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Sequencing the Treatment of High-Risk Prostate Cancer: A Way Towards Multimodal Tailored Approaches: A changing Landscape

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Introduction

Prostate cancer (PCa) prognosis and clinical outcome directly depend on metastatic occurrence. Patients with high-risk diseases have an increased risk of developing biochemical recurrence, metastases, Castrate resistant Prostate cancer, and death from prostate cancer. As the optimal management of high-risk disease in patients with prostate cancer continues to evolve, the contemporary treatment paradigm is moving toward a multidisciplinary integrated approach of systemic and local therapy for patients with high-risk diseases.

Risk Stratification

In 1998, D'Amico *et al*. suggested a model stratifying patients with prostate cancer into those with low, intermediate, or high-risk biochemical recurrence after Surgery according to the clinical TNM stage, biopsy Gleason score, and preoperative prostate-specific antigen level. The D'Amico classification system continues to stratify men into risk groups with statistically significant differences in Biochemical risk-free survival. However, the major shift in the distribution of patients among the three risk groups over time suggests that the clinical relevance of this classification scheme may be limited and diminishing in the contemporary era.

The strategies for definitive, adjuvant, and salvage local treatment, including radical prostatectomy or radiation therapy, serve as the backbone of therapy for patients with localized disease. Systemic therapy decisions regarding use in combination with Surgery, choice of therapy (hormone therapy, chemotherapy), and treatment duration continue to be refined. Integrating innovative blood and tissue-based biomarkers to guide therapy selection for patients with high-risk diseases is an active research area. Contemporary studies are using such biomarkers to stratify patients and select therapies. In this review, the current evidence for local treatment strategies, systemic therapy options, and biomarkers in development for managing high-risk prostate cancer in patients will be discussed for patients with high-risk prostate cancer who have an increased risk of disease recurrence and death from prostate cancer.

In addition to PSA level and MRI results, the decision to biopsy or not should be made in light of DRE findings, ethnicity, age, comorbidities, free/total PSA, history of previous biopsy, and patient values. Local treatment strategies include definitive radiotherapy or radical prostatectomy with or without adjuvant or salvage radiation therapy. Systemic therapy for patients with high-risk diseases includes androgen deprivation therapy, although many questions remain regarding the use with Surgery, intensity, and duration of androgen deprivation therapy. Blood and tissue-based biomarkers to guide therapy selection remain an area of active research, and contemporary clinical trials are integrating such predictive biomarkers to better guide therapy selection for patients at high risk.

High-risk Prostate Cancer

There are multiple definitions used to categorize individuals with high-risk prostate cancer. Pretreatment parameters, including clinical stage,

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prostate-specific antigen (PSA), and Gleason score, are established predictors of disease recurrence and have historically been used in high-risk disease classifications in 1998, using an endpoint of PSA recurrence, D'Amico et al· defined high-risk disease as a clinical T stage of at least cT2c, a Gleason score of at least 8, or a PSA more significant than 20 ng/mL.[1] This definition is widely used, given its simplicity and ease of use. The American Urologic Association has adopted it, the European Association of Urology, and the United Kingdom National Institute for Health and Clinical Excellence.[2]

High-risk prostate cancer is traditionally treated with Surgery or radiotherapy (RT), androgen deprivation therapy (ADT), and chemotherapy. However, recent advancements in systemic treatment and radiotherapy have widened the spectrum of treatment for this patient population.

Localized high-risk prostate cancer

Historically, strategies for treating localized high-risk prostate cancer comprise local approaches such as Surgery and radiotherapy and systemic approaches such as hormonal therapy. Nevertheless, since high-risk prostate cancer patients remain the group with a higher risk of treatment failure and mortality rates, nowadays, novel treatment strategies, comprising hypo fractionated-radiotherapy, second-generation anti-androgens, and hadron therapy, are being explored to improve their long-term oncological outcomes. This narrative review aims to report the current management of high-risk prostate cancer and to explore the future perspectives in this clinical setting.

Most patients in the current era will present with organ-confined disease, amenable to curative treatment in the developed world. In the developing world, the sceneries are different. Commonly the patients usually present at advanced stages. One can hope that increased awareness about Prostate Cancer will enhance the cure rate for Prostate cancer in the developing world.

The treatment for organ-confined disease includes watchful waiting, radical prostatectomy, radiation therapy, and focal cryosurgery in particular cases. Hormone therapy is the cornerstone of the treatment of patients with advanced prostate cancer.

Fig 1. *Diagnosis and staging Workup for prostate cancer.*

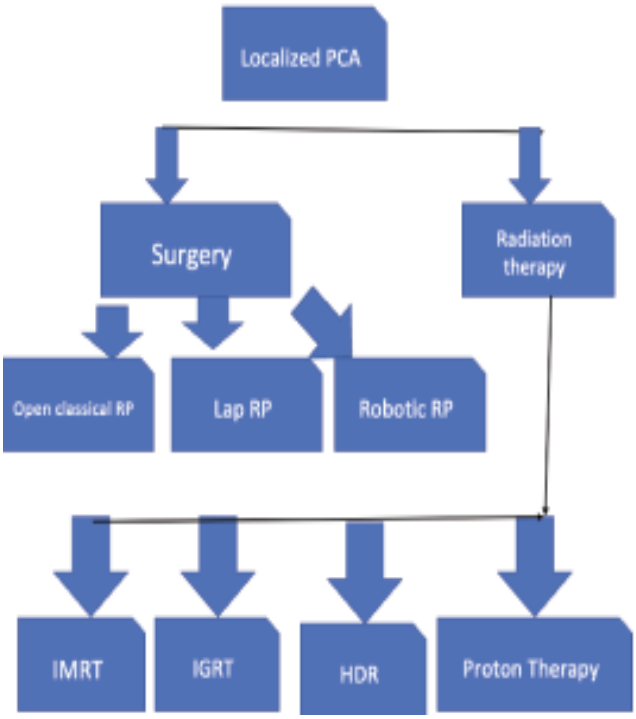


Fig.-2. *Treatment Algorithm for Localized prostate cancer.*

The availability of several therapeutic options for localized prostate cancer warrants careful consideration when planning treatment with curative

intent. Patients must be active participants in decision-making and be aware of the benefits and possible complications of the different types of treatment. Patients with advanced prostate cancer must be mindful that hormone treatment will usually provide temporization and palliation. Hormone-resistant prostate cancer is refractory to most forms of conventional and experimental therapy.

Watchful waiting with delayed ADT is an option for patients with localized or locally advanced disease whose Life expectancy is less than 10 years, and active surveillance is recommended for patients with low-risk disease

Organ-confined and locally advanced disease.

The specimen-confined or organ-confined disease was the only independent predictor of prostate cancer recurrence. Locally advanced prostate cancer is when cancer has grown through the capsule of the prostate and may have started to spread into tissue or organs nearby. These two groups of patients are best treated with the following:

- RP (Radical Prostatectomy) Path way or
- RT Pathway (external beam or brachytherapy or combination of both, e.g., HDR)

Are the options for patients with low-risk diseases who are anxious and not suitable for active surveillance and also suitable for intermediate-risk condition.

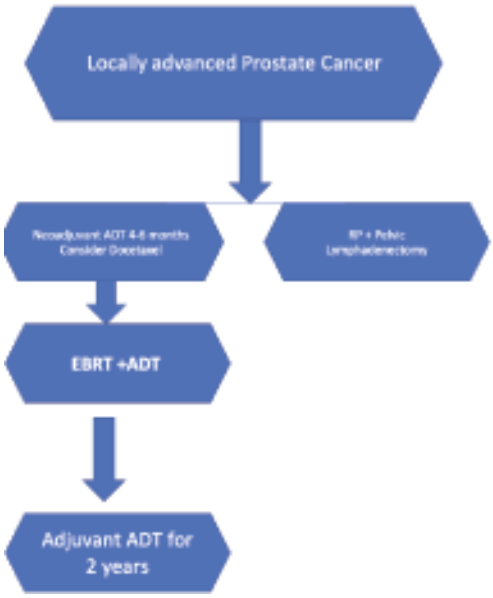


Fig.-3: *Treatment algorithm for locally advanced prostate cancer*

RP Pathway:

RP plus pelvic lymphadenectomy is an option for selected patients with locally advanced high-risk diseases. The essential local control and debulking improve the efficacy of sequential therapy with either radiation therapy or ADT aimed at micrometastatic and locoregional disease control and prevent clinical complications, such as hematuria and obstruction.[3]

Open Radical Prostatectomy (RP): Open classical Radical Prostatectomy is a common treatment choice for localized prostate cancer. While there is increasing utilization of robotic-assisted RP in some centers, open RP (ORP) remains well-established and commonly performed in many parts of the world. The goals of modern ORP are to remove the prostate *en-bloc* with negative surgical margins while minimizing blood loss and preserving urinary continence and erectile function.

Laparoscopic radical prostatectomy:

Laparoscopic radical prostatectomy was introduced in the 1990s. It aims to replicate the results that have been obtained by open radical retropubic prostatectomy while reducing the morbidity associated with Surgery. Since its introduction, laparoscopic radical prostatectomy has undergone numerous modifications in surgical technique, including approach, e.g. trans peritoneal vs extraperitoneal, anterior and posterior dissection, ascending and descending dissection, and most notably, robotic-assisted.[13]

Robotic radical prostatectomy

Robotic radical prostatectomy is a minimally invasive Surgery that uses surgical robotic equipment to remove the entire prostate. The robotic laparoscopic technique allows surgeons to operate through small ports rather than large incisions, resulting in shorter recovery times, fewer complications and reduced hospital stays. Surgical robotics combines minimally invasive techniques with highly advanced clinical technology. Robot-assisted radical prostatectomy is a safe procedure that can be performed in many ways using Single Port or Multiple Port robotic platforms.[9]

Radiation Pathway:

Patients receiving radical RT for intermediate-risk disease should be offered a short course of ADT for 4-6 months. Patients receiving radical RT for high-risk illnesses should have a long period of ADT (18-36 months). Patients receiving radical RT for high-risk diseases who fit the STAMPEDE trial criteria should

have a long course of ADT (18-36 months) plus AAP (24 months).

For patients with a local recurrence following RP and no distant metastases, the pros and cons of local salvage therapy should be discussed, taking into account life expectancy and the long natural history of isolated local recurrences. Patients with biochemical relapse after radical RT who may be candidates for local salvage or metastasis-directed treatment should undergo imaging with next-generation imaging tools such as 68Ga-PSMA-PET**e**CT or whole-body MRI.[7] Patients starting long-term ADT should be offered a bone health agent oral bisphosphonate or zoledronic acid every 12 months or Denosumab every 6 Months).

It is well established that treatment options for localized HR PCa should include a definitive local strategy, with 87 and 57% cancer-specific survival (CSS) rates observed among treated and untreated patients, respectively.[7] Following these data, both the National Comprehensive Cancer Network (NCCN) (8) and European Association of Urology (EAU) guidelines (1) strongly recommend a definitive treatment, stratifying patients following their life expectancy (with a threshold of 5 and 10 years, respectively). Guidelines' recommendations include radical prostatectomy (RP) + pelvic lymph node dissection (PLDN) or external beam RT (EBRT) + long-term ADT (1.5–3 years) ± a brachytherapy boost [8]. Since evidence from randomized controlled trials (RCTs) comparing Surgery and EBRT still lacks, no consensus exists on the best treatment choice. A recent international multidisciplinary systematic review[9] could not demonstrate the superiority of such approaches as primary local therapy. The ongoing randomized phase III SPCG-15 trial.[10] comparing CSS of locally advanced PCa patients treated with RP + ePLDN ± EBRT or EBRT + ADT is expected to provide evidence on this aspect.

The future robotic radical prostatectomy will be driven by artificial intelligence. Focusing on robot-assisted radical prostatectomy (RARP), several technical and technological innovations have been introduced to maximize functional and oncological outcomes.

The advent of three-dimensional (3D) technology meets patients' and surgeons' preferences allowing visualization of the anatomy three-dimensionally and enhancing the perception of the disease's location and characteristics, such as its relationship with the prostate capsule.

A step further in this direction is represented by the possibility of overlapping the 3D virtual images with the natural anatomy during *in vivo* robotic procedures, performing augmented reality procedures. As reported in our previous experiences, 3D prostatic models can be obtained from 2D-MRI images and consequently used during RARP, allowing the surgeon to focus on the tumor's characteristics, with particular attention to the potential presence of extracapsular extension.[41]

The intraoperative support of machine learning (ML) for autonomous camera positioning was promisingly explored by analyzing data obtained by instrument kinematics, laparoscopic video, and surgeon eye-tracking. On the contrary, the application of ML to more complex tasks (e.g., suturing, knot-tying, and tissue dissection) is more difficult to reach.

Thanks to specifically developed software, virtual models can be displayed on the da Vinci surgical console (Intuitive Surgical Inc.) and automatically anchored to the *in vivo* live images during Surgery. In conclusion, particularly in an intraoperative setting, the advent of AI is an obstacle by the lack of live data collection and by the complexity of privacy and data-sharing legislation.

EBRT + ADT

Androgen suppression is an established strategy for the treatment of HR PCa. Usually, it is accomplished via luteinizing hormone–releasing hormone (LHRH) analogs or antagonists, ± anti-androgens. It is widely recognized that improving OS may be obtained by adding ADT to RT in HR PCa patients with a life expectancy >10 years.[11-13] The latter evidence is supported by an RCT showing a 10-year OS of 40 to 58% among patients receiving RT alone or combined treatments, respectively ($p = 0.0004$). However, the appropriate ADT duration is undefined, considering its relation with the patient's reported quality of life (QoL). Two studies[14,15] addressing this issue have reported that long-term ADT [18–36 months) has better oncological outcomes for short-term ADT. Conversely, a recent phase III RCT[16] comparing long- (36 months) and intermediate- (18 months) term ADT did not observe a significant difference in clinical outcomes (CSS and distant metastases development), but only a benefit in QoL for the intermediate group. Currently, age, performance status, comorbidities, and the number of poor prognostic factors are recommended to be considered for establishing the ADT duration in clinical practice. In general, the current evidence

supports the fact that any ADT duration is better than no ADT at all[12,17-19], that long-term ADT (e.g., 3 years) is slightly better in OS than a short duration (6 months).[15] Still, it remains debated whether a period of 3 years in very HR patients is more appropriate.

Two RCTs[20-24] are ongoing and might provide more robust evidence. In particular, with an expected trial end date of August 2021, PIVOTAL-boost is a multicenter four-arm superiority phase III trial for intermediate and HR PCa patients with failure-free survival as the primary endpoint through administration of intensity-modulated RT (IMRT) on prostate ± pelvic and prostate boost on the dominant lesion(s). Similarly, the RTOG 0924, a phase III randomized trial, with primary outcome measure stated as OS assigning unfavorable intermediate or favorable HR PCa patients to ADT + EBRT ± WPRT. The estimated prior completion date is July 2027. Waiting for results from these RCTs, radiation oncologists are divided on the best strategy in the clinical practice. In the era of tailored treatments, to avoid unnecessarily more extensive treatment fields, Gallium 68 prostate-specific membrane antigen (Ga68 PSMA-PET) and whole-body Magnetic Resonance Imaging (MRI) could help to early identify pelvic lymph node localizations if PSA is still detectable[25,26] Such image-guidance techniques, mapping microscopic disease with improved sensitivity and sensibility, could also allow for dose escalation to nodes outside the conventional volumes.[27]

Hypo-fractionated and UltraHypofractionated RT and SBRT

Based on the radio sensibility of the PCa cells, it has been largely demonstrated that hypofractionation and extreme hypofractionation are safe and effective in low and intermediate-risk PCa.[28–31] In fact, the strong biologic rationale behind hypofractionation is based on the theory that the slow proliferation of PCa cells results in a different radiation response compared to other human cancers.[32,33] Therefore, the inability of PCa cells to overcome the higher rate of DNA damage induced by each fraction translates into increased sensitivity to higher doses per fraction. Currently, multiple clinical trials have shown the effectiveness and safety of moderate/standard hypofractionation for PCa treatment in terms of oncological outcomes and toxicity.[28-30,34-36] Thanks to modern techniques such as IMRT, highly conformal doses can be delivered to the target without affecting normal tissues, tilting the risk/benefit ratio more favorably towards RT.[37,38] The number of studies involving extreme hypofractionation (defined as the delivery of 5–10 Gy/fraction in four to seven fractions) is relatively low, and a direct comparison of different hypofractionation schemes is still lacking. Therefore, despite being cited in clinical practice guidelines next to moderate hypofractionation plans, the current level of evidence is too low to implement extreme hypofractionation as a standard of care.[39]

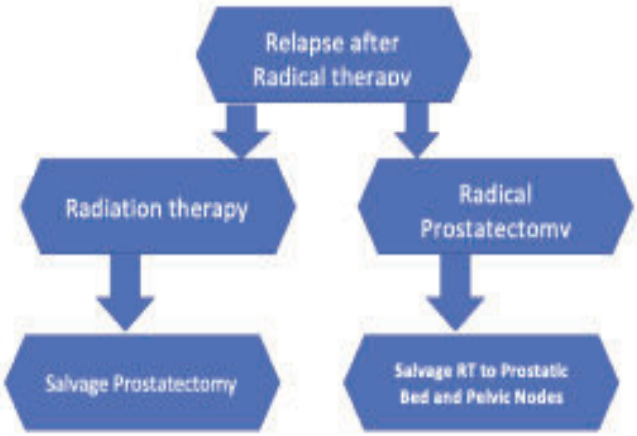


Fig.-4. *Treatment Algorithm of Patients after Relapse following Radical Treatment of PCa*

CyberKnife Radiotherapy in Prostate Cancer Patients

Based on the idea that large radiation fraction sizes are radio-biologically favorable over small fraction sizes in treating PCa, hypo fractionation with brachytherapy using high dose rate (HDR) brachytherapy showed promise as both a monotherapy and to boost external beam radiation therapy (EBRT). More recently, the use of the CyberKnife RT system (Accuracy, Sunnyvale, CA, USA) has been reported further to improve patient tolerance compared to HDR brachytherapy. Early results with the CyberKnife system have shown acceptable PSA responses and low toxicities; however, the data are still insufficient.[40]

Particle Therapy

Particle therapy has been gaining growing interest due to the particular physical and radiobiological properties of protons and other heavy ions, including carbon ions, compared to photons.[67]

In the late 1970s, improvements in accelerator technology, coupled with advances in medical imaging and computing, made proton therapy a viable option for routine medical applications. Although protons are used in several hospitals, the next step in radiation therapy is using carbon and other ions. These have some clear advantages over protons in providing local control of very aggressive tumors and a lower acute or late toxicity, thus enhancing the quality of life during and after cancer treatment.

Mainly, hadron therapy with protons and carbon ions has been considered a suitable strategy for treating localized and locally advanced PCa to reach high doses while maintaining a lower toxicity rate.

Carbon Ion Therapy

Carbon ion RT (CIRT) may represent an ideal treatment method for PCa due to carbon ion beams' unique physical and biological advantages. The dose distribution of CIRT is most advantageous for EBRT techniques because of its superior dose characteristics.[68] Firstly, steep dose gradients result in a better sparing of organs at risk (OARs) close to the target. Moreover, carbon ion beams have a high relative biological effectiveness (RBE), resulting from a high linear energy transfer, with their effect estimated to be approximately three times those of photons and protons.[69,70] Finally, carbon ions might affect radioresistant clusters, making them more sensitive to subsequent photon therapy. The first clinical trial of CIRT for PCa was initiated at the National Institute of Radiological Sciences (NIRS) in 1994, and the efficacy and feasibility of CIRT for localized PCa have been demonstrated through three phases I/II and two phases II clinical trials at NIRS. The studies published by the Japanese centers represent an essential starting point for the clinical use of carbon ions in this setting of patients.[71- 73]

A study by Kaseya and Colleagues analyzed the treatment outcomes of HR-localized PCa treated with CIRT + ADT compared with standard treatment modalities, focusing on PCa specific mortality (PCSM).[74] Despite differences in PCSM among the high risk groups, CIRT combined with ADT yielded relatively favorable treatment outcomes. The first prospective observational study conducted at a facility other than NIRS is by Kawamura et al.[75], which reported low GU and GI toxicities with reasonable biochemical control within 5 years following moderately hypo fractionated CIRT for localized PCa. The NCT02672449 is a prospective, multicentric, phase II open-label trial that might provide novel insights on a new mixed beam RT scheme of a carbon ion boost followed by pelvic photon RT, and CIRT in HR setting seems encouraging and could provide novel insight for the treatment of these patients.[76]

Proton Therapy

The idea of using protons for cancer treatment was first proposed in 1946 by the physicist Robert Wilson, who later became the founder and first director of the Fermi National Accelerator Laboratory (Fermilab) near Chicago. The first patients were treated in the 1950s in nuclear physics research facilities using non-dedicated accelerators. Initially, the clinical applications were limited to a few parts of the body, as accelerators were not powerful enough to allow protons to penetrate deep into the tissues.[77-81]

As of today, two studies report data about PBRT in an HR setting. Takagi et al. wrote the largest PBRT (± ADT) series in localized PCa with a 10-year follow-up.[82] Among a cohort of 2,021 patients, 792 belonged to HR or very HR groups. The control of PBRT resulted in favorable, with a biochemical control rate of 68 and 62% in HR and very HR patients, respectively. Five-year OS was 96% in the HR group and 92% in the same HR cohort. Arimura et al. conducted a prospective cohort study on 218 patients with intermediate-risk and HR PCa declining ADT, receiving PBRT.[83] Unexpectedly, results were similar to those of previously reported ones from studies concerning PBRT + ADT, where in a PBRT setting, ADT for 12 months and 21 months was shown as preferable for HR PCa patients.[84] Therefore, monotherapy PBRT can be considered an optional treatment in this setting, even if studies that include more patients and longer follow-ups are needed to clarify the definitive role of PBRT in treating HR-localized PCa.

Management algorithms for metastatic prostate cancer Hormone-naïve metastatic prostate cancer: Combination of therapeutic option is the gold standard. ADT plus docetaxel and Abiraterone Acetate + Prednisolone is recommended as first-line treatment for fit patients with hormone naive Prostate Cancer (mHNPC), especially in those with multiple bone metastases (>3) or visceral metastases. In other patients with mHNPC, ADT plus or Abiraterone Acetate + Prednisolone, or Apalutamide or Enzalutamide may also be recommended as first-line treatment for mHNPC].

ADT plus radiation to the primary tumor is recommended for patients with low-volume mHNPC. For patients starting on ADT, management to prevent cancer treatment-induced bone loss (CTIBL) is recommended. The use of multimodal therapy in treating advanced prostate cancer with the intent of cure is a reality today. A select case of Oligometastatic prostate cancer is called curable cancer.

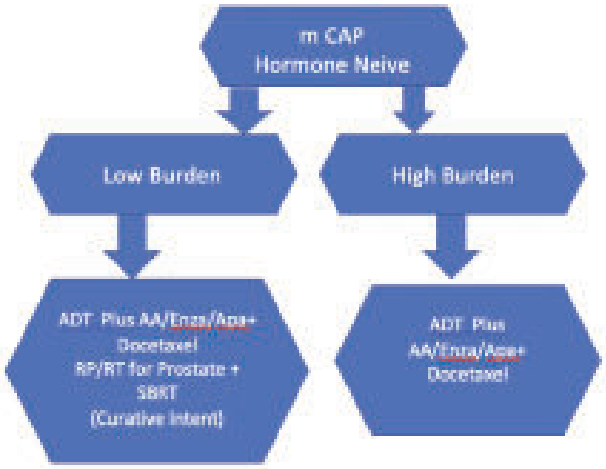


Figure 5. *Metastatic Prostate Cancer, Treatment Algorithm*

Treatment for metastatic prostatic cancer (mPCa) is an area of ongoing research with a lack of up-to-date clinical guidance. The most up-to-date guidelines, consensus statements, and emerging phase 3 trials were identified and used to inform the development of algorithms by a multidisciplinary genitourinary oncology panel outlining recommendations for managing mPCa.

PEACE-1 clinical trial data shows a dramatic OS benefit when using a triple combination. In addition, the ARCHES data have shown an OS benefit with ADT in combination with enzalutamide. We have seen the TITAN data, offering the apalutamide combination with ADT gives an OS benefit in a broad patient population. There is a lot of evidence supporting combined therapies in metastatic prostate cancer. The key message is that ADT alone is not enough in 2021 in metastatic prostate cancer.[38]

For newly diagnosed Metastatic Castrate Sensitive Prostate (CSPC) patients with high-volume/high-risk disease, either docetaxel or abiraterone acetate and prednisone (AAP) added to androgen-deprivation therapy (ADT) is recommended. Adding radiotherapy to ADT is suggested for those with low-volume disease and AAP to ADT for low-volume or low-risk disease. For first-line mCRPC, androgen receptor-axis-targeted (ARAT) therapy is recommended for most patients, while sequencing with docetaxel, radium-223, ARAT therapy, and cabazitaxel is recommended for later lines of treatment.[43]

Oligometastatic prostate cancer (OMPC).

OMPC, generally defined by the presence of five or fewer metastatic sites on imaging, represents a transitional state between localized and widespread metastatic disease and encompasses a broad spectrum of disease biologies and clinical behaviors.

It is an intermediate state between localized disease and widespread metastases, including a spectrum of disease biology and clinical behaviors. The oligometastatic disease will be redefined as novel imaging tools continue to be adopted as it is an individual, heterogeneous entity with distinct M1 phenotypes and wide prognostic variability.

Local cytoreductive therapies, such as radical prostatectomy with or without pelvic LN dissection and RT, seem well tolerated in patients with OMPC. Pelvic RT has been demonstrated to improve outcomes in patients with high-volume metastatic prostate cancer receiving abiraterone plus aDT. Participation in clinical trials or institutional registries is strongly encouraged for patients with OMPC who opt for an aggressive multimodality approach.

Systemic therapies for metastatic prostate cancer are noncurative and associated with significant toxicities over long exposure durations. Focal therapies may allow a subset of patients to delay or interrupt systemic treatment and decrease the burden of adverse effects.

The mainstay of OMPC treatment remains systemic therapy, either with androgen-deprivation therapy (ADT) alone or combined with other agents (docetaxel, abiraterone, etc.). Focal therapies, including resection or radiotherapy (RT), to the primary tumor have improved outcomes, including failure-free survival in several retrospective studies. In a clinical trial, RT to the prostate has specifically demonstrated an overall survival (OS) advantage in patients with low-volume disease. In retrospective studies, improvements in outcomes have been observed with focal therapies for retroperitoneal and more distant metastatic sites.

OMPC is a unique clinical state with inherently more indolent tumor biology susceptible to multidisciplinary

treatment (MDT). With the development of new imaging techniques, patients with OMPC are likely to be identified at an earlier stage. The treatment paradigm is shifting towards a more aggressive approach to treating potentially curable patients. Multimodal management is necessary to improve patient outcomes due to the combination of available therapies, such as local therapy of primary tumor and metastasis directed therapy or systemic therapy, to reduce tumor load and prevent further disease progression.

Treatment of Distant Oligometastatic Sites

Multiple retrospective studies have demonstrated improved outcomes with metastasis-directed therapies (MDT), including retroperitoneal LN dissection for patients with nodal-only prostate cancer recurrences. In one such study of patients with biochemical recurrence, 1,816 patients in the standard-of-care cohort received ADT only. In contrast, patients in the MDT cohort underwent either salvage LN dissection (166 patients) or SBRT to PET-avid nodes (97 patients). MDT was associated with improved cancer-specific survival (HR, 0.33; 95% CI, 0.17–0.64), suggesting this may be an option in selected patients.[61] A total of 23 patients with M1 PCa (with 3 or fewer bone lesions) undergoing cytoreductive radical prostatectomy (CRP) were compared to 38 men with M1 PCa treated with ADT without local therapy. Clinical PFS and cancer-specific survival was improved with CRP, and CRP effectively prevented complications of the lower and upper urinary tract.[42] A retrospective case series comprising 106 patients with newly diagnosed M1 PCa examined perioperative outcomes.[43] CRP for men with locally resectable, distant M1 PCa appeared safe and feasible. Complication rates related to CRP were not higher than when radical prostatectomy was performed for standard indications, and CRP avoided complications related to local progression. RT to the primary tumor is a promising treatment option in low-volume mCSPC. Additional prospective data are needed to select patients most likely to benefit from a therapeutic approach.

Treatment of Metastatic Castrate Resistant Prostate Cancer CRPC

Prostate Cancer is a typical androgen-dependent disease; thus, hormonal therapy is commonly used as standard care for mPCa by inhibiting androgen receptor (AR) activities or androgen metabolism. Almost all PCa will eventually acquire resistance and become castration-resistant PCa (CRPC) associated with AR gene mutations or amplification, AR variants, loss of AR expression toward a neuroendocrine phenotype, or other hormonal receptors. Surgery or radiation is potentially curative treatment for localized disease. Since PCa is characterized as a typical androgen-dependent disease[2], hormone therapy (i.e., androgen deprivation therapy (ADT)) is the most effective therapy to control metastatic disease. However, almost all patients eventually develop castration-resistant PCa (CRPC) within 12 to 18 months, with a median survival of 14 to 26 months.

Treating CRPC poses a significant challenge to clinicians. Research efforts in the last decade have developed several new anti-androgen agents to prolong the overall survival of CRPC patients. In addition, many potential targeting agents have been at the stage of being able to translate many preclinical discoveries into clinical practices. Nowadays, new anti-androgens (Enzalutamide or Abiraterone), radiotherapy (177), or immunotherapy (sipuleucel-T) have been approved for metastatic CRPC (mCRPC) patients to prolong overall survival. Inevitably, mCRPC further acquires resistance and becomes therapy- and castration-resistant PCa (t-CRPC), considered an end-stage disease. Some cancer cells exhibit neuroendocrine phenotypes with neuronal markers expression and neuronal factors secretion in an endocrine fashion [8], considered neuroendocrine PCa (NEPC), a subpopulation of t-CRPC. However, the primary site has identified small-cell carcinoma of the prostate (SCPC) with very low incidence (1% of the prostatic malignancies). Although SCPC is associated with a highly proliferative area of tumor mass and poor prognosis, it is still sensitive to chemotherapy [9,10]. On the other hand, NEPC is known to resist many therapeutic regimens. Currently, no effective targeted therapy for NEPC has been approved by the FDA. Based on molecular profiling from NEPC patients, this article has discussed several potential new therapeutic strategies for this disease.[74]. The following

1. AR Receptor Blocker

1a.) Enzalutamide. In PCa, the androgen receptor (AR) activated by androgens still represents a critical oncogenic pathway. Enzalutamide is a novel anti-androgen agent that can block AR with high affinity compared to traditional anti-androgens such as bicalutamide or flutamide.[11] Besides direct binding to

AR, it can reduce AR translocation into the nucleus and prevent its transcription by binding to DNA. Enzalutamide was approved by the Food and Drug Administration (FDA) in 2012 for use on metastatic CRPC based on the randomized, phase III trial study (AFFIRM). Enzalutamide demonstrated the benefit of metastasis-free survival rate compared to placebo (36.6 months vs. 14.7 months, $p < 0.001$) in patients with non-metastatic CRPC. Therefore, the FDA has expanded the use of enzalutamide in patients with nmCRPC since 2018.

1b.) Apalutamide. Apalutamide is a second-generation androgen inhibitor approved for use in nmCRPC and mHSPC. A double-blind, placebo-controlled, phase III trial (SPARTAN) demonstrated that apalutamide improved median metastasis-free survival compared with placebo (40.5 vs. 16.2 months. $p < 0.001$) in patients with non-mCRPC.[76]

Darolutamide Like other second-generation androgen inhibitors, darolutamide can inhibit AR translocation, DNA binding, and AR-mediated transcription. From the phase I/II study, darolutamide inhibited cell proliferation more efficiently than enzalutamide in a castration animal model.[75] Besides, it also blocks the activity of the mutant ARs, like the F876L mutation caused by enzalutamide or apalutamide.

1c.) Darolutamide.

Like other second-generation androgen inhibitors, darolutamide can inhibit AR translocation, DNA binding, and AR-mediated transcription (Figure 1). The phase I/II study showed that darolutamide inhibited cell proliferation more efficiently than enzalutamide in a castration animal model.[77] Besides, it also blocks the activity of the mutant ARs like the F876L mutation caused by enzalutamide or apalutamide.[77] In a randomized, double-blind, placebo-controlled, phase III trial (ARAMIS), darolutamide improved metastasis-free survival (40.4 months vs. 18.4 months, $p < 0.001$) compared with placebo in patients with nmCRPC

2.Androgen Axis inhibitor

2a.) Abiraterone acetate.

Abiraterone Acetate is a selective CYP17 enzyme inhibitor that can decrease androgen synthesis of the testis, adrenal gland, and prostate gland.[78] In the double-blind, placebo-controlled phase 3 study (CO-AA-301 clinical trial), it demonstrated that abiraterone combined with prednisolone improved OS compared to the placebo plus prednisolone group (15.8 vs. 11.2 months. $p < 0.0001$) in patients with mCRPC who progressed after chemotherapy.[78]

3. AR Splice Variant-7 (AR-V7) Inhibitors

For mCRPC patients, drug resistance to 2nd-generation AR signaling inhibitors (ARSi), such as abiraterone and enzalutamide is essentially universal in tumor cells that often come with significantly elevated expression of truncated AR splice variant-7 (AR-V7). Therefore, there is an urgently needed new treatment to reduce the impact of the elevated AR-V7 expression, leading to lethal progression of CRPC. **Niclosamide** is an anthelminthic drug approved by the FDA; it can decrease the protein expression of AR-V7 in CRPC cells through the ubiquitin– proteasome pathway.[79]

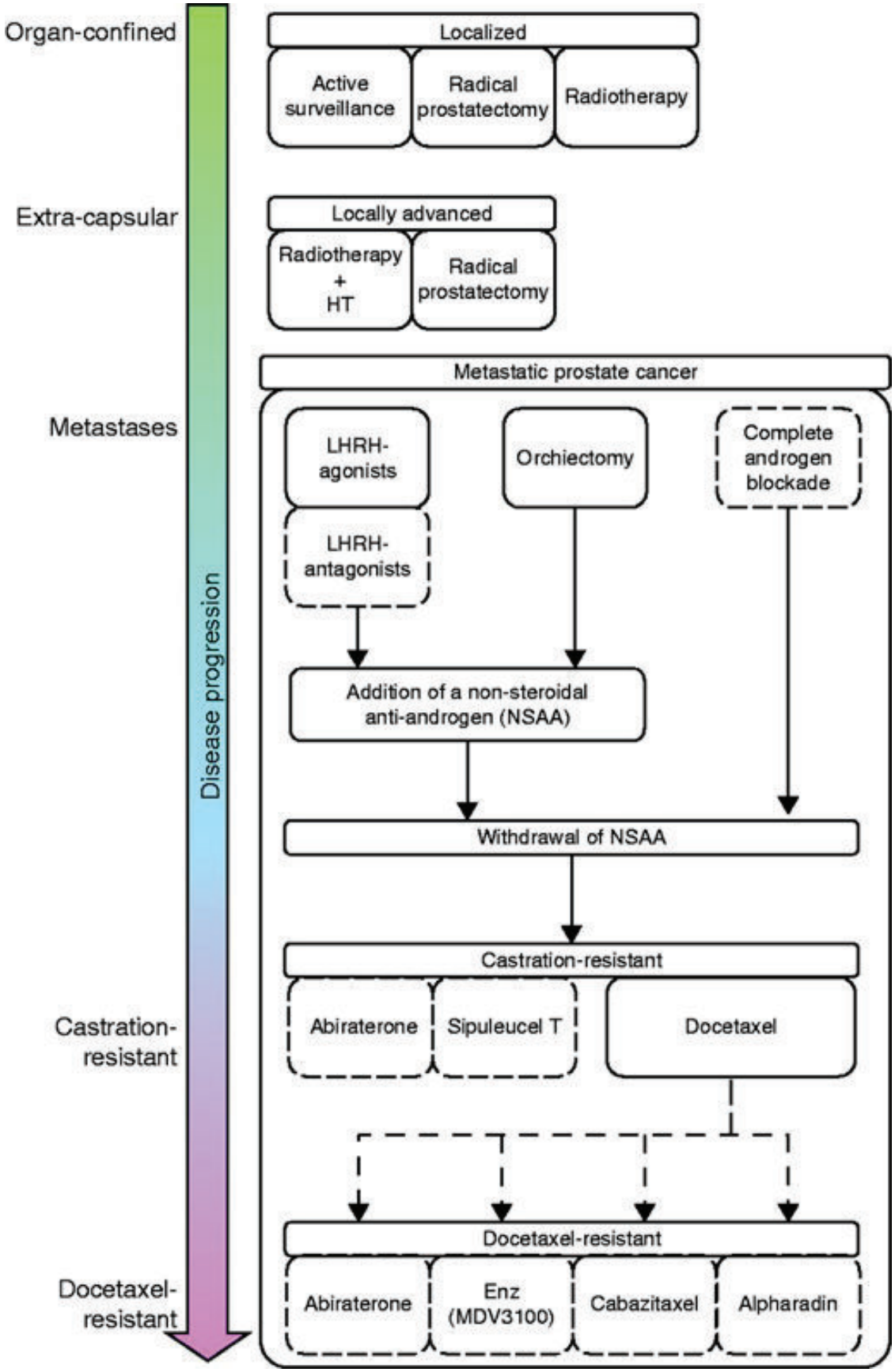
4. Radiotherapy

4a). Ra-223: A phase III clinical trial (ALSYMPCA) demonstrated that **Ra-223** revealed OS benefit in mCRPC patients with symptomatic bony metastasis (14.9 vs. 11.3 months, $p < 0.001$).[29]

4b). 177Lu-PSMA Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein expressed in the prostate epithelium. The PSMA receptor has an internalization process that can cause endocytosis in the putative ligand into the cell, which allows the PSMA-labelled radioisotope to be more concentrated within the cell.[72] Due to the above characteristic, it is helpful to develop novel therapeutic methods to target the delivery of drugs, short-range radioisotopes, and toxins specifically for mCRPC.

5. PARP Inhibitors

One of the potential reasons for radioresistance is the ability of tumor cells to repair the damage inflicted by radiotherapy. Following the induction of DNA double-strand breaks (DSB) by ionizing radiation, cancer cells mount a rapid response involving an extensive network of pathways. This response involves the cellular machinery required to repair damaged DNA, allowing the malignant cell to survive and retain its reproductive integrity. This network is called the DNA damage response (DDR). It is well known how high rates of genomic mutations in DDR genes result directly related to multiple malignancies. More recently, it has been suggested that tumors with such homologous recombination defects may be sensitive to iPARP.


Organ-confined
Extra-capsular
Metastases
Castration-resistant
Docetaxel-resistant
Disease progression
Localized
Active surveillance
Radical prostatectomy
Radiotherapy
Locally advanced
Radiotherapy + HT
Radical prostatectomy
Metastatic prostate cancer
LHRH-agonists
LHRH-antagonists
Orchiectomy
Complete androgen blockade
Addition of a non-steroidal anti-androgen (NSAA)
Withdrawal of NSAA
Castration-resistant
Abiraterone
Sipuleucel T
Docetaxel
Docetaxel-resistant
Abiraterone
Enz (MDV3100)
Cabazitaxel
Alpharadin

Currently, multiple agents, such as Olaparib, Olaparib, and rucaparib, target the DDR pathway. Among these, iPARP, Olaparib, and rucaparib are effective in men with metastatic castration-resistant PCa (mCRPC). Since DDR pathway alterations were seen at a similar rate between localized and metastatic PCa, iPARP may also have a therapeutic effect in localized PCa.

Overall, the above-reported findings suggest that a dysregulated DDR pathway may occur earlier during PCa progression than previously thought and that available inhibitors of the DDR pathway, such as iPARPs, may have an influential therapeutic role in localized PCa.

6. CART cell therapy for prostate cancer: status and promise

Chimeric antigen receptor (CAR) T-cell therapy is a way to get immune cells called *T cells* to fight cancer by changing them in the lab so they can find and destroy cancer cells. CAR T-cell therapy is also sometimes talked about as *cell-based gene therapy* because it involves altering the genes inside T cells to help them attack cancer.

In recent years, chimeric antigen receptor T (CAR-T) cell therapy as adoptive immunotherapy has received significant attention and made great breakthroughs. CAR-T cells show excellent specificity, targeting, and less substantial histocompatibility complex restriction in tumor immunotherapy, significantly different from traditional T cells. Despite the progress of CART-T technology in treating lymphoma, leukemia, and other blood system tumor, CAR-T technology still has many difficulties in treating solid tumors. In this review, we will summarize the present situation of CAR-T cells in the treatment of prostate cancer and discuss the promise of applying this technology to prostate cancer therapy.

In CAR T-cell therapies, T cells are taken from the patient's blood and are changed in the lab by adding a gene for a receptor (called a *chimeric antigen receptor* or *CAR*), which helps the T cells attach to a specific cancer cell antigen. The CAR T cells are then given back to the patient.

Since different cancers have different antigens, each CAR is made for specific antigens. For example, cancer cells have an antigen called CD19 in certain kinds of leukemia or lymphoma. The CAR T-cell therapies to treat these cancers are made to attach to the CD19 antigen and will not work for cancer that does not have the CD19 antigen.

Preparation of the CAR T cells: After the white cells are removed, the T cells are separated, sent to the lab, and altered by adding the gene for the specific chimeric antigen receptor (CAR). This makes them CAR T cells. These cells are then grown and multiplied in the lab. It can take several weeks to make the large number of CAR T cells needed for this therapy.

The CAR T-cell infusion: Once enough CAR T cells have been made, they will be returned to the patient. A few days before the CAR T-cell infusion, the patient might be given chemotherapy to help lower the number of other immune cells. This gives the CAR T cells a better chance to get activated to fight the cancer. This chemotherapy is usually not very strong because CAR T cells work best when there are still some cancer cells to attack. Once the CAR T cells start binding with cancer cells, they increase in number and can help destroy even more cancer cells. CAR T-cell therapies are approved by the US Food and Drug Administration (FDA) to treat some kinds of lymphomas, leukemias, and multiple myeloma. CAR T-cell therapy is typically used after other types of treatment have been tried.

Side effects of CAR T-cell therapy: CAR T-cell therapy can be very effective against some types of resistant cancers but can sometimes cause serious or life-threatening side effects. Because of this, it needs to be given in a medical center that is specially trained in its use, and patients need to be watched closely for several weeks after getting the CAR T cells. As CAR T cells multiply, they can release large amounts of chemicals called *cytokines* into the blood, which can ramp up the immune system. Serious side effects from this release can include High fever and chills, Dyspnea, Severe nausea, vomiting, diarrhea, Headaches, Feeling very tired, Changes in consciousness, Confusion or agitation, Seizures, tremors, and allergic reactions during the infusion. Only a small number of prostate cancer patients have been treated with CAR-T therapy to date, and data on human off-tumor toxicities, optimal treatment combinations, durability, persistence, and efficacy of treatment are mainly derived from studies in other tumor types. In the era of precision medicine, CAR-T cell therapy provides hope to patients; however, a more excellent range of preclinical models is required to guide its clinical utility in men with mCRPC [85]. Until now, two anti-PSMA CAR-T trials have been reported. In the clinical trial (NCT00664196) of the first generation of anti-PSMA CAR-T-cells therapy, PSA decline in 50% and 70% was

found in two patients. Still, three other patients experienced disease progression.[86]

7. PTP1B Inhibitors

In recent years, the protein tyrosine phosphatase 1B (PTP1B; also known as PTPN1) has emerged as a critical regulator of multiple signaling networks involved in human disorders, such as obesity, diabetes, and cancers. Moreover, several studies point toward PTP1B as a potential therapeutic target in various tumors, such as Prostate Cancer, pancreatic cancer, ovarian cancer, colon cancer,[182] and breast cancer. Wu et al. indicated that PTP1B elevation was detected in neuroendocrine differentiation in PCa specimens. Also, one study suggested that PTP1B deletion or inhibition (PTP1B inhibitor; MSI-1436) could enhance T-cell antitumor activity and improve the therapeutic efficacy of chimeric antigen receptor (CAR) T cells in solid tumors. Generally, the accumulative evidence suggested that PTP1B may serve as a promising therapeutic target for t-CRPC treatment.[87]

Follow-up and Long-term Implications of Prostate Cancer

ADT may cause hot flushes, lethargy, mood changes, osteoporosis, insulin resistance, and muscle loss. Because survival in mCRPC has improved substantially, men live longer on ADT. They were taken together with the adverse effects of abiraterone, enzalutamide, and steroids on bone health. The risk of fragility fracture in men on long-term ADT exceeds accepted intervention thresholds. Even before starting ADT, many men diagnosed with prostate cancer have osteopenia or osteoporosis.

Conclusion.

Multidisciplinary teams of urologists, medical oncologists, radiation oncologists, radiologists, and pathologists will be instrumental in shifting the treatment tide for the patients. Although we celebrate the life-prolonging effects of the new hormonal therapies, the diagnosis of metastatic prostate cancer currently leads to lifelong androgen deprivation therapy. Despite progress on multiple research fronts, we have imperfect tools to identify patients who need treatment in the first place. Once the disease spreads beyond the control of local therapies, we do not know how best to sequence or combine the expanding number of active treatments.

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