Review Article

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 of 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.[5,10] 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].[2,3,11,12]

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%.[13] The varying definitions for high-risk PCa can lead to significant differences in the published prevalence of high-risk disease.[5,10] 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.[14]

Guidelines typically recommend definitive treatment for high-risk disease, i.e., RP or RT with ADT. RP for high-risk PCa is associated with good long-term oncological outcomes.[8] RP has consistently been shown to improve the cancer-specific and overall mortality in the subgroup analysis of patients with high-risk features.[15,16] A large systematic review and meta-analysis showed that RP improved cancer-specific and overall survival compared to conservative therapy in patients with high-risk PCa but not with low-risk disease.[17] A single-surgeon study of 175 men with high-risk PCa demonstrated acceptable oncological outcomes: organ-confined disease in the RP specimen in 36%, 10-year BCR-free survival of 68%, 10-year metastasis-free survival of 84%, 10-year ADT-free survival of 71%, and 10-year PCa-specific survival of 92%.[8] Of the high-risk criteria, a Gleason score of 8–10 was the strongest predictor of recurrence, metastasis, and cancer-specific death. Similarly, a multicenter study of RP in 1100 high-risk patients demonstrated a 10-year BCR-free, clinical recurrence-free, and salvage therapy rates of 50%, 97%, and 37% respectively.[9] Furthermore, a recent population-based study of men with locally-advanced clinically node-positive PCa suggests that RP is associated with both cancer-specific and overall survival benefits compared to the nondefinitive therapy.[18]

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.[19] 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.[20] 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.[21] Multimodal therapy using a combination of surgery and RT is often required for the optimal management of high-risk PCa.[3,22] 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.[23] 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.[24]

Table 1: Definitions of high-risk prostate cancer

Classification system	PSA (ng/ml)	Grade group	Clinical stage
D'Amico[11]	>20	4-5	T2c
AUA/ASTRO/SUO[2]	≥20	4-5	≥T3
EAU (localized)[3]	>20	4-5	T2c
EAU (locally advanced)[3]	Any	Any	T3-4 or N1
NCCN (high)[12]	>20	4-5	T3a
NCCN (very high)[12]	Any	Primary 5 or >4 cores of 4-5	T3b-4

PSA=Prostate-specific antigen, AUA=American Urological Association, ASTRO=American Society for Radiation Oncology, SUO=Society of Urologic Oncology, EAU=European Urology Association, NCCN=National Comprehensive Cancer Network

NEOADJUVANT THERAPY OBJECTIVES

BCR can be seen in approximately 30%–50% of the men with high-risk PCa within 10 years of surgery.[8,9,25] Positive surgical margins has been found to be a predictor of PSA recurrence and secondary cancer treatment including adjuvant ADT or RT.[26] 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.[27] 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 orchiectomy, or medical castration via luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, as well as androgen-receptor blockers.[28] Bilateral orchiectomy was historically performed to eliminate testicular androgen production. Serum testosterone levels after orchiectomy are typically <15 ng/dL.[29] 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.[30] 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.[31-33]

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.[34,35] 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.[36] 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.[37] PCa 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.[38] Since the 1940s, hormone therapy has been used independently and in combination with surgery and radiotherapy in the management of PCa.[37] The first description of hormone therapy, in a neoadjuvant fashion before prostatectomy, was given by Vallett in 1944.[39] Following the work of Huggins and Vallett, 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.[40] 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.[41,42] 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.[41,43]

RATIONALE FOR NEOADJUVANT IMMUNOTHERAPY

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

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	GVAX, bevacizumab

LHRH=Luteinizing hormone-releasing hormone, DHT=Dihydrotestosterone, 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.[44] 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.[41,42] 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).[45] 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].[46-61] 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.[46] 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.[47]

Subsequently through the 1990s, several other RCTs were conducted using a variety of neoadjuvant therapies including goserelin alone,[50] cyproterone alone,[51] triptorelin with cyproterone,[52,54] leuprolide with flutamide,[48] and goserelin with flutamide.[53] 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.[49] These early trials did not report survival outcomes. In the 2000s, several RCTs evaluated oncological outcomes in addition to the pathological specimen findings using various ADT combinations [Table 4].[53-56,58,59,61-63] Initial nADT studies evaluating the oncological outcomes included goserelin and bicalutamide,[57] leuprolide and cyproterone,[59] and bicalutamide alone.[60] 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.[56] 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.[58,61-63] 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.[64] 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.[57] These studies were limited in that they only assessed pathological findings and did not provide follow-up oncological data.

Table 3: Pathology specimen findings in randomized trials of neoadjuvant androgen deprivation therapy and radical prostatectomy versus immediate radical prostatectomy alone for clinically localized prostate cancer

Author	Year	*n*	Clinical Stage	Neoadjuvant therapy	Therapy duration	Clinical downstaging (%)	Pathological downstaging (%)	Organ confined (%)	Positive margins (%)	Seminal vesicle invasion (%)	pN+ (%)
Labrie *et al.*[46]	1993	142	B0-C2	Leuprolide, Flutamide	3 months		Neo 43, RP 8	Neo 77, RP 34	Neo 13, RP 39	Neo 12, RP 34	Neo 3, RP 6
Debruyne *et al.*[47]	1994	125	T2-3N0M0	Goserelin, Flutamide	3 months	Neo 34	Neo 19, RP 8		Neo 27, RP 39		
Soloway *et al.*[48]	1995	303	T2bNxM0	Leuprolide, Flutamide	3 months			Neo 53, RP 22	Neo 18, RP 48	Neo 15, RP 22	Neo 6, RP 6
Van Poppel *et al.*[49]	1995	130	T2b-T3	Estramustine Phosphate~	1.5 months	Neo 22	Neo 26, RP 23	Neo 72, RP 63	Neo 32/31/19^, RP 44/27/10^		
Dalkin *et al.*[50]	1996	56	T1c-T2b	Goserelin	3 months			Neo 57, RP 61			Neo 4, RP 4
Goldenberg *et al.*[51]	1996	213	T1b-T2c	Cyproterone	3 months			Neo 42, RP 20	Neo 28, RP 65	Neo 28, RP 14	Neo 7, RP 3
Hugosson *et al.*[52]	1996	111	T1b-3aN0M0	Triptorelin, Cyproterone	3 months				Neo 23, RP 41		
Witjes *et al.*[53]	1997	354	T2-3N0M0	Goserelin, Flutamide	3 months	Neo 32	Neo 16, RP 6	Neo 45, RP 21	Neo 27, RP 46		Neo 13, RP 23
Aus *et al.*[54]	1998	122	T1b-3aNxM0	Triptorelin, Cyproterone	3 months				Neo 24, RP 46	Neo 15, RP 22	Neo 5, RP 14
Fair *et al.*[55]	1999	140	T1-T2	Goserelin, Flutamide	3 months			Neo 70, RP 59	Neo 19, RP 37		
Schulman *et al.**[56]	2000	402	T2-3N0M0	Goserelin, Flutamide	3 months	Neo 30	Neo 15, RP 7	Neo 45, RP 24	Neo 26, RP 48		Neo 15, RP 23
Selli *et al.*[57]	2002	393	T2-3N0M0	Goserelin, Bicalutamide	3/6 months			Neo 49/64, RP 34	Neo 28/23, RP 53	Neo 11/11, RP 11	Neo 8/4, RP 12
Soloway *et al.**[58]	2002	303	T2bNxM0	Leuprolide, Flutamide	3 months				Neo 18, RP 48	Neo 15, RP 22	Neo 6, RP 6
Prezioso *et al.*[59]	2004	183	T1a-2bN0M0	Leuprolide, Cyproterone	3 months				Neo 39, RP 60		Neo 3, RP 11
Gravina *et al.*[60]	2007	430	T2-T3a	Bicalutamide	4 months				Neo 13, RP 35		
Yee *et al.**[61]	2010	148	T1b-T3	Goserelin, Flutamide	3 months			Neo 85, RP 80	Neo 19, RP 38	Neo 4, RP 6	Neo 1, RP 3

*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

Table 4: Oncological outcomes in randomized trials of neoadjuvant androgen deprivation therapy and radical prostatectomy versus immediate 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*.[53]	1997	354	T2-3N0M0	Goserelin, Flutamide	3 months	Neo 22, RP 23			15 months	
Aus *et al*.[54]	1998	122	T1b-3aNxM0	Triptorelin, Cyproterone	3 months	Neo 26, RP 22			38 months	
Schulman *et al*.*[56]	2000	402	T2-3N0M0	Goserelin, Flutamide	3 months	Neo 26, RP 33	Neo 10, RP 16	Neo 7, RP 6	4 years	Neo 96, RP 96
Aus *et al*.*[62]	2002	126	T1b-3aNxM0	Triptorelin, Cyproterone	3 months	Neo 33, RP 29		Neo 5, RP 3	7 years	Neo 83, RP 86
Soloway *et al*.*[58]	2002	303	T2bNxM0	Leuprolide, Flutamide	3 months	Neo 35, RP 32			5 years	
Klotz *et al*.*[63]	2003	213	T1b-T2c	Cyproterone	3 months	Neo 38, RP 34		Neo 5, RP 1	6 years	Neo 93, RP 95
Prezioso *et al*.[59]	2004	183	T1a-2bN0M0	Leuprolide, Cyproterone	3 months	Neo 10, RP 16				
Yee *et al*.*[61]	2010	148	T1b-T3	Goserelin, Flutamide	3 months	Neo 24, RP 20	Neo 1, RP 2	Neo 4, RP 5	8 years	Neo 86, RP 92

*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

Randomized trials comparing different neoadjuvant androgen deprivation therapy agents

Sayyid *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.[65] 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.[66,67] 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.[68] 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 recieved nADT prior to the surgery.[69] 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.[70] 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.[71] 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.[72,73] 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,[73] warranting further evaluation of chemohormonal therapy (CHT) in high-risk and locally

advanced non-metastatic PCa. 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.[74] They evaluated 177 men with very high-risk locally advanced PCa, 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.[75] 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).[75]

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.[76] 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.[77-81] 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 bicalutamide, degarelix, and docetaxel prior to RP in newly diagnosed high-risk or oligometastatic PCa. The study aims to evaluate complete pathologic response at the time of prostatectomy, PSA response, time to PSA recurrence, and safety and toxicity of combination CHT prior to RP. The study, however, has been suspended temporarily due to protocol modifications. The NCT02494713 trial was an open-label, single-arm study of nCHT in men with nonmetastatic, locally-advanced PCa eligible for RP. Patients were to receive four injections of degarelix and two 8-week cycles of chemotherapy with doxorubicin and ketoconazole. Unfortunately, the study was terminated after enrolment of only 4 patients over 2 years. Similarly, the NCT01531205 trial, a single-arm study evaluating neoadjuvant cabazitaxel and a LHRH agonist before salvage RP was terminated due to poor accrual of only 2 patients over 16 months.

In the GETUG 12 trial, men with high-risk PCa 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

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

Author	Year	Study design	Total patients	Clinical risk	Eligibility criteria	Neoadjuvant therapy	Undetectable PSA (%)	Stage pT0 (%)	Stage pT4 (%)	Stage pN1 (%)	PSM (%)	BCR (%)	10-year OS
Pan	2019	Retrospective study	177	Very high risk or locally advanced	>cT3a disease or primary Gleason pattern 5 or ≥5 cores with Gleason sum 8-10 or PSA ≥50 ng/mL or with pelvic metastatic lymph node involvement	4-6 cycles of goserelin acetate/bicalutamide/ docetaxel every 3 weeks (nCHT) versus goserelin acetate/bicalutamide (nADT) versus immediate RP	RP 48 nADT 73 nCHT 81	RP 0 nADT 9 nCHT 17	RP 30 nADT 14 nCHT 19	RP 30 nADT 14 nCHT 19	RP 32 nADT 22 nCHT 17	RP 81 nADT 47 nCHT 14	-
Narita	2019	Retrospective propensity matched	56 matched pairs	High-risk	cT3 disease or PSA ≥ 15 ng/mL, or any Gleason pattern 5	Complete androgen blockage, 6 cycles docetaxel and entramustine versus immediate RP	-	-	-	-	-	RP 45 (approx.) nCHT 70 (approx.)	-
Eastham	2009	Randomized Trial	391 nCHT versus 297 immediate RP	High-risk	Stage T3-T4 disease or Gleason score ≥8, or PSA >20 ng/mL	Neoadjuvant ADT and docetaxel versus immediate RP	-	-	-	-	-	-	RP 74% nCHT 80%

ADT = Androgen deprivation therapy, PSA = Prostate specific antigen, nCHT = Neoadjuvant chemohormonal therapy, nADT = Neoadjuvant ADT, RP = Radical prostatectomy,

3 months after commencing systemic therapy.[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 788 men with high-risk, clinically localized PCa (T1-T3aNxM0) randomized to immediate surgery versus nCHT followed by surgery.[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.[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 *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.[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.[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 .[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.[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.[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.

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