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Neoadjuvant Systemic Therapy Prior to Radical Prostatectomy for Clinically Localized High-Risk Prostate Cancer

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Radical prostatectomy (RP) remains a standard treatment option for clinically localized high-risk prostate cancer. While RP provides excellent local control, patients with high-risk disease remain at considerable risk for recurrence after surgery. Disease relapse may be the result of occult distant metastases or regional micrometastatic disease at the time of surgery. Accordingly, the role of systemic (neoadjuvant) therapy prior to RP has been investigated. Proposed neoadjuvant regimens: include monotherapy or combinations of chemotherapy, hormonal deprivation, and immunologic agents. Randomized trials using androgen deprivation have demonstrated improved pathologic outcomes, including pathologic downstaging and decreased risk of positive surgical margins, extracapsular extension, and seminal vesical invasion. However, these, albeit early, trials did not reliably demonstrate improved post-prostatectomy oncologic outcomes. More recent trials have evaluated novel combinations of chemo-hormonal therapy and immunologic based therapies. These studies are currently maturing and offer the promise, pending findings, of potentially informing future practice. In this review, we highlight the pathophysiologic basis and contemporary evidence for neoadjuvant therapy prior to RP for clinically localized high-risk prostate cancer.

Keywords: prostatectomy, neoadjuvant, hormonal deprivation, chemohormonal therapy, immunotherapy

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INTRODUCTION

Prostate cancer remains as one of the commonest cancers in the developed world, of which a majority are clinically organ-confined at diagnosis (1). In the setting of low and intermediate-risk prostate cancer, active surveillance, radical prostatectomy (RP), and radiotherapy results in excellent prostate cancer specific survival (2, 3). In the setting of higher-risk disease, the role of local treatment with RP remains controversial. However, over the past decade, there has been a gradual shift to performing RP on increasingly higher risk patient cohorts (4, 5).

Controversy regarding RP in clinically localized high-risk prostate cancer exists due to a higher risk biochemical-recurrence (BCR) compared to RP performed in men with lower-risk prostate cancer. A high-volume multi-center study reported BCR of 50% and a salvage therapy rate of 37%

after RP in high-risk patients (6). Such recurrences result from either post-RP residual local disease and/or undiagnosed occult metastatic disease at the time of surgery.

Increasingly, research has been directed to improving outcomes in patients with clinically localized high-risk prostate cancer treated with RP. Administration of systematic therapies prior to surgery (neoadjuvant therapy) may downstage the local tumor and improve local cancer control and further, these therapies may address occult micrometastatic disease improving oncologic outcomes.

In this review, we highlight the pathophysiologic basis and contemporary evidence assessing neoadjuvant therapy prior to RP for clinically localized high-risk prostate cancer.

RATIONALE

Neoadjuvant therapy is proposed to provide benefit by treating occult distant disease (micrometastases) and as well as to improve local disease control by downstaging the primary tumor. Additionally, monitoring the *in-vivo* disease response to systemic agents may provide prognostic information (7). Neoadjuvant therapies have been successfully introduced into other malignancies including esophageal (8) and bladder cancer (9).

As a general principal, neoadjuvant therapies may be considered feasible to investigate if (7):

- a successful local treatment already exists
- the risk of recurrence or progression is high, despite local therapy
- the drug candidate(s) is active against the disease

Following these principals above, high-risk prostate cancer appears particularly relevant for consideration of neoadjuvant therapies. In the PSA-era, high risk prostate cancer represents up to 30% of new prostate cancer diagnoses (10, 11). While subtle variations exist in the precise definition of high-risk disease, consensus suggests that this refers to patients with a Prostate Specific Antigen (PSA) over >20ng/mL, or Grade Group 4 or 5, or clinical stage of >T2c (12–15). Curative local treatment for high-risk clinically localized prostate cancer exists including RP. Nevertheless, in the setting of post-prostatectomy clinically localized high-risk disease, the 10 year BCR-free, cancer-recurrence-free survival and salvage therapy rates are 50%, 87% and 37%, respectively (6). Registry data, based on the SEER database, suggests a 5-year prostate cancer specific mortality of 2.3% and 3.5% in patients post-prostatectomy with high risk and very-high risk disease, respectively (16).

Several systemic therapies have proven beneficial in the setting of metastatic prostate cancer and are thereby potential candidates to be used earlier in the disease process to improve oncologic outcomes. These agents represent candidates as neoadjuvant therapies. Firstly, agents that manipulate the intra-tumoral hormonal environment are the mainstay of treatment in men with metastatic prostate cancer (14). Secondly, traditional chemotherapeutic agents that target prostate cancer cell cycle and replication have improved survival in men with advanced disease (17). Finally, novel immunotherapy agents that upregulate host immune response, such as checkpoint inhibitors, are of current interest and may prove beneficial in the neoadjuvant setting.

Based on the above principals for neoadjuvant therapy, investigation of RP combined with neoadjuvant systemic therapy in men with clinically localized high-risk prostate cancer is worthwhile, due to the high risk of recurrence after standard treatment options and the activity of various drug groups against this disease.

Neoadjuvant therapies, specifically hormonal deprivation, has been considered accepted practice prior to radiotherapy for localized prostate cancer (14). Indeed, in high-risk disease, hormonal deprivation in combination with radiotherapy is superior to radiotherapy along (18, 19). The proposed theory of mechanism of this is that hormonal deprivation may sensitize prostate cancer cells to radiotherapy. This sensitization is thought to be mediated by inhibition of androgen-receptor mediated repair of damaged DNA following radiotherapy injury. Given this proposed mechanism, the principals of neoadjuvant therapy prior to radiotherapy are not directly extrapolatable to the prostatectomy setting.

NEOADJUVANT HORMONAL THERAPY

Hormonal deprivation, or androgen deprivation therapy (ADT), has long been a therapeutic strategy for mitigating progression of prostate cancer since the works of Huggins in the 1940s (20). This early work recognized that prostate cancer is largely a hormone-driven tumor through the effects of physiologic and pathologic androgens (21). Androgen receptor (AR) expression by prostate cancer cells, and subsequent stimulation by androgens (including testosterone and dihydroxytestosterone), results in AR nuclear translocation and activation of pathways that promote cellular proliferation and cell survival (22).

AR stimulation primarily occurs as a result of dihydroxy-testosterone, following conversion from testosterone by 5α-reductase. A majority of testosterone production occurs in the testes and, to a lesser extent, the adrenal glands and the tumor itself. Testicular testosterone production is regulated *via* the hypothalamic-pituitary-gonadal axis, and thus this is the primary target to modulate testosterone production in the setting of ADT. Specifically, these agents include Luteinizing Hormone Releasing Hormone (LHRH) analogues. In the setting of metastatic prostate cancer, sustained castration eventually leads to progression to castration-resistance, which is variously mediated by upregulation of AR expression, AR gain-of-function mutations, and tumoral androgen production (23, 24).

While LHRH analogues reduce circulating serum testosterone by 90-95%, these agents only limit intratumoral testosterone production by 75% (25). Accordingly, novel anti-androgen agents have been developed. Such agents include rationally designed AR inhibitors that limit AR nuclear translocation and downstream effects, including enzalutamide, apalutamide,

durolutamide. Further, agents such as abiraterone act by irreversibly inhibiting CYP17A1 and thus blocking the production of androgens, including both adrenal and intratumoral production.

The potential benefit of neoadjuvant ADT must be considered in the context of potential adverse effects from these therapies. Adverse effects of LHRH analogues may be categorized as either sexual dysfunction (impotence, reduced libido), endocrine abberations (including weight gain, diabetes mellitus, obesity, gynecomastia, increased fracture risk, hot flushes), cardiovascular effects (acute myocardial infarction, ischemic heart disease or thrombosis), and compromised quality of life outcomes (mental health, mood, physical capacity) (24). In addition to these, novel anti-androgens may harbor specific adverse effects depending on the agent, including seizures (enzalutamide) and hypertension (abiraterone).

Neoadjuvant Hormonal Deprivation With Conventional ADT

Multiple trials have evaluated conventional ADT agents (LHRH analogues with or without first generation antiandrogens) in the setting of neoadjuvant therapy before radical prostatectomy for patients with clinically localized high risk-prostate cancer. Trials assessing these agents are summarized in **Table 1**.

Among the earliest of these trials was conducted by Labrie et al. in 1993, which demonstrated pathological downstaging and a reduction in positive surgical margins in the clinically localized high-risk population (26). These findings were corroborated by subsequent trials assessing goserelin monotherapy (29), cyproterone monotherapy (30) and combination therapy with either leuprolide plus flutamide (41) or goserelin plus flutamide (42). A systematic review and meta-analysis of trials demonstrated that, compared to surgery alone, neoadjuvant ADT resulted in reduced positive surgical margin rates (RR 0.49, 95% CI 0.42-0.56, p<0.001) and a higher likelihood of organ confined disease (RR 1.63, 95% 1.36-1.95, p<0.001) (43).

While a consistent effect on adverse pathologic features has been found with neoadjuvant ADT prior to RP, a benefit with regard to clinical oncologic outcomes has not been established. For example, Schulman et al. noted no difference in the risk of BCR between the groups receiving of not receiving neoadjuvant ADT prior to RP (44). Subsequent studies assessing varying conventional ADT agents with longer term follow-up have similarly reported no difference in the rates of BCR or overall survival (45–47). Moreover, in the aforementioned meta-analysis, no difference was observed between these groups with regard to prostate cancer specific- or overall-survival (43).

Of note, the duration of neoadjuvant therapy in these studies was typically limited to 3 to 4 months. Interestingly, Sayyid et al. compared 3 months and 8 months of leuprolide and a prior to RP and demonstrated that patients receiving 8 months of ADT demonstrated reduced risk of adverse pathologic features than those receiving 3 months of treatment (48). This notion was corroborated by Selli et al. using goserelin and flutamide (34). However, these studies did not report post-prostatectomy clinical outcomes and thus, the relevance of these pathologic findings is unclear.

Neoadjuvant Hormonal Deprivation Novel Anti-Androgens

The aforementioned development of more potent antiandrogens has reinvigorated interest of the role of neoadjuvant therapy for clinically localized high risk prostate cancer. However, due to the limited maturity of these agents, minimal long term oncologic clinical data exists.

Abiraterone, an irreversible CYP17A inhibitor, functions by reducing testicular, tumoral, and adrenal androgen production (49). In the setting of neoadjuvant therapy, abiraterone was the first novel antiandrogen assessed in high risk disease prior to RP (50). Taplin et al. randomized 58 patients to either 3-months of neoadjuvant abiraterone plus LHRH agonist or LHRH agonist monotherapy prior to prostatectomy. In the group with abiraterone, patients demonstrated a lower intratumoral testosterone (0.061pg/mg *vs* 0.098pg/mg, p=0.02) and DHT (0.180 pg/mg *vs* 1.307 pg/mg, p<0.001). This study reported reduced adverse pathologic features with the addition of abiraterone with higher proportions of complete response or minimally residual disease (MRD) (62% *vs* 48%). Efstathiou et al. performed a comparable Phase II open label trial, randomizing 65 men to 3-months of LHRH agonist with and without abiraterone in the neoadjuvant setting. This study similarly reported significant reduction in tumor volume measures favoring the abiraterone + LHRH agonist group (50).

Enzalutamide is an androgen receptor inhibitor that prevents androgen binding and receptor-ligand translocation. Similar to the findings observed in the abiraterone neoadjuvant trials, Phase II trials assessing neoadjuvant enzalutamide with LHRH agonist have reported outcomes regarding pathologic features. Montegomery randomized 52 patients, of which, 48 underwent prostatectomy after 6-months of enzalutamide monotherapy or enzalutamide with dutasteride and a LHRH analogue (37). Patients administered the combination therapy demonstrated lower intratumoral DHT (0.04pg/mg *vs* 3.34pg/mg, p<0.001) and intratumoral testosterone (0.18pg/mg *vs* 0.90pg/mg, p<0.001). The combination therapy group also demonstrated improved pathologic features including higher rates of either pathologic complete response or MRD (17.3% *vs* 0%) and lower residual cancer burden ($0.41cm^3$ *vs* $0.06cm^3$) (37). Results of this study suggests neoadjuvant monotherapy with enzalutamide, and perhaps other novel anti-androgens, may not produce sufficient castration for clinical benefit.

McKay et al. recently assessed 6-months of neoadjuvant androgen blockade by means of either LHRH agonist with enzalutamide plus/minus the additional of abiraterone. This trial enrolled 75 patients and reported a trend of complete pathologic response or MRD favoring the addition of abiraterone, without reaching statistical significance (30% v 16%, p=0.263). Rates of adverse pathology were comparable between the groups, including pT3 disease, positive surgical margins and positive lymph nodes (38). As such, data from these trials suggest intense castration with two novel anti-

TABLE 1 | Completed, published randomized trials assessing the role of neoadjuvant hormonal or chemohormonal therapy prior to prostatectomy.

Author	Year	Location	n	Abbreviated inclusion criteria	Agent (Duration)	Primary endpoint results
Neoadjuvant therapy with Convention Androgen Deprivation therapy agents						
Labrie (26)	1993	Québec, Canada	77	Early stage prostate cancer	Leuprolide + Flutamide (3 Months)	Cancer-positive margins were reduced from 38.5% in control patients to 13.0% in men who received neoadjuvant combination (p = 0.006).
Debruyne (27)	1994	Nijmegen, Netherlands.	65	cT2-3, N0, M0 stages of prostate cancer	Goserelin + Flutamide (3 Months)	Serum PSA levels and prostatic volume decreased from a mean of 12.8 ng/ml and 42.8 cm3 to a mean of 0.8 ng/ml and 29.5 cm3, respectively.
Van Poppel (28)	1995	Leuven, Belgium	65	Stages T2b and T3 prostate cancer	Estramustine + Phosphate (1.5 Months)	For T2b tumors, a significant decrease in positive surgical margins was found compared to the nonpretreated group. This difference was not found for clinical stage T3 tumors.
Dalkin (29)	1996	Tucson, AZ, USA	56	Clinically localized (stages T1C, T2A and T2B) prostatic cancer	Goserelin (3 Months)	No improvement in pathological outcome
Klotz (30, 31)	1999	Toronto, Canada	213	Localized (T1-T2) prostate cancer.	Cyproterone (3 Months)	No difference in risk of biochemical recurrence-free survival. Neoadjuvant group had a lower rate of apical margin involvement than those who did not (17.8 versus 47.8%, respectively, p < 0.0001).
Hugosson (32)	1996	Göteborg, Sweden	56	Prostate cancer (T1b-T3a, N0, M0, G1-3)	Triptorelin, Cyproterone (3 Months)	Neo-adjuvant treatment had a significantly lower frequency of positive margins (41 *vs*. 23%, p = 0.013).
Gleave (33)	2001	Vancouver, Canada	547	T1 or T2 prostate cancer	Leuprolide, flutamide (3 months *vs* 8 months)	Lower pre-operative PSA favored 8 month ADT group (0.052 *vs* 0.12mc/L, P<0.001). Surgical margins favored 8 month ADT group (12% *vs* 23%, p=0.01).
Selli (34)	2002	Pisa, Italy	265	Surgically resectable clinical stage (T2–T3, N0, M0) prostatic cancer	Goserelin, Bicalutamide (3/6 Months)	PSA progression: significant differences between treatment groups.
Prezioso (35)	2004	Naples, Italy	91	Prostatic cancer clinical stage T2b or less	Leuprolide, Cyproterone (3 Months)	Neoadjuvant group: 31% of patients had a decrease in tumor and prostate volume.
Gravina (36)	2007	L'Aquila, Italy	61	Prostate cancer clinical Stage T2-T3a	Bicalutamide (4 Months)	Neoadjuvant treatment had a reduction of positive surgical margins (13.1% versus 34.5%, *P* = 0.011).
Neoadjuvant therapy with Novel Antiandrogen agents						
Montgomery (37)	2017	Seattle, WA, USA	25	Surgically resectable, prostate cancer, clinical stage (T1c–T3, N0/NX, M0), Gleason score ≥7 or PSA >10 ng/mL.	Enzalutamide Vs. Enza + Dutasteride + Leu (6 Months)	0 in the Enza arm and 4.3% in the Enza/Dut/LHRHa arm achieved complete pathologic response. Neither treatment arm demonstrated a significantly higher pCR rate compared with the historical control rate of 5%.
McKay (38)	2019	San Diego, CA, USA	50	Prostate cancer, ISUP 3 or greater, PSA greater than 20 ng/mL, or T3 disease (by prostate MRI).	Enzalutamide + leuprolide plus/minus Apalutimide (6 Months)	Complete response or tumor volume reduction rate was numerically higher with additional apalutamide than without, though not significant (30% *vs* 16%, p=0.151)
Efstathiou (39)	2020	Houston, TX, USA	32	Localized (T1-T2), high-risk prostate cancer.	Apalutamide + LHRHa +/- AA (6 Months)	Organ confined disease (≤ypT2N0) found in 41% APA+LHRHa *vs*. 39% APA+AA+LHRHa treated.
Neoadjuvant therapy with Chemohormonal therapy						
Eastham (40)	2020	New York, NY, USA	367	Prostate cancer clinical T1-3a disease, serum PSA levels ≤ 100 ng/mL, and no radiographic evidence of metastatic disease	Docetaxel + ADT (4 Months) + RP Versus RP alone	No difference was observed in 3-year BPFS between the neoadjuvant and surgery arms (0.89 *v* 0.84, respectively.

androgen agents plus LHRH analogue may provide no additional benefit when compared to single novel anti-androgen therapy plus LHRH analogue.

Apalutamide, like enzalutamide, is an androgen receptor inhibitor and has recently been trialed in the neoadjuvant setting (39, 51, 52). While no randomized data comparing apalutamide with LHRH versus LHRH monotherapy exists, data assessing apalutamide in combination with other novel anti-androgens has been reported. Results of two phase II trials suggested no improvement in rates of complete pathologic response or reduction in residual tumor in patients treated with apalutamide in addition to abiraterone and LHRH agonist (39, 51). A single-arm Phase II trial reported pathologic features after 3-months of neoadjuvant apalutamide, abiraterone, degarelix and indomethacin prior to prostatectomy (53). The addition of indomethacin may further decrease production of

testosterone by inhibiting AKR1C3. Despite maximal blockade, 5% of patients had complete pathologic response, 30% had MRD and 90% had T3 disease at prostatectomy.

In sum, neoadjuvant ADT with novel antiandrogens consistently reduces intratumoral testosterone and inconsistently improves rates of pathologic complete response or tumor volume reduction. Current data suggests that more intense hormonal blockade with multiple novel anti-androgens does not appear to result in meaningful improvements in risk of adverse pathology at prostatectomy. Longer follow-up including clinical and oncologic outcomes is required to further define the role of novel antiandrogens in the neoadjuvant setting prior to RP.

CHEMOHORMONAL THERAPY

Previous groups have suggested that residual tumor may exist following neoadjuvant ADT due to a proportion of tumor clones exhibiting a degree of castration-resistance (54, 55). Accordingly, the addition of a cytotoxic chemotherapy agent has been proposed as a mechanism to target such cells (56). Regarding specific cytotoxic agents, as the efficacy of docetaxel has been demonstrated (with ADT) in metastatic prostate cancer (17, 57, 58), it is not surprising that this agent has thus been tested in the neoadjuvant setting as well. Specifically, neoadjuvant chemohormonal therapy has been investigated in several trials to date (40, 59–64). Despite the potential for therapeutic benefit of chemohormonal therapy, the potential morbidity must be carefully considered it the context of dual treatment pathways. In addition to the aforementioned adverse effects of ADT, docetaxel therapy is morbid and may be associated with fatigue, neuropathy, myelosuppression and rarely death (17).

Of the available studies assessing neoadjuvant chemohormonal therapy, a majority of these earlier trials represented single-arm Phase II safety and feasibility assessments of neoadjuvant chemohormonal therapy (59–64). Broadly speaking, these safety and feasibility trials reported acceptable tolerability of chemohormonal therapy with encouraging outcomes pertaining to pathologic downstaging and recurrence-free survival. Chi et al. performed one such Phase II trial and recruited 72 patients with high-risk disease (59). Prior to prostatectomy, patients received ADT and docetaxel (three cycles of docetaxel weekly for 6 weeks). Of these patients, two patients demonstrated complete pathologic response at the time of prostatectomy and at a median follow-up of 42.7 months, 30% had disease relapse. These findings have been corroborated by comparable Phase II single arm trials (59–64).

Subsequent comparative series have performed *post-hoc* comparative analysis of these patients enrolled on the single arm Phase II trials, matching patients with those that did not receive neoadjuvant therapies (63, 65, 66). For example, Narita et al. performed a propensity score matched analysis used patients from an aforementioned Phase II trial with a subgroup of patients from an existing database (66). In this analysis, neoadjuvant chemohormonal therapy was associated with a reduced risk of biochemical recurrence, compared to RP alone (p=0.021). Despite varying neoadjuvant chemohormonal regimes, comparable analysis by other groups has demonstrated improved BCR free-survival (63, 66), progression-free survival (65) and metastases-free survival (63) was observed when compared to RP alone.

A recent contemporary randomized trial examining the role of neoadjuvant chemohormonal therapy was published by Eastham et al. (40). The Preoperative Use of Neoadjuvant Chemotherapy (PUNCH) Alliance 90203 trial compared RP plus/minus neoadjuvant chemohormonal therapy with six cycles of docetaxel every 3-weeks and an LHRH analogue therapy for 18-24 weeks. The trial recruited a 788 patients with clinically localized high-risk disease (pT1-T3,NxM0) (40). At the time of prostatectomy, men receiving neoadjuvant chemohormonal therapy had lower pathologic stage (p<0.001), fewer positive surgical margins (p<0.001), and fewer metastatic lymph nodes (p=0.05) (40). However, the trial did not meet its primary endpoint of reducing BCR at 3 years. Though, longer term follow-up subsequently reported improved BCR-free survival (HR 0.69, 95% CI 0.48-0.99) and overall survival (80% *vs* 74%, HR 0.61, 95% CI 0.40-0.94), although the low event rate limits interpretation of these data. Additionally, rates of adjuvant or salvage treatment were lower in the neoadjuvant chemohormonal therapy group (HR 0.61, 95% 0.48-0.78).

Studies assessing chemohormonal therapy with novel anti-androgens are currently underway (**Table 1**).

IMMUNOTHERAPY

Immunotherapy agents have been developed and introduced into cancer care in alternate organs, such as kidney (67–70) and bladder (71, 72). Such agents act by improving the host immune response to cancer cells. Broadly speaking, this may be achieved by either upregulating the host immune response, or conversely, by limiting tumor cells escape pathways. The effectiveness of immunotherapy is determined by the immunogenicity of cancer cells, specifically by the characteristic expression of unique tumor associated antigens (73). Accordingly, immunotherapy in prostate cancer may have utility given the prostate expresses specific proteins (e.g. PSA, PSMA) and further, given it is not a vital organ, collateral damage to physiologic tissue is of minimal consequence (74). Additionally, patients with prostate cancer are known to have a disrupted immune system, particularly in the later stages of the disease, as characterized by a reduction in Natural Killer (NK) cell activity (75, 76).

Despite increasing interest, only limited data currently exists in the setting of neoadjuvant immunotherapy for high risk prostate cancer. Of the available data to date, agents assessed include GVAX, rituximab and Sipuleucel-T. GVAX is a granulocyte-macrophage colony stimulating factor (GM CSF) secreting vaccine which has been studied in a Phase II trial by the Johns Hopkins group (NCT01696877) (77). While data pertaining to clinical outcomes were limited, GVAX showed

improved immunologic infiltrates such as CD8+ and CD4+ T cells. Rituximab is an anti-CD20 antibody that results in B-cell ablation and has been trailed in an exploratory Phase II setting (NCT01804712) with primary immunologic end points. This trial demonstrated neoadjuvant administration of rituximab resulted in an altered immune tumor microenvironment; the implications on clinical outcomes from this therapy is unclear (78). Similar neoadjuvant exploratory analyses have been performed using Sipuleucel-T, a systemic agent that induces CD4 and CD8 T cell recruitment. Given the exploratory nature, a lack of clinical data exists; however, this study did demonstrate a upregulation of immune response scores in the tumor microenvironment following Sipuleucel-T administration (79)

Checkpoint inhibitors, such as CTLA4, PD1 and PDL1 inhibitors, act by directly or indirectly upregulating host T cell response to tumor cells (80). Such agents have been of intense interest in renal cell carcinoma and other tumor types (69, 70, 81). To date, in the setting of advanced prostate cancer, the efficacy of monotherapy with these agents has been underwhelming, with the exception of pembrolizumab in patients with mismatch repair (MMR) deficiency or a high microsatellite instability status (82, 83). Data is lacking assessing the role of immunotherapy in the earlier stages of high risk disease. Accordingly, current trials are currently in progress, assess in the role of these novel checkpoint inhibitors as neoadjuvant agents, including nivolumab (NCT02933255), atezolizumab (NCT03821246) and other CTLA4 agents (NCT04301414).

FUTURE DIRECTIONS/CURRENT ACTIVE TRIALS

There is significant interest in neoadjuvant therapies prior to RP for clinically localized high-risk prostate cancer exists, as evidenced by numerous active and recruiting trials (summarized in **Table 2**). Per the principals of neoadjuvant therapy, future directions of research may focus on alternate treatments that have known activity in prostate cancer. Emerging trials are underway assessing therapies such as novel antiandrogens and immunotherapy agents. Trials assessing

TABLE 2 | Current active trials assessing neoadjuvant therapies prior to radical prostatectomy for high-risk, localized disease.

Name (trial number)	Location	Phase	Abbreviated Oncologic Eligibility	Treatment arms
Neoadjuvant Degarelix With or Without Apalutamide Followed by Radical Prostatectomy (ARNEO) (NCT03080116)	Leuven, Belgium	II	-Intermediate risk: at least 2 of the following factors: cT2b, biopsy GS 7, PSA 10-20ng/ml -High risk: cT≥2c and/or biopsy GS≥8 and/or PSA>20ng/ml -cN0-cN1, cM0	-Apalutamide + Degarelix -Placebo + Degarelix
Neoadjuvant Pembrolizumab Plus Androgen Axis Blockade Prior to Prostatectomy for High Risk Localized Prostate Cancer (NCT03753243)	Portland, OR, USA	II	- Any one of the following three high risk features: Gleason grade > 8-10, PSA > 20 ng/ml, cT3a -cM0	-Pembrolizumab + Enzalutamide + GNRH agonist (Single arm)
Neoadjuvant Atezolizumab-Based Combination Therapy in Men With Localized Prostate Cancer Prior to Radical Prostatectomy (NCT03821246)	San Francisco, CA, USA	II	-Only high risk patients in the safety-lead in for each cohort -Intermediate risk patients eligible once safety confirmed on interim analysis -cM0	-Atezolizumab +/- either Tocilizumab OR Etrumadenant (Non-randomized, sequential cohorts)
A Study of Neoadjuvant Hormone Therapy in Patient With Advanced Prostate Cancer Undergoing Radical Prostatectomy. (NCT03971110)	Guangzhou, China	IV	-cT3/4, cN0/1, cM0/1 (with five or fewer extra-pelvic lesions)	-Zoladex + Casodex (Single Arm)
Ibrutinib as Neoadjuvant Therapy in Localized Prostate Cancer (NCT02643667)	San Francisco, CA, USA	II	-Suitable for radical prostatectomy -cM0	-Ibrutinib (Single Arm)
Biomarkers for Neoadjuvant Pembrolizumab in Non-Metastatic Prostate Cancer Positive by 18FDG-PET Scanning (NCT04009967)	Laval, Québec, Canada	II	-Gleason Score ≥ 8, cM0 -Intraprostatic maximum standardized uptake value (SUVmax) ≥4 at 18-FDG-PET/CT exam	-Pembrolizumab (Single arm)
Neoadjuvant Hiltonol® (PolyICLC) for Prostate Cancer (NCT03262103)	New York, NY, USA	I	-Gleason 7 – 10, cT2a - cT3b adenocarcinoma of the prostate with plans for radical prostatectomy and PSA ≥ 4 ng/ml -Tumor visible on multiparametric MRI	Intratumoral injection of Poly-ICLC
177Lu-PSMA-I&T Prior to Radical Prostatectomy for Locally Advanced Disease (NCT04297410)	Petach Tikva, Israel	NA	-cT3/4 and/or Gleason score ≥8 and/or PSA ≥ 20 ng/dl) -Loco-regional prostate cancer (pelvic lymphadenopathy of ≥2 cm on axial imaging) -High PSMA expression: with tracer uptake greater than normal liver (maximal SUV ≥1.5 of liver)	- 177Lu-PSMA-I&T Radionuclide (Single arm)
Neoadjuvant Therapy With Proxalutamide Combined With Androgen Deprivation Therapy (ADT) for High Risk Prostate Cancer (NCT05076851)	Nanjing, Jiangsu, China	II	- High-risk prostate cancer (cT≥2c or Gleason score ≥8 or PSA≥20ng/ml) -cM0	-Proxalutamide +ADT -Placebo + ADT

(Continued)

TABLE 2 | Continued

Name (trial number)	Location	Phase	Abbreviated Oncologic Eligibility	Treatment arms
Androgen Receptor Antagonist ARN-509 With or Without Abiraterone Acetate, Gonadotropin-Releasing Hormone Analog, and Prednisone in Treating Patients With High-Risk Prostate Cancer Undergoing Surgery (NCT02949284)	New Jersey, NJ, USA	II	-Gleason > 8 OR PSA > 20 and more than 1 positive core -cT ≤ 3 on CT or MRI	-Apalutamide -Apalutamide + Abiraterone + GNRH agonist -Prostatectomy alone
Aspirin and Rintatolimod With or Without Interferon-alpha 2b in Treating Patients With Prostate Cancer Before Surgery (NCT03899987)	Buffalo, NY, USA	II	- Localized prostatic adenocarcinoma and planning on prostatectomy	- aspirin, interferon alpha, rintatolimod, surgery - aspirin, rintatolimod, surgery -surgery alone
Neoadjuvant Androgen Deprivation Therapy Combined With Enzalutamide and Abiraterone Using Multiparametric MRI and 18FDCFPyL PET/CT in Newly Diagnosed Prostate Cancer (NCT03860987)	Bethesda, MD, USA	II	-Intermediate or high risk prostatic adenocarcinoma -cN0/1 -cM0	-Enzalutamide + Abiraterone + GNRH agonist
Neoadjuvant Androgen Deprivation, Darolutamide, and Ipatasertib in Men With Localized, High Risk Prostate Cancer (NCT04737109)	Chicago, IL, USA	II	- Histologically-confirmed diagnosis of localized, untreated prostate cancer with high-risk features. Including: Grade group 4 or higher, OR Stage T3-4, M0 -PTEN loss	- ADT + Ipatasertib + Darolutamide
Genomic Biomarker-Selected Umbrella Neoadjuvant Study for High Risk Localized Prostate Cancer (GUNS) (NCT04812366)	Vancouver, British Columbia, Canada	II	-High-risk localized prostate cancer as defined by: PSA >20, ISUP 4 or greater or high volume Gleason pattern 4 or 5 Participants with oligometastatic (< 3) metastases by PSMA imaging only who are deemed candidates for radical prostatectomy are eligible	-LHRHa + Apalutamide +/- Abiraterone -LHRHa + Abiraterone +/- either Docetaxel or niraparib
Non-fucosylated Anti-CTLA-4 (BMS-986218) + Degarelix Acetate *vs*. Degarelix Acetate Alone in Men With High-risk Localized Prostate Cancer (NCT04301414)	New York, NY, USA	I	-Prostate Cancer (clinical stage T1c-T3b, N0, M0) and shows at least 2 positive cores and a Gleason sum of ≥4+3	- Non-fucosylated Anti-CTLA-4 (BMS-986218) + Degarelix -Degarelix
A Randomized Trial of Cabazitaxel, Docetaxel, Mitoxantrone or Satraplatin (CDMS) Plus Surgery for Prostate Cancer Patients Without Metastasis (NCT03258320)	Qingdao, Shandong, China	I	-cT ≥ 2c -cN0 -cM0	- Cabazitaxel -Docetaxel -Mitoxantrone -Satraplatin
PROSTVAC in Combination With Nivolumab in Men With Prostate Cancer (NCT02933255)	Bethesda, MD, USA	I/II	-Surgical candidate who has chosen to proceed with prostatectomy	-Surgery alone - PROSTVAC-V (vaccinia) + PROSTVAC-F (fowlpox) + Nivolumab

pertinent immunotherapy agents such as PD1, PDL1 and CTLA4 inhibitors are underway.

Gene targeted therapy remains an area of intense research, particularly in the era of genomic profiling in the setting of high risk disease, per the NCCN guidelines (15). Recently, PARP inhibitors including olaparib, is recommended for patients with metastatic castrate resistance prostate cancer with pathogenic mutations in *BRCA1, BRCA2, ATM, MARD1, BRIP1, CDK12, CHEK1, CHEK2, PANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L*. While the role of gene-targeted therapy in earlier disease is yet to be defined, it may represent a particular focus as experience with such technologies mature.

A further focus of interest pertains to the potential consideration of radiopharmaceuticals and theranostics. For example, in the setting of castration-resistance prostate cancer, the recently published VISION trial demonstrated efficacy in Lu177-PSMA (84). The inclusion criteria of comparable active trials assessing Lu177-PSMA, suggest a minimum SUV avidity of 20 for metastases (85). Such values are plausible in intraprostatic disease, suggesting possible efficacy for PSMA rich intraprostatic disease prior to local definitive therapy.

RECOMMENDATIONS

At present, neoadjuvant therapy is not recommended prior to RP in men with clinically localized high-risk prostate cancer outside of a clinical trial. Robust studies including long term oncologic outcomes will be required to establish a role for initial systemic therapy in the management of clinically localized high-risk prostate cancer. Thus, current standard of care includes RP or

radiotherapy with neoadjuvant/concurrent/adjuvant ADT. Patients eligible for such ongoing neoadjuvant clinical trials should be encouraged to consider participation.

CONCLUSIONS

Patients with clinically localized high-risk prostate cancer is remain at significant risk of recurrence despite current local treatment options. Neoadjuvant therapy prior to RP is designed to reduce the risk of post-operative residual local disease and address micrometastatic disease prior to definitive treatment. However, evidence to date has demonstrated that neoadjuvant ADT or chemohormonal therapy may be associated with reduced adverse pathologic features but not oncologic outcomes. Clinical trials assessing novel therapeutic regimens are ongoing.

AUTHOR CONTRIBUTIONS

MP: manuscript preparation/drafting. BB: data collection and manuscript revision. ME: data collection and manuscript draft. CG: data collection. WY: data collection and manuscript revision. SB: supervision and manuscript revision. JE: supervision and manuscript revision. All authors contributed to the article and approved the submitted version.

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