phenomenon), followed by the downregulation of the receptor with decreased testosterone levels. LHRH antagonists (degarelix), on the other hand, directly block LHRH receptors leading to a reduction in LH and testosterone levels, without the flare phenomenon.

**RATIONALE FOR NEOADJUVANT ANDROGEN DEPRIVATION THERAPY**

The androgen-dependency of PCa was initially described by Huggins in 1941. PCs begins as prostatic intraepithelial neoplasia and progresses to adenocarcinoma as the epithelium and stroma are invaded. As the prostate cells are reliant on androgens, targeting androgen production or androgen receptors is the basis of ADT. In the prostate, testosterone is converted to DHT, which has 2.4 times greater potency on the intraprostatic androgen receptors. Since the 1940s, hormone therapy has been used independently and in combination with surgery and radiotherapy in the management of PCa. The first description of hormone therapy, in a neoadjuvant fashion before prostatectomy, was given by Vallott in 1944. Following the work of Huggins and Vallott, a retrospective review by Scott and Boyd was published, reporting on a 25-year experience with 44 patients treated with hormonal therapy and RP for advanced disease. Fifty-one percent of the patients were alive at 10 years, and 29% were alive at 15 years. Initial nonrandomized series comparing nADT before RP to historical controls who had not received ADT, had shown promising results. The data typically demonstrated a decrease in the prostate volume, PSA levels, and positive surgical margins. Since then, there have been several clinical trials investigating the effects and outcomes of nADT prior to RP, the results of which will be discussed in this review.

**RATIONALE FOR NEOADJUVANT IMMUNOTHERAPY**

The goal of immunotherapy is to stimulate the body’s immune response to recognize and destroy tumor cells.

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**Table 2: Types of neoadjuvant systemic therapies**

| Type                          | Mechanism of action                                      | Examples                                      |
|-------------------------------|----------------------------------------------------------|-----------------------------------------------|
| Nonsteroidal Antiandrogen     | Inhibit binding of DHT and testosterone to androgen receptor | Bicalutamide, Flutamide, Nilutamide           |
| Steroidal antiandrogen        | Inhibit binding of DHT and testosterone to androgen receptor | Cyproterone acetate                           |
| CYP17A1 inhibitor             | Inhibit testosterone synthesis in adrenal and prostate glands | Abiraterone                                   |
| LHRH agonist                  | Suppress hypothalamic–pituitary–gonadal axis             | Leuprolide Acetate, Triptorelin Pamoate, Goserelin Acetate, Histrelin Acetate |
| LHRH antagonist               | Suppress hypothalamic–pituitary–gonadal axis             | Degarelix                                     |
| Chemotherapy                  | Cytotoxicity                                              | Docetaxel                                     |
| Immunotherapy                 | Variable based on agent                                   | GWAX, bevacizumab                             |

LHRH = Luteinizing hormone-releasing hormone, DHT = Dihydrotosterone, GVAX = granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting allogeneic cellular vaccine
Several recent immunotherapy trials, for other urological malignancies, have intensified the interest in potential immunotherapy agents for early stage PCa. There is a biological rationale for using immunotherapeutic agents in localized PCa, which have a potential to be successful for three key reasons. Localized PCa can have a slow clinical course allowing sufficient time for the body to mount an immune response, which may take weeks to months. PCa cells express several tumor-specific antigens such as PSA, prostate-specific membrane antigen (PSMA) and prostatic acid phosphatase which can serve as targets for activated immune cells. Third, since the prostate is not a vital organ, collateral immunological injury to normal prostate tissue is not of any clinical significance.

RETROSPECTIVE STUDIES OF NEOADJUVANT ANDROGEN DEPRIVATION THERAPY

Initial nonrandomized series compared patients who received nADT before RP to historical controls who had not received ADT. The results typically demonstrated a decrease in the prostate volume, PSA levels, and positive surgical margins. Akitake et al. evaluated 711 men who underwent RP for clinically localized PCa, including 75 patients who received nADT for a median of 4 months (range 2–8 months). After a median follow-up of 2.2 years, nADT was not associated with an increased risk of BCR in the overall cohort. Interestingly, nADT was associated with an increased risk of BCR in patients aged >65 and in those with low baseline serum testosterone levels. In patients with normal testosterone levels, there was a signal towards improvement in BCR. This study, however, had several limitations including its retrospective design, short follow-up, and a significant likelihood for confounding due to vastly different groups at the baseline. The neoadjuvant group had higher PSA levels and clinical T stage, reflecting the preferential use of ADT in higher risk disease.

RANDOMIZED TRIALS OF NEOADJUVANT ANDROGEN DEPRIVATION THERAPY AND SURGERY VERSUS IMMEDIATE SURGERY

Several randomized controlled trials (RCTs) have shown that treatment with LHRH agonists prior to RP can significantly improve the pathologic findings typically associated with poor prognosis, such as higher BCR, clinical recurrence, and cancer-specific mortality (Table 3). The first prospective, randomized trial of nADT and RP versus RP alone was published by Labrie et al. in 1993, which demonstrated a significant reduction in positive surgical margins, as well as an increase in pathological downstaging, in 142 men who received 3 months of flutamide and leuprolide prior to the surgery as compared to the controls. This was followed by a multicenter RCT of 125 patients utilizing flutamide and goserelin as nADT, which similarly resulted in decreased positive surgical margins and increased pathologic downstaging, along with a decrease in the prostate volumes and PSA levels.

Subsequently through the 1990s, several other RCTs were conducted using a variety of neoadjuvant therapies including goserelin alone, cyproterone alone, triproterin with cyproterone, leuprolide with flutamide, and goserelin with flutamide. These studies consistently demonstrated an increase in the organ-confined disease and a reduction in positive surgical margins and seminal vesicle invasion. Another randomized study investigated the benefit of estramustine phosphate, which does have additional cytostatic activity due to its chemotherapy component, differentiating it from the typical hormonal therapies. These early trials did not report survival outcomes. In the 2000s, several RCTs evaluated oncological outcomes in addition to the pathologic specimen findings using various ADT combinations. Initial nADT studies evaluating the oncological outcomes included goserelin and bicalutamide, leuprolide and cyproterone, and bicalutamide alone. Schulman et al. were the first to report medium-term data with a follow-up of 4 years. There were no significant differences in the PSA progression rates between the neoadjuvant therapy and the immediate surgery groups. Further studies then reached maturity with follow-up intervals ranging from 5 to 8 years, none of which demonstrated any difference in the BCR or the overall survival rates. In summary, these randomized trials confirmed the prior findings of decreased positive surgical margin rates, but did not demonstrate improvement in biochemical progression, local recurrence, and metastasis rates, raising questions about the clinical and oncological significance of nADT. However, the studies were limited by the inclusion of low and intermediate-risk PCa, insufficient follow-up periods, and inadequate power to evaluate the long-term impacts on cancer-specific and overall mortality.

Randomized trials evaluating duration of neoadjuvant androgen deprivation therapy

One of the hypotheses was that the 3 months of nADT was insufficient for significant clinical impact, leading to trials with longer duration of therapy. A RCT of 547 men randomized to three versus 8 months of nADT with leuprolide and flutamide reported that the preoperative PSA nadir and the subsequent positive surgical margin rates were lower in the 8 month group, suggesting a potential benefit with longer duration of neoadjuvant therapy. Another trial by Selli et al. compared immediate RP to 3 and 6 months of nADT with goserelin and bicalutamide, and similarly, a greater decrease in the positive margin rates was seen in the extended therapy arm. These studies were limited in that they only assessed pathological findings and did not provide follow-up oncological data.
| Author               | Year | n    | Clinical Stage | Neoadjuvant therapy | Therapy duration | Clinical downstaging (%) | Pathological downstaging (%) | Organ confined (%) | Positive margins (%) | Seminal vesicle invasion (%) | pN+ (%) |
|---------------------|------|------|----------------|---------------------|------------------|--------------------------|-----------------------------|-------------------|----------------------|-------------------------------|----------|
| Labrie et al.       | 1993 | 142  | B0-C2          | Leuprolide, Flutamide | 3 months         | Neo 43, RP 8             | Neo 77, RP 34               | Neo 13, RP 39      | Neo 27, RP 39          | Neo 12, RP 34                   | Neo 3, RP 6 |
| Debruyne et al.     | 1994 | 125  | T2-3N0M0       | Goserelin, Flutamide | 3 months         | Neo 34                   | Neo 19, RP 8                | Neo 18, RP 48      | Neo 32/31/19^a | Neo 15, RP 22                  | Neo 6, RP 6 |
| Soloway et al.      | 1995 | 303  | T2bNxM0        | Leuprolide, Flutamide | 3 months         | Neo 53, RP 22             | Neo 72, RP 63               | Neo 32/31/19^a | Neo 15, RP 22          | Neo 15, RP 22                  | Neo 6, RP 6 |
| Van Poppel et al.   | 1995 | 130  | T2b-T3         | Estramustine Phosphate~ | 1.5 months      | Neo 22                   | Neo 26, RP 23               | Neo 53, RP 22      | Neo 44/27/10^a | Neo 15, RP 22                  | Neo 6, RP 6 |
| Dalkin et al.       | 1996 | 56   | T1c-T2b        | Goserelin            | 3 months         | Neo 57, RP 61             | Neo 42, RP 20               | Neo 28, RP 14      | Neo 28, RP 14          | Neo 4, RP 4                    | Neo 7, RP 3  |
| Goldenberg et al.   | 1996 | 213  | T1b-T2c        | Cyproterone         | 3 months         | Neo 45, RP 21             | Neo 53, RP 34               | Neo 15, RP 22      | Neo 28, RP 14          | Neo 4, RP 4                    | Neo 7, RP 3  |
| Hugosson et al.     | 1996 | 111  | T1b-3aN0M0     | Triptorelin, Cyproterone | 3 months     | Neo 45, RP 21             | Neo 53, RP 34               | Neo 15, RP 22      | Neo 28, RP 14          | Neo 4, RP 4                    | Neo 7, RP 3  |
| Witjes et al.       | 1997 | 354  | T2-3N0M0       | Goserelin, Flutamide | 3 months         | Neo 72, RP 23             | Neo 72, RP 63               | Neo 15, RP 22      | Neo 4, RP 4            | Neo 7, RP 3                    | Neo 3, RP 6  |
| Aus et al.          | 1998 | 122  | T1b-3aNxM0     | Triptorelin, Cyproterone | 3 months     | Neo 70, RP 23             | Neo 45, RP 24               | Neo 15, RP 22      | Neo 5, RP 14           | Neo 8/4, RP 12                  | Neo 12, RP 11 |
| Fair et al.         | 1999 | 140  | T1-T2          | Goserelin, Flutamide | 3 months         | Neo 70, RP 59             | Neo 45, RP 24               | Neo 15, RP 22      | Neo 5, RP 14           | Neo 8/4, RP 12                  | Neo 12, RP 11 |
| Schulman et al.     | 2000 | 402  | T2-3N0M0       | Goserelin, Flutamide | 3 months         | Neo 70, RP 23             | Neo 45, RP 24               | Neo 15, RP 22      | Neo 5, RP 14           | Neo 8/4, RP 12                  | Neo 12, RP 11 |
| Selli et al.*       | 2002 | 393  | T2-3N0M0       | Goserelin, Bicalutamide | 3/6 months    | Neo 30                   | Neo 15, RP 7                | Neo 49/49/49, RP 7 | Neo 28/33/33, RP 48   | Neo 11,11, RP 11                | Neo 12, RP 11 |
| Soloway et al.*     | 2002 | 303  | T2bNxM0        | Leuprolide, Flutamide | 3 months         | Neo 30                   | Neo 15, RP 7                | Neo 49/49/49, RP 7 | Neo 28/33/33, RP 48   | Neo 11,11, RP 11                | Neo 12, RP 11 |
| Prezioso et al.     | 2004 | 183  | T1a-2bN0M0     | Leuprolide, Cyproterone | 3 months     | Neo 30                   | Neo 15, RP 7                | Neo 49/49/49, RP 7 | Neo 28/33/33, RP 48   | Neo 11,11, RP 11                | Neo 12, RP 11 |
| Gravina et al.*     | 2007 | 430  | T2-T3a         | Bicalutamide        | 4 months         | Neo 30                   | Neo 15, RP 7                | Neo 49/49/49, RP 7 | Neo 28/33/33, RP 48   | Neo 11,11, RP 11                | Neo 12, RP 11 |
| Yee et al.*         | 2010 | 148  | T1b-T3         | Goserelin, Flutamide | 3 months         | Neo 30                   | Neo 15, RP 7                | Neo 49/49/49, RP 7 | Neo 28/33/33, RP 48   | Neo 11,11, RP 11                | Neo 12, RP 11 |

*Follow-up report of prior study. ~Cytotoxic agent, not truly ADT, ^Margins reported as posterolateral, apical, base margins. pN+ = Pathological lymph node positive status, Neo = Neoadjuvant androgen deprivation therapy, RP = Radical prostatectomy
Randomized trials comparing different neoadjuvant androgen deprivation therapy agents

Sayyd et al. randomized 39 patients into 3 different regimens of 3 months nADT prior to prostatectomy: degarelix only, degarelix with bicalutamide, or an LHRH agonist with bicalutamide. Thirty-one patients (79%) had at least GG 3 disease, while 20 (51%) had GG 4 disease. The primary endpoint was the effect of treatment on the intra-tumoral DHT levels. Secondary endpoints included pathological outcomes, PSA failure, serum hormone levels, and immunohistochemical staining including alpha-methylacyl-CoA racemase (AMACR) to confirm the presence of residual foci of PCa. Interestingly, the degarelix-only arm had a higher intratumoral DHT and higher AMACR levels on immunohistochemistry staining compared to the degarelix/bicalutamide and the LHRH agonist/bicalutamide arms with no differences in the other intratumoral androgens.

NEOADJUVANT ANDROGEN DEPRIVATION THERAPY IN HIGH-RISK PROSTATE CANCER

A few studies have assessed the outcomes of nADT specifically in the setting of high-risk PCa. The feasibility of neoadjuvant systemic therapy has been demonstrated in this cohort with low morbidity and good local disease control. The SWOG 9109 trial was a single arm Phase II study of 55 patients with cT3–4 N0 M0 PCa who received goserelin acetate and flutamide before the surgery. This study reported a 10-year progression-free and overall survival rates of 40% and 68%, respectively. More recently, Tosco et al. reported on a multi-center retrospective study of 1573 men with high-risk PCa, of which 1170 underwent upfront surgery and 403 received nADT prior to the surgery. After a median follow-up of 56 months, nADT was associated with a significant reduction in the risk of PCa death (hazard ratio [HR] 0.5; 95% confidence interval [CI] 0.3–0.8; P < 0.01). A subset analysis of the patients who received adjuvant RT also demonstrated a reduced 5-year PCa-specific mortality (2.3% vs. 7.5%) in the neoadjuvant therapy group. We await the results of the Neoadjuvant Degarelix with or without Apalutamide (ARN-509) followed by RP (ARNEO) trial, which is a single-center, Phase II, double blind, placebo-controlled randomized trial of degarelix/apalutamide versus degarelix/placebo in high-risk PCa. The study aims to assess the residual pathological disease, intratumor molecular changes, and the impact on functional imaging (68Ga-PSMA positron emission tomography/magnetic resonance imaging).

Other neoadjuvant agents in high-risk prostate cancer

A Phase II study evaluating neoadjuvant everolimus at two different doses for 8 weeks prior to RP did not demonstrate an improvement in pathological outcomes. No patients had complete pathological response and almost 90% of the patients had rising PSA leading to an early termination of the study due to lack of efficacy.

NEOADJUVANT CHEMOHORMONAL THERAPY

To date, there have been no formal recommendations in any guidelines for neoadjuvant therapies prior to RP. Docetaxel chemotherapy in combination with ADT was shown to have a significant survival benefit in hormone-sensitive metastatic PCa in landmark randomized trials. Furthermore, one of these studies, the Systemic Therapy in Advancing or Metastatic PCa: Evaluation of Drug Efficacy (STAMPEDE) trial, also included patients with very high risk locally advanced PCa, warranting further evaluation of chemohormonal therapy (CHT) in high-risk and locally advanced PCa.

Table 4: Oncological outcomes in randomized trials of neoadjuvant androgen deprivation therapy and radical prostatectomy alone for clinically localized prostate cancer

| Author          | Year | Total patients | Clinical stage | Neoadjuvant therapy | Therapy duration | BCR/PSA progression (%) | Local recurrence (%) | Met disease (%) | Follow-up | Overall survival (%) |
|-----------------|------|----------------|----------------|---------------------|------------------|------------------------|---------------------|----------------|-----------|---------------------|
| Witjes et al.   | 1997 | 354            | T2-3N0M0       | Goserelin, Flutamide | 3 months         | Neo 22, RP 23          | Neo 38, RP 32       | Neo 10, RP 16   | 15 months |                    |
| Aus et al.      | 1998 | 122            | T1b-3N0M0      | Triptolizin, Cyproterone | 3 months         | Neo 26, RP 22          | Neo 33, RP 29       | Neo 7, RP 6     | 38 months |                    |
| Klotz et al.    | 2002 | 126            | T1b-3N0M0      | Goserelin, Flutamide | 3 months         | Neo 26, RP 33          | Neo 33, RP 29       | Neo 7, RP 6     | 4 years   | Neo 96, RP 96       |
| Prezioso et al. | 2004 | 183            | T1a-2bN0M0     | Leuprolide, Cyproterone | 3 months         | Neo 38, RP 34          | Neo 10, RP 16       | Neo 5, RP 3     | 6 years   | Neo 83, RP 86       |
| Yee et al.      | 2010 | 148            | T1b-T3         | Leuprolide, Cyproterone | 3 months         | Neo 24, RP 16          | Neo 4, RP 5        | Neo 86, RP 92   | 8 years   |                    |

*Follow-up report of prior study. BCR = Biochemical recurrence, Met = Metastasis; Neo = Neoadjuvant androgen deprivation therapy, OS = Overall survival, RP = Radical prostatectomy, PSA = Prostate specific antigen.
advanced non-metastatic PCAs. Comparative studies of neoadjuvant CHT (nCHT) and immediate RP are shown in Table 5.

Pan et al. reported on pathological findings and short-term BCR after nCHT. They evaluated 177 men with very high-risk locally advanced PCAs, treated in 3 groups: nCHT, nADT and immediate RP. The nCHT group had the highest rate of undetectable PSA (81% vs. 73% and 48%, P < 0.01) and the lowest rate of BCR (14% vs. 47% and 81%, P < 0.01). Narita et al. evaluated nCHT comprising of complete androgen blockage, 6 cycles of docetaxel and estramustine in 60 men with high-risk PCa, and demonstrated impressive pathological outcomes with a 10% complete pathological response and 3% positive margin rate. nCHT, however, was associated with major complication rate of 13% after RP. The authors also performed a propensity-matched comparison of 56 pairs of men undergoing nCHT versus immediate RP, and showed a significantly lower rate of BCR with nCHT (P = 0.02).

Several prospective single-arm trials assessing the impact of nCHT prior to surgery have been reported. Thalgott et al. reported on a single-arm Phase II study of nCHT with docetaxel, trimestral buserelin, and bicalutamide in 30 high-risk patients, whose eligibility was defined by the absence of metastatic disease and a BCR risk of > 40% within 5 years, according to Kattan's preoperative nomogram. Significant pathological downstaging was observed (48%) and 5-year BCR free survival was 40%, though severe hematological toxicity was common. Other prospective Phase II trials of < 100 participants have reported similar findings. However, several other trials have also been suspended or terminated due to poor accrual. The NCT03358563 trial is a single-arm Phase I pilot study of nCHT comprising of complete androgen blockage, 6 cycles of docetaxel and estramustine in 60 men with high-risk PCa, and demonstrated impressive pathological outcomes with a 10% complete pathological response and 3% positive margin rate. nCHT, however, was associated with major complication rate of 13% after RP. The authors also performed a propensity-matched comparison of 56 pairs of men undergoing nCHT versus immediate RP, and showed a significantly lower rate of BCR with nCHT (P = 0.02).

In the GETUG 12 trial, men with high-risk PCAs were randomized to two different neoadjuvant therapy regimens: three years of ADT or 3 years of ADT with 4 cycles of docetaxel and estramustine. Local therapy (RP or RT) was administered

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**Table 5: Comparative studies of neoadjuvant chemohormonal therapy and radical prostatectomy versus immediate radical prostatectomy for high-risk prostate cancer**

| Author | Year | Study design | Total patients | Study eligibility criteria | Neoadjuvant therapy | Undetectable PSA (%) | Stage pT0 (%) | Stage pN1 (%) | Stage pM1 (%) | OS (years) | pFS (years) | Stage BCR/PSM (%) | Immediate RP vs nCHT | Immediate RP vs nADT |
|--------|------|--------------|----------------|---------------------------|---------------------|----------------------|---------------|--------------|---------------|------------|-------------|---------------------|---------------------|---------------------|
| Pan    | 2019 | Retrospective | 177 | Very high risk or primary ≥50 ng/mL or locally advanced T3a disease or Gleason score 5 or >75% Gleason 3 ≤50 ng/mL or primary Gleason pattern 4 ≥75% Gleason 3 ≤50 ng/mL or primary Gleason pattern 5 | nCHT (docetaxel, bicalutamide) with or without pelvic lymph node irradiation | 51 | 81 | 17 | 60 | 81 | 0 | 14 | 0.02 |
| Narita | 2019 | Retrospective | 56 | High-risk T3a disease or PSA ≥15 ng/mL or PSA >20 ng/mL | Goserelin + bicalutamide (nCHT) | 17 | 9 | 19 | 70 | 80 | 0 | 45 | 0.001 |
| Eastham | 2009 | Randomized | 301 | High-risk T3 disease or PSA >20 ng/mL or PSA >20 ng/mL | Goserelin + bicalutamide (nCHT) | 207 | 14 | 17 | 5 | 80 | 0 | 45 | 0.001 |

ADT = Androgen deprivation therapy; PSA = Prostate specific antigen; nCHT = Neoadjuvant chemohormonal therapy; nADT = Neoadjuvant ADT; RP = Radical prostatectomy.
3 months after commencing systemic therapy.\textsuperscript{[82]} nCHT was associated with an improved 8-year relapse-free survival as compared to ADT alone (62% vs. 50%). The vast majority of patients received RT as the local therapy (358 of 413 patients, 87%). The Investigators of the Preoperative Use of Neoadjuvant Chemotherapy (PUNCH) CALGB 90203 trial are to be commended for completing a trial of 288 men with high-risk, clinically localized PCa (T1-T3aNxM0) randomized to immediate surgery versus nCHT followed by surgery.\textsuperscript{[83]} Patients in the experimental arm received 6 cycles of docetaxel every 3 weeks and a concurrent LHRH agonist for 18–24 weeks (4.5–6 months). Men treated with nCHT had improvements in most of the pathologic outcomes compared to immediate RP, including lower pathologic T-stages and rates of seminal vesical invasion, positive surgical margins, and positive pelvic lymph nodes.\textsuperscript{[83]} Longer-term oncological results were presented at the AUA annual meeting in 2019, demonstrating a significant improvement in 8-year biochemical progression-free survival (bPFS) over the course of the study, although not in 3-year bPFS, which was the primary endpoint \textit{a priori}. Further oncological outcomes were presented at the annual meeting of the SUO in 2019, this time demonstrating an improvement in the 10-year overall survival rate in the entire cohort with nCHT as compared to surgery alone (80% vs. 74%, HR 0.61, 95% CI 0.4–0.94). nCHT also led to a reduction in the need for further adjuvant or salvage treatment after RP (HR 0.61, 95% CI 0.48–0.78) with a median treatment-free survival of 4.5 years in the nCHT arm as compared to 1.8 years in the surgery alone arm. We await the final peer-reviewed publication with great anticipation. The GETUG 12 and PUNCH trial findings are of clinical significance and may impact our management of high-risk PCa in the near future.

**NEOADJUVANT IMMUNOTHERAPY STUDIES**

Immunotherapy in PCa remains a burgeoning area of research. The feasibility of neoadjuvant docetaxel/GVAX has been demonstrated in a Phase II trial of high-risk localized PCa.\textsuperscript{[84]} GVAX is a granulocyte-macrophage colony-stimulating factor (GM-CSF)-secreting allogeneic cellular vaccine whose immunogenicity may be enhanced by androgen deprivation and low-dose chemotherapy.\textsuperscript{[85]} The Johns Hopkins group performed a trial (NCT01696877) of 28 men randomized to degarelix alone versus degarelix with GVAX and a single intravenous dose of cyclophosphamide, with additional comparison to a control group (n = 20) who underwent immediate RP.\textsuperscript{[87]} Immunologic endpoints were intraprostatic CD8+ T-Cell, CD4+ T Cell, and Treg infiltration and tissue androgen concentration. Clinical endpoints were time-to-PSA-relapse, time-to-next-therapy, and time-to-metastasis. Intratumoral CD8+ and Treg densities were elevated in both the study arms compared to the control group, supporting the immunogenic effects of androgen ablation. Intratumoral immune infiltrates were marginally augmented by cyclophosphamide/GVAX/degarelix compared to degarelix alone. Time-to-PSA relapse and time-to-next-therapy were improved in the experimental arm compared to degarelix alone with a HR of approximately 0.40, though statistical significance was not reached. Bevacizumab is a humanized monoclonal antibody that targets and inhibits vascular endothelial growth factor thereby downregulating tumor angiogenesis. Ross et al. reported a Phase II trial of neoadjuvant docetaxel and bevacizumab prior to RP in 41 men with high-risk PCa, demonstrating a low rate of significant adverse events, and signals of clinical activity with >50% reduction in tumor volume in 29% and >50% reduction in PSA in 22% of the patients although none exhibited a complete pathological response.\textsuperscript{[86]}

**FUTURE DIRECTIONS**

PCa research with any therapeutic agent is limited by the inherent nature of the disease. The long clinical course of early stage PCa makes for a challenging research environment, as it takes a long time for the clinical trials to mature. While cancer-specific and overall survival rates have traditionally been the accepted endpoints in oncological trials, innovative surrogate short-term clinical indicators of oncological benefit should be considered to evaluate the flurry of newly available agents in PCa. Furthermore, the favorable long-term survival in PCa highlights the importance of other nononcological endpoints such as patient satisfaction, functional outcomes and quality-of-life assessments.\textsuperscript{[88]}

Neoadjuvant therapy is broad research area in PCa. This review provides an overview of important contemporary research in the neoadjuvant arena prior to RP. Immunologic neoadjuvant trials are in their infancy, and more robust data from larger cohorts with longer follow-up is required. Further research is required to help identify and define the optimal candidates for neoadjuvant therapy in a more granular and nuanced way than the broad definitions of high-risk PCa we currently employ.

**CONCLUSIONS**

Several randomized trials have shown that nADT prior to RP significantly improves pathologic findings, including downsizing of the tumor, reduced positive surgical margin rates, and tumor downstaging, without a demonstrable intermediate-term oncological benefit. These trials were limited by short follow-up periods and included large cohorts of men with low- and intermediate-risk PCa, which may have diluted the potential survival benefits in the higher risk PCa. Retrospective and nonrandomized prospective studies in patients with high-risk PCa demonstrate promising longer-term survival outcomes. More recently, an increasing body of literature including level 1 evidence suggests that nCHT may be associated with pathological downstaging, and
improved longer-term recurrence-free and overall survival in high-risk PCa. The wide array of newly available agents in metastatic PCa will drive ongoing study of these agents earlier in the disease process including in the neoadjuvant setting. While immunotherapy trials are in their infancy, we look forward to mature data from contemporary neoadjuvant chemohormonal and ADT trials. These data will help establish the role of neoadjuvant therapies in the multimodal therapeutic landscape of high-risk and locally advanced PCa.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018; 68:394-424.

2. Sandra MG, Cadeddu JA, Kirky E, Chen RC, Crispino T, Fontanarosa J, et al. Clinically localized prostate cancer: AUA/ASTRO/SIOG guideline. Part 1: Risk stratification, shared decision making, and care options. J Urol 2018;199:683-90.

3. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71:618-29.

4. Carroll PH, Mohler JL. NCCN guidelines updates: Prostate cancer and prostate cancer early detection. J Natl Compr Canc Netw 2019;17:479‑505.

5. Meng MV, Ekin EP, Latin MD, Duchane J, Carroll PR. Treatment of patients with high risk localized prostate cancer: Results from cancer of the prostate strategic urological research endeavor (CaPSURE). J Urol 2005;173:1557-61.

6. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holder P, et al. 10-Year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375:1415‑24.

7. Boorjian SA, Karnes RJ, Viterbo R, Rangel LJ, Bergstralh EJ, Horwitz EM, et al. Natural history of progression after PSA elevation following radical prostatectomy, RAVES” Trial. Int J Radiat Oncol Biol Phys 2019;105:S37‑8.

8. Loeb S, Schaeffer EM, Tock BJJ, Epstein JI, Humphreys EB, Walsh PC. What are the outcomes of radical prostatectomy for high-risk prostate cancer? Urology 2010;76:710-4.

9. Abdollah F, Sood A, Sammon JD, Hsu L, Beyer B, Moschini M, et al. Long-term cancer control outcomes in patients with clinically high-risk prostate cancer treated with robot-assisted radical prostatectomy: Results from a multi-institutional study of 1100 patients. Eur Urol 2015;68:497-505.

10. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. J Clin Oncol 2010;28:1117-23.

11. D’Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. JAMA 1998;280:969-74.

12. Mohler JL, Antonarakis ES, Armstrong AJ, D’Amico AV, Davis BJ, Dorff T, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:479-505.

13. Gosselaar C, Krane R, Roobol MJ, Roemeling S, Schröder FH. The interobserver variability of digital rectal examination in a large randomized trial for the screening of prostate cancer. Prostate 2008;68:985-93.

14. Yossepowitch O, Eggeger SE, Bianco FJ Jr., Carver BS, Serio A, Scardino PT, et al. Radical prostatectomy for clinically localized, high-risk prostate cancer: Critical analysis of risk assessment methods. J Urol 2007;178:493-9; discussion 9.

15. Johnston TJ, Shaw GL, Lamb AD, Parashar D, Greenberg D, Xiong T, et al. Mortality among men with advanced prostate cancer excluded from the protect trial. Eur Urol. 2017;71:381‑8.

16. Bill-Axelson A, Holmberg L, Garino H, Taari K, Busch C, Nordling S, et al. Radical prostatectomy or watchful waiting in prostate cancer 29-year follow-up. N Engl J Med 2018;379:2319‑29.

17. Tian Z, Wang X, Wu P, Shi T, Liu M. Comparison of radical prostatectomy versus conservative treatment in localized prostate cancer: Systematic review and meta-analysis. J BUON 2019;24:239‑48.

18. Sarkar RR, Bryant AK, Parsons JK, Ryan ST, Karim Kader A, Kane CJ, et al. Association between radical prostatectomy and survival in men with clinically node-positive prostate cancer. Eur Urol Oncol 2019;2:584-8.

19. Greenberger BA, Zaorsky NG, Den BR. Comparison of radical prostatectomy versus radiation and androgen deprivation therapy strategies as primary treatment for high-risk localized prostate cancer: A systematic review and meta-analysis. Eur Urol Focus 2020;6:404‑18.

20. Jayadevappa R, Lee DI, Chhatre S, Guizzo TJ, Malkowicz SB. Comparative effectiveness of treatments for high-risk prostate cancer patients. Urol Oncol 2019;37:574.e1-5.74E+20.

21. Yin M, Zhao J, Monk P, Martin D, Folefoc E, Joshi M, et al. Comparative effectiveness of surgery versus external beam radiation with/without brachytherapy in high-risk localized prostate cancer. Cancer Med 2020;9:27‑34.

22. Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, de Reijke TM, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: Long-term results of a randomised controlled trial (EORTC trial 22911). Lancet 2012;380:2018‑27.

23. Faria EF, Chapin BF, Muller RL, Machado RD, Reis RB, Matin SF. Radical prostatectomy for locally advanced prostate cancer: Current status. Urology 2015;86:10-5.

24. Kneebone A, Fraser-Browne C, Delprado W, Duchesne G, Fisher R, Frydenberg M, et al. A phase III multi-centre randomised trial comparing adjuvant versus early salvage radiotherapy following a radical prostatectomy: Results of the TROG 08.03 and ANZUP &#x201c; RAVES&amp;#x201d; Trial. Int J Radiat Oncol Biol Phys 2019;105:S37-8.

25. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA 1999;281:1591-7.

26. Grossfeld GD, Chang JJ, Broering JM, Miller DP, Yu J, Flanders SC, et al. Impact of positive surgical margins on prostate cancer recurrence and the use of secondary cancer treatment: Data from the CaPSURE database. J Urol 2000;163:1171‑7.

27. Kumar S, Shelley M, Harrison C, Coles B, Wilt TJ, Mason MD. Neo-adjuvant and adjuvant hormone therapy for localised and locally advanced prostate cancer. Cochrane Database Syst Rev 2006;4:CD006019.

28. Ganm M, McNeil DG. Androgen deprivation and immunotherapy for the treatment of prostate cancer. Endocr Relat Cancer. 2017;24:279-310.

29. Oeifelein MG, Feng A, Sclicetti MJ, Ricchiutti D, Resnick MI. Reassessment of the definition of castrate levels of testosterone: Implications for clinical decision making. Urology 2000;56:1021-4.

30. Verhelst J, Denis L, van Vliet P, van Poppel H, Braeckman J, van Ganh P, et al. Endocrine profiles during administration of the new non-steroidal anti-androgen Casodex in prostate cancer. Clin Endocrinol (Oxf) 1994;41:525-30.

31. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:33-51.

32. Fizazi K, Tran N, Fein L, Matsubara N, Rodrigue-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): Final overall survival analysis of a randomised,
double-blind, phase 3 trial. Lancet Oncol 2019;20:686-700.
33. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med 2011;364:1995-2005.
34. Cooke BA, Sullivan MH. The mechanisms of LHRH agonist action in gonadal tissues. Mol Cell Endocrinol 1985;41:11-22.
35. Gründler C, Emons G. The role of gonadotropin-releasing hormone in cancer cell proliferation and metastasis. Front Endocrinol (Lausanne) 2017;8:187.
36. Crawford ED, Heidenreich A, Lawrentschuk N, Tombal B, Pompeo ACL, Mendoza-Valdes A, et al. Androgen-targeted therapy in men with prostate cancer: Evolving practice and future considerations. Prostate Cancer Prostatic Dis 2019;22:24-38.
37. Huggins C, Hodges CV. Studies on prostate cancer I: The effect of castration, of oestrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1:293-7.
38. Wright AS, Thomas LN, Douglas RC, Lazier CB, Rittmaster RS. Relative potency of testosterone and dihydrotestosterone in preventing atrophy and apoptosis in the prostate of the castrated rat. J Clin Invest 1996;98:2558-63.
39. Vallett BS. Radical perineal prostatectomy subsequent to bilateral orchectomy. Del State Med J 1944;16:19-20.
40. Scott WW, Boyd HL. Combined hormone control therapy and radical prostatectomy in the treatment of selected cases of advanced carcinoma of the prostate: A retrospective study based upon 25 years of experience. J Urol 1969;101:86-92.
41. Häggman M, Hellström M, Aus G, Pedersen K, Wijkström H, Stege R, et al. Neoadjuvant GnRH-agonist treatment (tripotrenol and cyproterone acetate for flare protection) and total prostatectomy. Eur Urol 1993;24:456-60.
42. Macfarlane MT, Abi-Aad A, Stein A, Danella J, Belldegrun A, deKernion JB. Neoadjuvant androgen-privation therapy with radical prostatectomy in patients with locally advanced prostate cancer. J Urol 1993;150:132-4.
43. Flamm J, Fischer M, Höltl W, Pflüger H, Tomshi W. Complete androgen deprivation prior to radical prostatectomy in patients with stage T3 cancer of the prostate. Eur Urol 1991;19:192-5.
44. Gulley JL, Drake CG. Immunotherapy for prostate cancer: Recent advances, lessons learned, and areas for further research. Clin Cancer Res 2011;17:3884-91.
45. Akitake N, Shiota M, Obata H, Takeuchi A, Kashiwagi E, Imada K, et al. Effects of complete androgen blockade for 12 and 24 weeks on the pathological stage and resection margin status of prostate cancer. J Clin Pathol 2002;55:508-13.
46. Gründker C, Emons G. The role of gonadotropin-releasing hormone in prostate cancer cell proliferation and metastasis. Front Endocrinol (Lausanne) 2017;8:187.
47. Debruyne FM, Witjes WP, Schulman CC, van Cangh PJ, Oosterhof GO. Preliminary results of a prospective randomized study comparing radical prostatectomy alone and neoadjuvant androgen withdrawal in the treatment of localized prostate cancer. Canadian Urologic Oncology Group. J Urol 1996;156:877-9.
48. Hugosson J, Abrahamsson PA, Ahlgren G, Aus G, Lundberg S, Schelin S, et al. The risk of malignancy in the surgical margin at radical prostatectomy reduced almost three-fold in patients given neo-adjuvant hormone treatment. Eur Urol 1996;29:413-9.
49. Witjes WP, Schulman CC, Debruyne FM. Preliminary results of a prospective randomized study comparing radical prostatectomy versus radical prostatectomy associated with neoadjuvant hormonal combination therapy in T2-3 N0 M0 prostate carcinoma. The European Study Group on Neoadjuvant Treatment of Prostate Cancer. Urology 1997;49:65-9.
50. Aus G, Abrahamsson PA, Ahlgren G, Hugosson J, Lundberg S, Schain M, et al. Neoadjuvant GnRH-agonist treatment (tripotrenol and cyproterone acetate for flare protection) and total prostatectomy. Eur Urol 1993;24:456-60.
51. Scardino PT, Lepor H. Androgen-targeted therapy in men with localized prostate cancer. J Urol 1994;26 Suppl 1:4.
52. Hugosson J, Abrahamsson PA, Ahlgren G, Aus G, Lundberg S, Schelin S, et al. Effects of complete androgen blockade for 12 and 24 weeks on the pathological stage and resection margin status of prostate cancer. J Clin Pathol 2002;55:508-13.
53. Witjes WP, Schulman CC, Debruyne FM. Preliminary results of a prospective randomized study comparing radical prostatectomy versus radical prostatectomy associated with neoadjuvant hormonal combination therapy in T2-3 N0 M0 prostate carcinoma. The European Study Group on Neoadjuvant Treatment of Prostate Cancer. Eur Urol 2000;38:706-13.
54. Vallett BS. Radical perineal prostatectomy subsequent to bilateral orchectomy. Del State Med J 1944;16:19-20.
55. Scott WW, Boyd HL. Combined hormone control therapy and radical prostatectomy in the treatment of selected cases of advanced carcinoma of the prostate: A retrospective study based upon 25 years of experience. J Urol 1969;101:86-92.
56. Macfarlane MT, Abi-Aad A, Stein A, Danella J, Belldegrun A, deKernion JB. Neoadjuvant androgen-privation therapy with radical prostatectomy in patients with locally advanced prostate cancer. J Urol 1993;150:132-4.
57. Flamm J, Fischer M, Höltl W, Pflüger H, Tomshi W. Complete androgen deprivation prior to radical prostatectomy in patients with stage T3 cancer of the prostate. Eur Urol 1991;19:192-5.
58. Gulley JL, Drake CG. Immunotherapy for prostate cancer: Recent advances, lessons learned, and areas for further research. Clin Cancer Res 2011;17:3884-91.
59. Akitake N, Shiota M, Obata H, Takeuchi A, Kashiwagi E, Imada K, et al. Effects of complete androgen blockade for 12 and 24 weeks on the pathological stage and resection margin status of prostate cancer. J Clin Pathol 2002;55:508-13.
60. Soloway MS, Pareek K, Sharifi R, Wajsman Z, McLeod D, Wood DP Jr., et al. Neoadjuvant androgen ablation before radical prostatectomy in T2bN0M0 prostate cancer: 5-year results. J Urol 2002;167:112-6.
61. Prezioso D, Lotti T, Polito M, Montironi R. Neoadjuvant hormone treatment with leuprolide acetate depot 3.75 mg and cyproterone acetate, before radical prostatectomy: A randomized study. Urol Int 2004;72:189-95.
62. Gravina GL, Festuccia C, Galatioto GP, Muzi P, Angelucci A, Ronchi P, et al. Surgical and biologic outcomes after neoadjuvant bicalutamide treatment in prostate cancer. Urology 2007;70:728-33.
63. Yee DS, Lowrance WT, Eastham JA, Maschino AC, Cronin AM, Rabbani F. Long-term follow-up of 3-month neoadjuvant hormone therapy before radical prostatectomy in a randomized trial. BJU Int 2010;105:185-90.
64. Aus G, Abrahamsson PA, Ahlgren G, Hugosson J, Lundberg S, Schain M, et al. Effects of complete androgen blockade for 12 and 24 weeks on the pathological stage and resection margin status of prostate cancer. J Clin Pathol 2002;55:508-13.
65. Gravina GL, Festuccia C, Galatioto GP, Muzi P, Angelucci A, Ronchi P, et al. Surgical and biologic outcomes after neoadjuvant bicalutamide treatment in prostate cancer. Urology 2007;70:728-33.
66. Yee DS, Lowrance WT, Eastham JA, Maschino AC, Cronin AM, Rabbani F. Long-term follow-up of 3-month neoadjuvant hormone therapy before radical prostatectomy in a randomized trial. BJU Int 2010;105:185-90.
et al. Neoadjuvant systemic therapy before radical prostatectomy in high-risk prostate cancer does not increase surgical morbidity: Contemporary results using the elavien system. Clin Genitourin Cancer 2016;14:130-8.

67. Konety BR, Eastham JA, Reuter VE, Scardino PT, Donat SM, Dalbagni G, 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;171:709-13.

68. Berglund RK, Tangen CM, Powell JJ, Lowe BA, Haas GP, Carroll PR, et al. Ten-year follow-up of neoadjuvant therapy with goserelin acetate and flutamide before radical prostatectomy for clinical T3 and T4 prostate cancer: Update on Southwest Oncology Group Study 9109. Urology 2012;79:633-7.

69. Tosco L, Laenen A, Briganti A, Gontero P, Karnes RJ, Albersen M, et al. The survival impact of neoadjuvant hormonal therapy before radical prostatectomy for treatment of high-risk prostate cancer. Prostate Cancer Prostastic Dis 2017;20:407-12.

70. Tosco L, Laenen A, Gevaert T, Salmon I, Decaestecker C, Davicioni E, et al. Neoadjuvant degarelix with or without apalutamide followed by radical prostatectomy for intermediate and high-risk prostate cancer: ARNEO, a randomized, double blind, placebo-controlled trial. BMC Cancer 2018;18:354.

71. Koshkin VS, Mir MC, Barata P, Gul A, Gupta R, Stephenson AJ, et al. Randomized phase II trial of neoadjuvant everolimus in patients with high-risk localized prostate cancer. Invest New Drugs 2019;37:559-66.

72. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, et al. Long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163‑77.

73. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): Survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387:1163‑77.

74. Pan J, Chi C, Qian H, Zhu Y, Shao X, Sha J, et al. Neoadjuvant chemohormonal therapy combined with radical prostatectomy and extended PLND for very high risk locally advanced prostate cancer: A retrospective comparative study. Urol Oncol 2019;37:991-8.

75. Narita S, Nara T, Kanda S, Numakura K, Saito M, I noe T, et al. Radical prostatectomy with and without neoadjuvant chemohormonal pretreatment for high-risk localized prostate cancer: A comparative propensity score matched analysis. Clin Genitourin Cancer 2019;17:e113-22.

76. Thalgott M, Horn T, Heck MM, Maurer T, Eiber M, Retz M, et al. Long-term results of a phase II study with neoadjuvant docetaxel chemotherapy and complete androgen blockade in locally advanced and high-risk prostate cancer. J Hematol Oncol 2014;7:20.

77. Mellado B, Font A, Alcaraz A, Aparicio LA, Veiga FJ, Areal J, et al. Phase II trial of short-term neoadjuvant docetaxel and complete androgen blockade in high-risk prostate cancer. Br J Cancer 2009;101:1248-52.

78. Prayer-Galetti T, Sacco E, Pagano F, Gardiman M, Cisternino A, Betto G, et al. Long-term follow-up of a neoadjuvant chemohormonal taxane-based phase II trial before radical prostatectomy in patients with non-metastatic high-risk prostate cancer. BJU Int 2007;100:274‑80.

79. Chi KN, Chiu JL, Winquist E, Klotz L, Saad F, Gleave ME. 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;180:565-70.

80. Sella A, Zisman A, Kovel S, Yarom N, Leibovici D, Lindner A. Neoadjuvant chemohormonal therapy in poor-prognosis localized prostate cancer. Urology 2008;71:323‑7.

81. Enokida H, Yamada Y, Tatarano S, Yoshino H, Yonemori M, Sakaguchi T, et al. Oncological outcome of neoadjuvant low-dose estramustine plus LHRH agonist/antagonist followed by extended radical prostatectomy for Japanese patients with high-risk localized prostate cancer: A prospective single-arm study. Jpn J Clin Oncol 2020;50:66-72.

82. Fizazi K, Faire L, Lesaunier F, Delva R, Gravis G, Rolland F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high-risk localised prostate cancer (GETUG 12): A phase 3 randomised controlled trial. Lancet Oncol 2015;16:787-94.

83. Eastham JA, Heller G, Halabi S, Monk P, Clinton SK, Szmulowitz RZ, et al. CALGB 90203 (Alliance): Radical prostatectomy (RP) with or without neoadjuvant chemohormonal therapy (CHT) in men with clinically localized, high-risk prostate cancer (CLHRPC). J Clin Oncol 2019;37:5079.

84. Vuky J, Cormnj AM, Porter C, Olsgc S, Auerbach E, Dahl K. Phase II trial of neoadjuvant docetaxel and CG1940/CG8711 followed by radical prostatectomy in patients with high-risk clinically localized prostate cancer. Oncologist 2013;18:687-8.

85. Simons JW, Sacks N. Granulocyte-macrophage colony-stimulating factor-transduced allogeneic cancer cellular immunotherapy: The GVAX vaccine for prostate cancer. Urol Oncol 2006;24:419-24.

86. Ross RW, Galsky MD, Fedbo P, Barry M, Richie JP, Xie W, et al. Phase 2 study of neoadjuvant docetaxel plus bevaxizumab in patients with high-risk localized prostate cancer: A Prostate Cancer Clinical Trials Consortium trial. Cancer 2012;118:4777-84.

87. Antonarakis ES, Zahurak M, Schaeffer EM, Partin AW, Ross A, Allaf M, et al. Neoadjuvant randomized trial of degarelix (Deg)+cyclophosphamide/GVAX (Cy/GVAX) in men with high-risk prostate cancer (PCA) undergoing radical prostatectomy (RP). Journal of Clinical Oncology 2017;35:5077.

88. Seisen T, Abdollah F. Surgery-based multimodal management of high-risk prostate cancer patients: What is the functional price to pay for optimal disease control? Eur Urol 2017;71:337-9.

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